4th International Congress on Leukemia – Lymphoma – Myeloma

May 22 – 25, 2013 • Istanbul, Turkey

Proceedings & Abstract Book

Turkish Society of Hematology

Organizing Committee

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Teoman Soysal
Istanbul University, Cerrahpasa School of Medicine, Department of Hematology, Istanbul, Turkey

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Trakya University, School of Medicine, Department of Hematology, Edirne, Turkey

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Hacettepe University, School of Medicine, Department of Hematology, Ankara, Turkey

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Myelodysplastic Syndromes	H. Joachim Deeg *Fred Hutchinson Cancer Research Center, Seattle, Washington, USA*
Chronic Lymphocytic Leukemia	Peter Dreger *University of Heidelberg, Germany*
Infections	Thomas J. Walsh *National Cancer Institute Bethesda, USA*
Hodgkin Lymphoma	Andreas Engert *University Hospital Cologne, Cologne, Germany*
Acute Lymphoblastic Leukemia	Nicola Gökbuget *J.W. Goethe University Hospital, Frankfurt, Germany*
Indolent Lymphomas	Robert E. Marcus *King's College Hospital, London, United Kingdom*
Diffuse Large B-Cell Lymphoma	Christian Gisselbrecht *Hôpital Saint Louis, Paris, France*
New Advances in Pediatric Acute Lymphoblastic Leukemia	Sima Jeha *St. Jude Children's Research Hospital, Memphis, USA*
Aggressive Lymphomas	Anna Sureda *Hospital de la Santa Creu i Sant Pau, Barcelona,Spain*
Acute Myeloid Leukemia	Martin Tallman *Memorial Sloan-Kettering Cancer Center, New York , USA*
Chronic Myeloprolierative Disorders	Ayalew Tefferi *Mayo Clinic, Mayo Graduate School of Medicine, Minnesota, USA*
Chronic Myeloid Leukemia	Nora Heisterkamp *Childrens Hospital of Los Angeles, Los Angeles, USA*

Dear Colleagues,

It gives us great pleasure to host the 4th International Congress on Leukemia-Myeloma-Lymphoma (ICLLM 2013) in Istanbul, Turkey.

The 4th ICLLM Congress provides a unique forum for scientists and medical professionals gathered from around the world to meet and exchange ideas and information in the fields of hematology and oncology. The scientific program of the ICLLM Congress boasts most of the hematology masters who aim to provide a perfect balance between clinical education and news of the latest scientific developments.

Istanbul as the capital of culture in Europe for 2010 started to associate with culture and the arts all over the world. Istanbul will achieve lasting gains in the fields of urban renewal, urban living and environmental and social development. Those who come to Istanbul for cultural and artistic projects will visit the city's cultural riches, mosques, churches, palaces and museums.

The cultural program also promises to be special, highlighting Istanbul's proud culture and national heritage. Istanbul has been inhabited since the end of the 4th century B.C. Remains from the Hellenic, Roman, Byzantine and Ottoman periods are scattered throughout the city, prominent among them the Hagia Sophia, Basilica Cistern, Blue Mosque, Grand Bazaar, Topkapı Palace and Turkish Baths, making Istanbul a fascinating open air museum. You would have the opportunity to discover Turkish music, art and architecture, enjoy the delicious tastes of Turkish and Ottoman cuisine, and experience the world famous Turkish hospitality. The unique geography of Istanbul gives the opportunity to meet where the two continents meet.

The Istanbul Wow Convention Center, located near the airport and easily accessible by public transport, offers excellent facilities, including all the necessary infrastructure and professionalism to successfully host a medical convention of this import. Participants from 22 countries are registered, and the Congress has been accredited by both the European Hematology Association (EHA) and the Turkish Medical Association.

On behalf of the Board of the Turkish Society of Hematology and scientific faculty, I would like to welcome you to the 4th International Congress on Leukemia-Myeloma-Lymphoma. I believe that you will enjoy both the scientific and cultural aspects of the program, and that you also take advantage of the pleasure of the nice İstanbul spring.

Prof. Dr. Teoman Soysal
Congress President

4th International Congress on Leukemia Lymphoma Myeloma (ICLLM)

'Play it again, Sam'
An original misquotation of "Play it, Sam"
from the 1942 film Casablanca

The face of a thing is its essence or reality. On the common language, however, the face is that which looks. We, the physicians and scientists from all over the World dealing with the hematological neoplastic disorders, again have set foot upon the city of Istanbul where the continents meet.

This is our fourth meeting being an essential and realistic tool for better understanding and management of leukemia, lymphoma, and plasma cell myeloma. The names of those diseases refer to the cellular neoplasia suggesting the concepts look in keeping with the demands of their own essence, their own specific characteristics.

Facing the limits of knowledge in the twiligt of the complicated clinical course of leukemic disease is a common state for the physicians seeing the people of leukemia in the hospital practice. The data of randomized clinical trials, guidelines, recommendations, and expert opinions represent the current truth in this state. Developments in the basic hematology-related sciences, pathobiological experiments in the field of leukemia, and the setting of hypotheses-generating neoplastic models represent the hope for all of us. The scientific programme of this Istanbul meeting has been prepared to supply the balance between the truth and the hope for the diseases; leukemia, lymphoma, and plasma cell myeloma. The aim of this meeting is to maintain the balance between the valuable solid research data and the very valuable expert perspectives obtained with the years of scientific experience and being physicians of the patients with leukemia, lymphoma, and plasma cell myeloma.

The abstracts and the educational lectures have been designated to establish an area suitable for the exchange of ideas during the meeting days. Furthermore, the manuscripts will reveal a long-term scientific source in the library of physicians dealing with the management of those hematological neoplastic disorders. Likewise, the full text content of the educational books of the meetings of International Congress on Leukemia Lymphoma Myeloma (ICLLM), including the fourth latest one, will be freely available to everybody in the website of Turkish Society of Hematology (www.thd.org.tr) just after the completion of the conference.

The first thought that flashed into our minds when we first saw the completed scientific collections of the fourth International Congress on Leukemia Lymphoma Myeloma (ICLLM) was that the supreme genius of the scientists, researchers, and mentors that make possible to organize such an outstanding conference in the city of Istanbul. We hope that those days will be remembered as the days of science, friendship, and light for the physicians dealing with their patients with the diseases of leukemia, lymphoma, and plasma cell myeloma.

Best regards.

Prof. Dr. Muzaffer Demir

Prof. Dr. Ibrahim C. Haznedaroğlu

Scientific Secreteriat,
Fourth International Congress on Leukemia Lymphoma Myeloma (ICLLM), Istanbul

Contents

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Organization Services

4th International Congress on Leukemia – Lymphoma – Myeloma

May 22 – 25, 2013 • Istanbul, Turkey

SCIENTIFIC PROGRAM

May 23, 2013, Thursday

HALL A

TIME	MEETING
07:15 - 08:15	**Meet The Expert** New administration methods in NHL: **Andy Davies** *(Southampton General Hospital,United Kingdom)*
08:30 - 10:00	**Acute Myeloid Leukemia** Chair: **Martin Tallman** *(Memorial Sloan-Kettering Cancer Center, New York , USA)* **Muhit Özcan** *(Ankara Üniversitesi Tıp Fakültesi, Ankara, Turkey)* Speakers: • New Insights into the Molecular Genetics in AML : **Omar Abdel-Wahab** *(Memorial Sloan-Kettering Cancer Center, New York, USA)* • New Developments in Induction and Post Remission Therapy in AML : **Martin Tallman** *(Memorial Sloan-Kettering Cancer Center, New York, USA)* • New Directions in Transplantation in AML : **Steve MacKinnon** *(University College London, London, UK)*
10:00 - 10:30	COFFEE BREAK
10:30 - 12:00	**Multiple Myeloma : Provocative Diagnostics and Therapies** Chair: **Bart Barlogie** *(University of Arkansas, Myeloma Institute for Research and Therapy, USA)* **Meral Beksaç** *(Ankara Üniversitesi Tıp Fakültesi, Ankara, Turkey)* Speakers: • Genomics and Imaging : **Bart Barlogie** *(University of Arkansas, Myeloma Institute for Research and Therapy, USA)* • Myeloma Metastasis Model : **Irene Ghobrial** *(Department of Medicine, Harvard Medical School Active Medical Staff, Myeloma Program, Dana-Farber Cancer Institute, USA)* • Cure or Control : **Michele Cavo** *(University of Bologna, Italy)* • Sequelae of MM Therapy : **Saad Usmani** *(Myeloma Institute for Research and Therapy, UAMS, USA)*
12:00 - 14:00	LUNCH
12:30 - 13:30	**CELGENE SATELLITE SYMPOSIUM** **Highlights From International Myeloma Workshop: Focus On IMIDs** • The latest understanding of MM pathophysiology and Continuous Treatment in MM : **Antonio Palumbo** *(Molinette Hospital in Turin, Italy)* • IMiD based regimes in the present and future of MM: **Meletios Dimopoulos** *(University Athens School of Medicine, Athens, Greece)*

14:00 - 15:30 **Diffuse Large B-Cell Lymphoma**

Chair: **Christian Gisselbrecht** *(Service d'Onco-Hématologie, Hôpital Saint Louis, Paris, France)*

Mutlu Arat *(İstanbul Bilim Üniversitesi Tıp Fakültesi, İstanbul, Turkey)*

Speakers:
- Biological Heterogeneity of DLBCL: **Laurence de Leval** *(CHUV Centre Hospitalier Universitaire, Switzerland)*
- First Line Treatment of DLBCL: Do We Need to Adapt Treatment to Subtypes? : **Wyndham Wilson** *(NCI, Bethesda, USA)*
- Relapsed DLBCL : Where Are We? **Christian Gisselbrecht** *(Hopital Saint Louis, Paris, France)*

15:30 - 16:00 COFFEE BREAK

16:00 - 17:30 **Chronic Myeloproliferative Disorders**

Chair: **Ayalew Tefferi** *(Mayo Clinic, Mayo Graduate School of Medicine, Minnesota, USA)*

A. Selim Yavuz *(İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, İstanbul , Turkey)*

Speakers:
- Molecular Pathogenesis Update : **Richard Van Etten** *(Stanford University, Boston, USA)*
- Prognostic Models : **Tiziano Barbui** *(Ospedali Riuniti di Bergamo, Italy)*
- JAK inhibitors Value and Limitations : **Ayalew Tefferi** *(Mayo Clinic, Mayo Graduate School of Medicine, Minnesota, USA)*

17:30 - 19:00 OPENING CEREMONY

May 24, 2013, Friday

HALL A

TIME	MEETING

08:30 - 10:00 **Acute Lymphoblastic Leukemia**

Chair: **Nicola Gökbuget** *(J.W. Goethe University Hospital, Frankfurt, Germany)*
Gülsan Sucak Türköz *(Gazi Üniversitesi Tıp Fakültesi, Ankara, Turkey)*

Speakers:
- Conventional and Molecular Prognostic Factors In Adult ALL : **Herve Dombret** *(Institut Universitaire d`Hematologie Hopital St. Louis, Paris, France)*
- How to Improve Outcome of Adult ALL : **Nicola Gökbuget** *(J.W. Goethe University Hospital, Frankfurt, Germany)*
- Current and Future Management of Ph/BCR-ABL positive ALL : **Renato Bassan** *(Venice Hospital, Venice, Italy)*

10:00 - 10:30 COFFEE BREAK

10:30 - 12:00 **Hodgkin Lymphoma**

Chair: **Andreas Engert** *(University Hospital of Cologne, Köln, Germany)*
Tülin Fıratlı Tuğlular *(Marmara Üniversitesi Tıp Fakültesi, Istanbul, Turkey)*

Speakers:
- Prognostic Factors and the Role of PET in Hodgkin Lymphoma: **Martin Hutchings** *(Copenhagen University Hospital,Copenhagen, Denmark)*
- Early Stage Hodgkin Lymphoma: Open Questions and Controversies: **Anton Hagenbeek** *(Academic Medical Center, Amsterdam, the Netherlands.)*
- Treatment of Advanced and Relapsed Hodgkin Lymphoma: **Andreas Engert** *(University Hospital of Cologne, Köln, Germany)*

12:00 - 14:00 LUNCH

14:00 - 15:30 **Infections in Hematological Malignancies**

Meeting the Challenge of Emerging Pathogens in Patients with Hematological Malignancies: Rational Approaches to Diagnosis, Treatment, and Prevention

Chair: **Thomas J Walsh** *(National Cancer Institute Bethesda, USA)*
Hamdi Akan *(Ankara Üniversitesi Tıp Fakültesi, Ankara, Turkey)*

Speakers:
- Global Threat of Multidrug Resistant Bacteria in Patients with Hematological Malignancies: **Thomas J Walsh** *(National Cancer Institute Bethesda, USA)*
- Patterns of Invasive Fungal Infections in Patients with Hematological Malignancies: **Maria Gamaletsou** *(National and Kapodistrian University of Athens, Greece)*
- Emergence of Respiratory and Systemic Viral Infections in Patients with Hematological Malignancies: **Nikolas Sipsas** *(National and Kapodistrian University of Athens, Greece)*

15:30 - 16:00 COFFEE BREAK

16:00 - 17:30 **Myelodysplastic Syndromes**

Chair: **H. Joachim Deeg** *(Fred Hutchinson Cancer Research Center, Seattle, USA)*
Deniz Sargın *(İstanbul Üniversitesi İstanbul Tıp Fakültesi, İstanbul, Turkey)*

Speakers:
- Molecular Pathogenesis of MDS: **Jacqueline Boultwood** (*John Radcliffe Hospital, Oxford, United Kingdom)*
- The Biology and Management of Non-del(5q) Low-risk MDS: **David Bowen** *(Leeds Teaching Hospitals NHS Trust, Yorkshire, United Kingdom)*
- Transplantation for MDS: for Whom, When and How?: **H. Joachim Deeg** *(Fred Hutchinson Cancer Research Center, Seattle, USA)*

HALL B

TIME MEETING

14:00 - 15:30 **Pediatric Acute Lymphoblastic Leukemia**

Chair: **Sima Jeha** *(St. Jude Children's Research Hospital, Memphis, USA)*
Lebriz Soycan *(Kadıköy Florence Nightingale Hastanesi, Istanbul, Turkey)*

Speakers:
- Significance of Minimal Residual Disease in Acute Lymphoblastic Leukemia: **Dario Campana** *(National University of Singapore, Singapore)*
- Molecular Genetics of Acute Lymphoblastic Leukemia: **Charles Mullighan** *(Saint Jude Children's Research Hospital, Memphis, USA)*
- Advances in the Treatment of Acute Lymphoblastic Leukemia: **Sima Jeha** *(St. Jude Children's Research Hospital, Memphis, USA)*

16:00 - 17:30 **Pediatric Acute Myeloid Leukemia**

Chair: **Ursula Creutzig** *(University of Münster, Münster, Germany)*
Tiraje Celkan *(İstanbul Üniversitesi, Cerrahpaşa Tıp Fakültesi, İstanbul, Türkiye)*

Speakers:
- Differences in the Genetic Characterization and Therapeutic Approach in Paediatric and Adult AML: **Ursula Creutzig** *(University Children's Hospital Muenster, Germany)*
- Differences in Treatment for Paediatric and Adult APL: **Gertjan Kaspers** *(VU University Medical Center, the Netherlands)*
- Supportive Care During High Intensive Chemotherapy for Paediatric Patients with Acut)e Myeloid Leukaemia: **Thomas Lehrnbecher** *(Klinikum der Johann Wolfgang Goethe-Universität, Frankurt, Germany)*

May 25, 2013, Saturday

HALL A

TIME	MEETING

08:30 - 10:00 **Indolent Lymphomas**

Chair: **Robert Marcus** *(King's College Hospital, London, United Kingdom)*
İhsan Karadoğan *(Akdeniz Üniversitesi Tıp Fakültesi, Antalya, Turkey)*

Speakers:
- Conventional Therapy for Low Grade B Cell Lymphoma: **Robert Marcus** *(King's College Hospital, London, United Kingdom)*
- The Biology of Low Grade B Cell Lymphoma and How It Might Inform Future Therapies: **Daniel Hodson** *(NCI, Bethesda, USA)*
- A Non "Genotoxic " Future for the Therapy of Low Grade B Cell Lymphoma: **Nathan Fowler** *(The University of Texas MD Anderson Cancer Center, Houston, USA)*

10:00 - 10:30 COFFEE BREAK

10:30 - 12:00 **Chronic Myeloid Leukemia**

Chair: **Nora Heisterkamp** *(Childrens Hospital of Los Angeles, USA)*
Hakan Göker *(Hacettepe Üniversitesi Tıp Fakültesi, Ankara, Turkey)*

Speakers:
- BCR-ABL: Past, Present and Future : **Nora Heisterkamp** (Childrens Hospital of Los Angeles, USA)
- Current Management of CML with TKIs : **İbrahim Haznedaroğlu** *(Hacettepe Üniversitesi, Ankara)*
- Hematopoietic Stem Cell Transplantation for CML in the TKI Era: **Nelson J. Chao** *(Professor, Dunham, USA.)*

12:00 - 14:00 LUNCH

12:30 - 13:30 **TAKEDA SATELLITE SYMPOSIUM**
Evolving New Management Approach in relapsed/ refractory CD30-expressing lymphomas: Hodgkin lymphoma and systemic anaplastic large cell lymphoma

- Evolving New Management Approach in Hodgkin Lymphoma: Role of Brentuximab Vedotin: **Andreas Engert** *(University Hospital of Cologne, Köln, Germany)*
- Management of Anaplastic Large Cell Lymphoma and Peripheral T Cell Lymphoma: Role of Brentuximab Vedatin: **Burhan Ferhanoğlu** *(İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Istanbul, Turkey)*

14:00 - 15:30 **Chronic Lymphocytic Leukemia**

Chair: **Peter Dreger** *(University of Heidelberg, Hamburg, Germany)*
Fatih Demirkan *(Dokuz Eylül Üniversitesi Tıp Fakültesi, İzmir, Turkey)*

Speakers:
- Standard CLL Treatment: Goals vs. Endpoints: **Emili Montserrat** *(Hospital Clinic, Barcelona, Spain)*
- Toward a "Biological" Treatment of CLL: **Eva Kimby** *(Huddinge University Hospital, Stockholm, Sweden)*
- High-Risk CLL: Definition and Treatment Options: **Peter Dreger** *(University of Heidelberg, Hamburg, Germany)*

15:30 - 16:00 COFFEE BREAK

16:00 - 18:00 **Aggressive Lymphomas**

Chair: **Anna Sureda** *(Hematology Department Addenbrooke's Hospital. Cambridge, UK)*
Hakan Özdoğu *(Başkent Üniversitesi Tıp Fakültesi Adana Hastanesi, Adana, Turkey)*

Speakers:
- Inside the Mantle Cell. Treatment of High-Risk Mantle Cell Patients: **Olivier Hermine** *(Hôpital Necker Paris, France)*
- Stem Cell Transplantation for Peripheral T cell Lymphomas. How, Who and When?: **Norbert Schmitz** *(Asklepios Klinik St. Georg, Hamburg, Germany)*
- Biology, Prognostic Factors and Treatment of Primary Central Nervous System Lymphoma: **Gerald Illerhaus** *(University of Freiburg, Freiburg, Germany)*

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PROCEEDINGS

ICLLM 2013

Acute Myeloid Leukemia

I want to welcome attendees to the session on Acute Myeloid Leukemia (AML). Major progress has been made recently in our understanding of the biology of the disease as well as in treatment. There has been a dramatic increase in information which further deciphers the molecular pathogenesis of the disease. In addition, new strategies in induction, postremission therapy, and transplantation have emerged and the standards of care are changing. This session will begin with a presentation by Dr. Abdel-Wahab from Memorial Sloan-Kettering Cancer Center in New York City who will address the new insights into the molecular genetics in AML and how they might be used to guide therapy. Dr. Martin Tallman, also from the Memorial Sloan-Kettering Cancer Center, will discuss new developments in induction and postremission therapy including exciting new agents, many targeted towards a specific molecular or antigenic determinant, with unique mechanisms of action currently being explored clinically. Finally, Dr. Steve MacKinnon from University College London in the UK will focus on new approaches to transplantation in AML. As transplant-related mortality is reduced, together with improvements in transplant techniques, such an approach can be applied to more patients who may benefit from graft-versus-leukemia effect which has curative potential. We hope that this session will address both major progress as well as the remaining issues in the study and care of patients with AML in 2013.

Martin Tallman, MD

CURRICULUM VITAE

Omar Abdel-Wahab, M.D.
Assistant Attending, Leukemia Service
Assistant Member, Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center
Instructor, Weill Cornell Medical College
1275 York Avenue, Box 20
New York, NY 10065
Tel: 646-888-3487
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abdelwao@mskcc.org

Education and Training

2007-2009	Memorial Sloan Kettering Cancer Center, New York, NY. Fellow, Hematology/Oncology.
2004-2007	Massachusetts General Hospital, Boston, MA Intern/Resident in Internal Medicine,
2000-2004	Duke University School of Medicine, M.D., Alpha Omega Alpha
1996-2000	Duke University, Durham, N.C. B.Sc. Biology, Summa Cum Laude

Research Fellowships:

2008-2011	Postdoctoral Research Fellow Human Oncology & Pathogenesis Program, Memorial Sloan-Kettering Cancer Center Ross L. Levine, MD, Associate Member
2002-2003	Medical Student Research Fellowship Dept. of Surgery, Duke University School of Medicine Doug Tyler, MD, Professor and Vice Chair Dept. of Surgery

Positions and Employment:

2011- Current	Assistant Level I, Dept. of Medicine, Leukemia Service Assistant Member, Human Oncology and Pathogenesis Program Memorial Sloan-Kettering Cancer Center
2010-2011	Instructor, Dept. of Medicine Memorial Sloan-Kettering Cancer Center

Honors and Awards:

2012	Dept. of Defense Post-doctoral Award in Bone Marrow Failure Research
2012	Josie Robertson Young Investigator Award
2012	Paul Sherlock House-staff Teaching Award
2011	Gabrielle's Angel Foundation Fellow Scholar Award
2010-2012	American Society of Hematology (ASH) Fellow Scholar Award
2009	American Society of Hematology (ASH) Research Training Award for Fellows
2008	Chief Fellow, Memorial Sloan Kettering Cancer Center, Medical Oncology/Hematology
2008-2010	Dana Foundation Research Fellowship
2008	John Mendelsohn House-staff Teaching Award
2004	Phillips Medical Systems Award
2004	Alpha Omega Alpha, Duke University School of Medicine
2003	Duke University School of Medicine Barham Merit Scholarship
2002	Duke University Medical Research Scholarship in General and Cardiothoracic Surgery.
1999	Phi Beta Kappa, Duke University

Licensure and Board Certification:

2007	Certification, Internal Medicine (American Board of Internal Medicine)
2007	Medical License, State of New York, #243567-1
2010	Certification, Medical Oncology (American Board of Internal Medicine)

Professional Societies:

2007	Member, American Society of Hematology

Editorial Board:
Editorial Board of *Blood*
Assistant Editor of *Leukemia* and *Blood Cancer Journal* (both Nature publishing group)

***Ad Hoc* Reviewer:**
Blood, *New England Journal of Medicine, Journal of Clinical Investigation, Journal of Clinical Oncology, Leukemia*, *Cancer Research, Clinical Cancer Research, Leukemia Research, British Journal of Hematology, Blood Cancer Journal, PLos One*, *Critical Reviews in Oncology/Hematology, and Journal of Molecular Diagnostics*

Oral Presentations:

2009	International Conference on Differentiation Therapy, Samuel Waxman	Foundation, Chicago, IL
2010	Post-ASH Myeloproliferative Neoplasm Workshop, Orlando Fla.	
2011	International Working Group for Myelofibrosis Research and Treatment Florence , Italy	Workshop,
2011	Leukemia Grand Rounds, Leuekmia Dept, MD Anderson Cancer Center,	Houston, TX
2011	Lineberger Cancer Center Grand Rounds, UNC Chapel Hill, Chapel Hill, NC	

2011 FASEB Hematologic Malignancies, Saxtons River, VT
2011 Northwestern University, Hematology Grand Rounds, Chicago, IL
2011 American Society of Hematology, Oral Presentation in "Oncogenes and Tumor Suppressors"
2011 Post-ASH Myeloproliferative Neoplasm Workshop, La Jolla, CA
2012 UTSW Simmons Cancer Center Molecular Therapeutics of Cancer Program, Dallas, TX
2012 University of Pennsylvania, Dept of Cancer Biology, Phildelphia, Pennsylvania
2012 Cincinatti Children's Hospital, Experimental Hematology and Cancer Pathology Program, Cincinatti, Ohio
2012 Dept. of Hematology/Oncology, Mount Sinai College of Medicine, New York, NY
2012 Dept. of Genetics, Albert Einstein College of Medicine, Bronx, NY
2012 Chromatin Club of New York, Mount Sinai College of Medicine, New York, NY
2012 Division of Hematologic Neoplasia, Dept. of Medicine, Dana Farber Cancer Institute, Boston, MA
2012 Institut Gustave Roussy Research Seminar, INSERM, Villejuif cedex, France
2012 International Working Group for Myelofibrosis Research and Treatment Workshop, Florence, Italy
2012 Hematologic Malignancies Grand Rounds, Massachusetts General Hospital Cancer Center, Boston MA
2012 Mayo Clinic Arizona, Cancer Center Grand Rounds, Scottsdale AZ
2012 Dept. of Hematology Grand Rounds, First Affiliated Hospital of Nanjing Medical University, Nanjing, China
2012 Plenary Speaker, Chinese Society of Hematology 2012 Annual Meeting, Suzhou China
2012 XII Uruguayan Congress of Hematology, Punta Del Este Uruguay
2012 Innovation Approaches to JAK Inhibition and Continued Clinical Questions in th Management of Myelofibrosis. Atlanta, GA.
2012 American Society of Hematology, Biology of MDS Oral Session, Atlanta, GA.
2012 Post-ASH International CML and MPN Workshop, Atlanta, GA.
2013 Clinical Translation of Epigenetics in Cancer Therapy, Asheville NC

ACTIVE RESEARCH SUPPORT:

Josie Robertson Investigator (PI: Abdel-Wahab) **9/1/12** – 8/31/17
Josie Robertson Investigator Program $500,000/yr
This award is intended to provide funding for exceptional junior faculty members to support for their research expenses over the first five years of their independent lab work.

Post-doctoral fellowship in Bone Marrow Failure Research 7/1/12 – 6/30/15
DOD, BM110172 $100,000/yr.
Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure
To understand and target aberrant epigenetic modifiers in the pathogenesis of myelodysplastic syndromes.

Clinical Scientist Research Career Development Award (K08) 9/20/11 – 8/31/16
NIH, 1K08CA160647-01 $169,884/yr
"Role of ASXL1 mutations in myeloid malignancies."
To understand role of ASXL1 in normal and malignant hematopoiesis.

PRIOR RESEARCH SUPPORT

When Everyone Survives Award in Leukemia Research (Abdel-Wahab) 7/1/11 – 6/30/12
When Everyone Survives Foundation $50,000/yr
"Understanding the biologic and therapeutic relevance of ASXL1 mutations in acute myeloid leukemia"
To determine how exactly mutations in ASXL1 contribute to leukemia development.

LSLF Discovery Research Grant (Abdel-Wahab) 4/1/11 – 3/31/12
Lauri Strauss Leukemia Foundation $45,000/yr "Role of ASXL1 mutations in AML"
The goal of this project is to fully uncover (1) the effect of ASXL1 mutations of outcome in AML, (2) a comprehensive list of the genes whose expression is regulated by ASXL1 and a genome-wide view of the effects of ASXL1 loss on histone proteins at the sites of those genes and (3) the role of ASXL1 loss in the blood cells in a mouse model which we are currently creating.

ASH Scholar Award (Abdel-Wahab) 7/1/11 – 6/30/13
American Society of Hematology $50,000/yr
"Role of ASXL1 mutations in myeloid malignancies"
The goal of this project is to investigate the biologic and clinical relevance of ASXL1 mutations and how ASXL1 regulates the epigenetic state of genes involved in normal and malignant hematopoiesis.

Gabrielle's Angel Foundation Fellow Award (Abdel-Wahab) 1/1/11 – 12/31/11
Gabrielle's Angel Foundation $25,000/yr
"The Role of ASXL1 mutations in leukemia patients"
To identify strategies to aid in the therapy of AML patients with this genetic abnormality.

Dana Fellowship in Biomedical Research 7/1/08 – 6/30/11
Memorial Sloan Kettering Cancer $45,000/year for 2 years
"Allele-specific signaling differences in myeloproliferative neoplasms." (no funding during 2010)
Clinical Scholars Training Award, Dana Foundation, MSKCC. .

American Society of Hematology (ASH) Research Training Award for Fellows 7/1/09 – 6/30/10
"Cytokine Signaling in Myeloproliferative Neoplasms." $55,000/yr
American Society of Hematology, Research Training Award for Fellows.

Molecular Genetics of Acute Myeloid Leukemia: Clinical Implications and Opportunities for Integrating Genomics into Clinical Practice

Omar Abdel-Wahab

Leukemia Service and Human Oncology and Pathogenesis Program

Memorial Sloan-Kettering Cancer Center

Abstract:

Advances in sequencing technologies have led to the discovery of a series of mutations in a sizeable proportion of patients with acute myeloid leukemia (AML) over the last ten years. Clinical correlative studies are now beginning to decipher the clinical importance, prevalence and potential prognostic significance of these mutations in AML but few studies have assessed the clinical implications of these mutations in a comprehensive fashion. Nonetheless, mutations in *DNMT3A, TET2,* and *ASXL1* are emerging as important adverse prognosticators in subsets of patients with AML independent of *FLT3* mutations whereas mutations in *IDH2* at residue 140 are potential predictors of improved outcome in AML. Further improvements in cost, throughput, and clinical validation of second-generation sequencing technologies may allow for clinical implementation of comprehensive genetic profiling in the clinical care of AML patients.

Key Words: AML, TET2, ASXL1, IDH1/2, DNMT3a

Introduction

Advances in the molecular characterization of myeloid malignancies, including acute myeloid leukemia (AML), has resulted in the discovery of a series of recurrent genetic abnormalities found in patients with AML. Prior to 2009, this included the discovery of gain-of-function alterations in *FLT3*[1] [1], *MLL*, *c-KIT,* the *RAS* family of oncoproteins, as well as loss-of-function/dominant-negative alterations in *NPM1*, *CEBPa*, and *TP53*. Findings from concurrent clinical correlative analyses have resulted in the routine clinical application of molecular testing for mutations in *FLT3, NPM1,* and *CEBPA* for improved risk stratification of AML patients[2,3]. Since 2009, however, an even larger number of recurrent molecular alterations have been discovered in a sizeable proportion of patients with AML, including mutations in *TET2, IDH1/2, ASXL1, DNMT3A,* and *PHF6.* In addition to furthering our understanding of the molecular basis for AML, discovery of these mutations may be clinically relevant as many of these mutations appear to hold prognostic importance which may aid in risk stratification and/or therapeutic decision-making. Additionally, mutations in several of these genes may specifically impact leukemic cells in such a manner that is therapeutically targetable.

The widening spectrum of clinically relevant molecular alterations in AML presents the potential for applying genomic technologies to clinical care of AML patients. In addition, rapid developments in new technologies for genomic analysis may allow for comprehensive genetic analysis of AML patients in real-time clinical practice. Here we discuss the relevance of recently discovered molecular genetic alterations in AML in the context of currently clinically utilized risk stratification of AML patients as well as the potential for implementation of detailed molecular genetic approaches to routine practice.

Molecular Genetics in Current Clinical Practice in AML: Cytogenetics and mutations in *FLT3, c-KIT, NPM1,* and *CEBPA*

Currently, the maximal genetic characterization of AML patients performed in routine clinical care of AML patients consists of determination of gross structural chromosomal abnormalities in leukemic cells by karyotype/FISH and testing for the presence of internal tandem duplications in *FLT3 (FLT3-ITD),* tyrosine kinase domain mutations in *FLT3* (*FLT3 D835A),* mutations in the extracellular (exon 8) or PTK2 domain (D816 mutations) of *C-Kit* and mutations in *NPM1* and *CEBPA*. The karyotype of leukemic cells remains the strongest established predictive factor for response to induction therapy and survival and patients are roughly subdivided

into one of three prognostic categories with favorable, intermediate, or adverse outcome based on their cytogenetic findings[4,5,6]. Within each of these cytogenetic groupings of AML patients, further molecular analysis identifies additional subsets of patients with a heterogeneity of clinical outcomes based on the presence of additional mutations.

Currently, molecular genotyping for improved risk stratification within cytogenetic groups is based on the use of *FLT3, NPM1,* and *CEBPA* mutational testing in patients with intermediate-risk cytogenetics and use of *KIT* mutational testing in patients with the otherwise prognostically favorable core-binding factor translocations (topics reviewed extensively elsewhere[4]). As mentioned earlier, however, a number of additional molecular genetic events have been more recently described to hold prognostic significance in AML patients overall as well as in cytogenetically-defined intermediate-risk AML patients.

New mutations with potential prognostic importance in AML patients: mutations in *DNMT3A, IDH1, IDH2, TET2, ASXL1*, and *PHF6*

Mutations in *DNMT3A* were initially discovered in 2010 based on whole genome sequencing of AML patients as well as array-based sequencing platforms. Since then, it has become clear that mutations in *DNMT3A* are present in 20-25% of AML patients, making mutations in *DNMT3A* the second most commonly mutated gene in AML patients overall (following mutations in *FLT3*). The initial correlative studies of *DNMT3A* mutations in AML patients strongly suggested that *DNMT3A* mutations confer an adverse prognosis in AML patients overall, independent of *FLT3* mutational status. Ley *et al.* found that *DNMT3A* mutant patients had a median survival of 12.3 months compared with 41.1 months in *DNMT3A*-wildtype counterparts ($p<0.0001$)[7].[7][7] Yan *et al.* specifically studied the effect of *DNMT3A* mutations on the outcome of 91 patients with M5 AML and found an abysmal effect of *DNMT3A* mutations on overall survival (OS) and time-to-treatment failure such that *DNMT3A*-mutant patients had a median survival of 7 months compared with 19.5 months in *DNMT3A*-wildtype patients ($p=0.004$)[8]. Looking specifically at patients with cytogenetically-normal AML, both Ley *et al.* and Thol *et al.* found that *DNMT3A* mutations predicted shorter OS and lower complete response (CR) rate in AML, independent of *FLT3* mutational status[7,9].

As with mutations in *DNMT3A,* mutations in isocitrate dehydrogenase 1 and 2 (*IDH1/2)* were also discovered by whole genome sequencing of AML patients. In contrast to mutations in *DNMT3A,* however, mutations in *IDH2* at the R140 codon appear to confer improved outcome in AML patients overall [10,11]. All discovered *IDH* mutations reside in the active site of the enzyme and participate in isocitrate binding. They are missense alterations affecting arginine 132 (R132) in IDH1, and either the analogous arginine residue (R172), or the residue at arginine 140 (R140), in the IDH2 protein. Although each of these mutations is mutually exclusive of one another and all have been shown to result in production of the metabolite 2-hydroxyglutarate, it appears that each of these mutations has differing prognostic impact in AML and studies which cluster the various *IDH1/2* alleles together may obscure the prognostic effect of *IDH1/2* mutations in AML. As such, the largest studies correlating *IDH1/2* alleles separately with outcome in AML have come from analysis of more than 1,000 patients treated on 2 United Kingdom Medical Research Council Trials who were also tested for *FLT3ITD/TKD, NPM1,* and *CEBPA* mutations [10,12]. In both studies, patients with either *IDH1* or *IDH2* mutations were significantly enriched with *NPM1* mutations. Amongst the entire cohort of patients, they found that those patients with an *IDH2R140Q* mutation had an improved OS and decreased response rate (RR) compared with all other patients. This finding was even more striking amongst the subset of *FLT3* wildtype/*NPM1* mutant patients who had survival similar to the most favorable subsets of patients. In contrast, *IDH2R172* mutations had a neutral effect on outcome and response to therapy while *IDH1R132* mutations seemed to impart worsened outcome on *FLT3* wildtype patients. The latter finding of an adverse effect of IDH1R132 mutations on FLT3 wildtype subsets of AML patients have also been reported by Paschka *et al.* and Abbas *et al* as well.

Comprehensive genetic analysis of AML patients has revealed that mutations in *TET2* and *IDH1/2* are mutually exclusive in AML patients[13]. This finding identified a novel complementation group and served as the basis for understanding some of the biological effects of *IDH1/2* mutations in leukemia development. Although mutations in *IDH1/2* may have differing effects on prognosis depending on the mutated allele, the strongest data on *TET2* mutations in AML suggests that *TET2* mutations are important adverse predictors of prognosis in subsets of AML patients with normal cytogenetics without the *FLT3-ITD*. This data comes from (1) a study by Chou et al. of 486 *de novo* AML patients treated with standard induction chemotherapy where *TET2* mutations were clearly associated with shorter OS only in the subset of 171 CN AML patients with intermediate-risk cytogenetics and *NPM1* wildtype/*TET2*

mutant genotype [14] and (2) a study by Metzeler *et al.* of 427 CN AML patients who received cytarabine/daunorubicin-based first line therapy which found that *TET2* mutations adversely affected survival in patients within the European Leukemia Net (ELN) favorable-risk category of CN AML (CN AML patients with mutated *NPM1* and/or *CEBPA* without *FLT3ITD* mutations)[15].

Shortly after the discovery of mutations in *TET2,* mutations in the *Addition of Sex Combs Like 1* were discovered using similar SNP-array based studies to identify regions of microscropic deletion in the genome of patients with myeloid malignancies[16]. Although, there is some controversy of whether a repeatedly reported variant in *ASXL1* is a bona fide somatic mutation[17], it appears that *ASXL1* mutations represent important markers of adverse overall survival in patients with myelodysplasia and AML. By studying samples from 398 AML patients in an Eastern Cooperative Group (ECOG) E1900 trial, we found that mutations in *ASXL1,* although rare in AML patients less than age 60, were associated with worsened overall survival in the overall cohort of AML patients as well as in the subset of cytogenetically-defined intermediate risk AML patients[18]. More recently, Metzeler *et al.* identified that *ASXL1* mutations are associated with an unfavorable CR rate (P=.03), disease-free survival (P<.001), OS (P<.001) and event-free survival (P<.001) amongst ELN Favorable patients[19]. Also, Pratcorona *et al.* studied the impact of *ASXL1* mutations on 882 AML patients treated on a number of different HOVON protocols[20]. Similar to the results from the CALGB study, this analysis likewise revealed that ASXL1 mutations are associated with worsened survival (median OS 15.9 months vs. 22.3 months; P=0.019) and significantly lower CR rate (61% vs. 79.6%; P=0.004). The studies from CALGB and HOVON also found a significantly higher-rate of ASXL1 mutations in AML patients beyond the age of 60 years old.

In addition to noting that mutations in ASXL1 impart worsened overall survival in the entire subset of AML patients in the ECOG E1900 trial, mutations in plant homeodomain finger 6 (*PHF6)* were also identified to be associated with worsened overall survival amongst AML patients overall[18]. PHF6 mutations were initially identified in ~20% of patients with T-cell acute lymphoblastic lymphoma[21] and have more recently been identified in 3-5% of de novo AML patients[22]. Although not as common in AML as mutations in the aforementioned genes, the correlation with worsened OS in overall and CN AML patients from a uniformly treated patient cohort suggests that PHF6 mutations should be studied further in AML.

Conclusion: The potential for comprehensive genetic characterization of AML patients in clinical practice

The identification of the currently known 5-10 recurrent molecular genetic alterations in AML patients with prognostic importance presents a significant challenge for implementing testing of all of these genetic alterations into clinical practice. Current genetic testing of AML clinical patient samples relies on characterization of metaphase karyotype, FISH, restriction enzyme digestion of PCR products, and capillary sequencing. However, these currently clinically utilized technologies will be inadequate for comprehensive genetic characterization of AML patients in the future and conventional Sanger sequencing will be overly costly and unwieldy for these purposes as well. Moreover, it is expected that genetic discovery efforts will continue to uncover additional clinically important genetic alterations in AML in the near future. Mass-spectrometric genotyping as well as high-resoluting melting genotyping have emerged as cost-effective and rapid means of genotyping patient samples for individual recurrent mutations at specific amino acid residues (eg. mutations in *N/K-Ras, IDH1, IDH2*). However, these methodologies cannot be used to identify the full catalogue of mutations which might occur throughout the open-reading frame of a gene (eg. mutations in *TP53, TET2, ASXL1).* Thus, it appears that so-called "second-generation" sequencing technologies (eg. Illumina and SOLiD) and/or the use of array-based sequencing platforms (the Roche NimbleGen and Agilent Capture Array being two examples) may be the best candidates for initiating comprehensive genetic profiling of patient samples in clinical practice. This will allow for detection of somatic mutations, structural rearrangements, and copy-number changes simultaneously. The current limitations which prevent implementation of such sequencing in clinical practice include the high cost, slow turnaround time, and lack of clinical validation. Efforts to limit the sequencing to panels of candidate target genes may improve all of these limitations however. Array-based sequencing using hybrid capture technology may be time-saving compared with other next-generation sequencing approaches and is cost-effective compared to PCR based methods. This technique involves hybridizing shotgun libraries of genomic DNA to target-specific sequences on a microarray. However, this method is limited by the need for expensive hardware, bioinformatic analysis, and a relatively large amount of DNA.

Despite the difficulties of implementing comprehensive genetic profiling of molecular alterations in

the clinical care of AML patients, it is clear that a more detailed genetic profiling of AML patients may be useful in improving risk stratification and possibly in providing therapeutic information and disease monitoring in the future.

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CURRICULUM VITAE

A. GENERAL INFORMATION

1. Name:	**Martin S.Tallman, MD**
2. Office Address:	Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065
Office Phone:	212-639-3842
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Home Phone:	914-576-0836
Cell Phone:	646-467-4670
5. Beeper:	5392
6. Email:	tallmanm@mskcc.org
7. Citizenship:	US
8.Optional Information:	
a. Date of Birth:	07/06/1954
b. Place of Birth:	Chicago, IL
c. Marital Status:	Married
d. Spouse's Name:	Wendy S. Tallman
e. Children's Name:	Sarah Chaya, born September 14, 1985 Miriam Leah, born December 8, 1986 Samuel Joseph, born March 12, 1990 Jacob Ezra, born May 12, 1992
f. Race/Ethnicity:	
g. Languages Spoken:	
h. Gender:	Male

B. EDUCATIONAL BACKGROUND

Degree	Institution	Dates Attended	Year Awarded
BS	University of Michigan Ann Arbor, MI	8/1972-5/1976	1976
MD	Chicago Medical School Chicago, IL	9/1976-6/1980	1980

C. PROFESSIONAL POSITIONS AND EMPLOYMENT

1. Post-doctoral training including residency/fellowship

Title	Institution name and location	Dates held
Intern Internal Medicine	Northwestern University Evanston Hospital/McGaw Medical Center Evanston, IL	1980-1981
Resident Internal Medicine	Northwestern University Evanston Hospital/McGaw Medical Center Evanston, IL	1981-1983
Chief Resident Department of Medicine	Northwestern University Evanston Hospital/McGaw Medical Center Evanston, IL	1983-1984
Fellow Hematology/Oncology	University of Washington Fred Hutchinson Cancer Research Center Seattle, WA	1984-1987

2. Academic Positions (teaching and research)

Title	Institution name and location	Dates held
Instructor	Department of Medicine Evanston Hospital Northwestern University Feinberg School of Medicine Evanston, IL	1983-1984
Acting Instructor	Division of Hematology University of Washington Seattle, WA	1987-1988
Assistant Professor	Division of Hematology/Oncology Northwestern University Feinberg School of Medicine Evanston, IL	1988-1996
Member	Robert H. Lurie Comprehensive Cancer Center of Northwestern University Evanston, IL	1988-2010
Associate Professor (tenure)	Division of Hematology/Oncology Northwestern University Feinberg School of Medicine Evanston, IL	1996-2002

Co-Director	Hematologic Malignancy Program Robert H. Lurie Comprehensive Cancer Center Northwestern University Evanston, IL	2001-2010
Professor (tenure)	Division of Hematology/Oncology Northwestern University Feinberg School of Medicine Evanston, IL	2002-2010
Associate Chief	Division of Hematology/Oncology Northwestern University Feinberg School of Medicine Evanston, IL	2006-2010
Member	Memorial Sloan-Kettering Cancer Center New York, NY	2010-present
Professor of Medicine	Weill Cornell Medical College New York, NY	2011-present

3. Hospital Positions (e.g.,attending physician)

Title	**Institution name and location**	**Dates held**
Assistant Attending Physician	Evanston Hospital Northwestern University Feinberg School of Medicine Evanston, IL	1983-1984
Attending Physician	Division of Oncology VA Medical Center Seattle, WA	1987-1988
Attending Physician	Division of Hematology/Oncology Lakeside VA Medical Center Chicago, IL	1988-2001
Adjunct Attending Physician	Division of Hematology/Oncology Northwestern Memorial Hospital Chicago, IL	1988-2010
Adjunct Attending Physician	Division of Hematology/Oncology Evanston Hospital Evanston, IL	1989-1993
Attending Physician	Memorial Hospital for Cancer and Allied Diseases, Department of Medicine New York, NY	2010-present
Chief	Memorial Hospital for Cancer and Allied Diseases, Leukemia Service Department of Medicine, New York	2010-present

D. LICENSURE, BOARD CERTIFICATION, MALPRACTICE

1. Licensure

a. **State**	**Number**	**Date of Issue**	**Date of expiration**
New York	NY257325	2010	5/31/2012
Illinois (active)	036-064414	1984	7/31/2011
Washington (inactive)	MD22399	1988	7/6/1988

2. Board Certification

Full Name of Board	Certificate #	Date (MM/DD/YY)
Internal Medicine	094968	9/14/1983
Hematology	094968	11/1/1988
Medical Oncology	094968	11/10/1987
c. DEA number:	BT1467338	
d. NPI number:	1154340792	

3. Malpractice Insurance

Do you have malpractice Insurance? Yes
Name of Provider: MSK insurance US, Inc
Premiums paid by: Memorial Sloan-Kettering Cancer Center

E. PROFESSIONAL MEMBERSHIPS

Member/officer	Name of Organization	Dates held
Member	American Society of Clinical Oncology	1987-present
Member	Illinois Medical Oncology Society	1990-present
Member	American Association for Cancer Research	1992-1998
Member	International Society of Thrombosis and Haemostasis	1992-1999
Member	Eastern Cooperative Oncology Group	1993-present
Member	American Society for Blood and Marrow Transplantation	1994-2006
Member	American Society of Hematology	1997-present
Member	American College of Physicians	1998-2000

International Society of Thrombosis and Haemostasis:

Member	DIC Subcommittee	1992-Present
Member	Haemostasis and Malignancy Subcommittee	1992-Present

American Society of Hematology:

Member	Subcommittee on Neoplasia	1998-Present
Member	International Society of Hematology: African and European Division International Scientific Committee	1999-Present
Member	Subcommittee on Publications	2000-Present
Member	International Society of Experimental Hematology	2001-Present
Member	ASH/FDA Endpoints in Hematologic Malignancies Work Group	2004-Present
Member	Nominating Committee	2006-Present

Other Memberships, Offices and Committee Assignments in Other Professional Societies:

Illinois Cancer Center, Leukemia/Lymphoma Committee, Chairman	1990-1992
Leukemia Research Foundation, Medical Advisory Board	1992-1997
Leustatin Advisory Board, Ortho Biotech, R.W. Johnson Pharmaceuticals Research Institute, Raritan, NJ	1993-Present
National Marrow Donor Program, Acute Leukemia Subcommittee	1994-Present
Clinical Affairs Committee, International Bone Marrow Transplant Registry	1995-Present
AML Collaborative Group, Member	1995-Present
Pharmacia, International Advisory Group	1995-Present
Autologous Bone Marrow Transplant Advisory Group United States General Accounting Office Department of Health and Human Services	1995-Present
Medical Advisory Board, Earl J. Goldberg Aplastic Anemia Foundation	1995-Present
Hematology Advisory Board, Chiron Therapeutics, Emerville, CA	1996-Present
Medical Advisory Board, Hairy Cell Leukemia Research Foundation	1996-Present
ABMT Clinical Advisory Group, AML Collaborative Group, Member	1996-Present
Chairman, Leukemia Research Foundation, Medical Advisory Board	1997-1999
National Comprehensive Cancer Network (NCCN), CML Panel	1997-Present
National Comprehensive Cancer Network (NCCN), MDS Panel	1997-Present
National Comprehensive Cancer Network (NCCN), AML Panel	1997-Present
Adult ALL and Hematologic Malignancy Advisory Board	1997-Present
Rhone-Poulenc Rore Advisory Board, Supergen	1997-Present
Member, Safety Board, Canadian Leukemia Study Group	1999-Present
Searle/Monsanto Advisory Board	1999-Present
Wyeth-Ayerst Pharmaceuticals AML Advisory Board	1999-Present
Program Committee, American Society of Clinical Oncology	2000-2002
Data Monitoring Committee, Canadian Leukemia Study Group	2000-Present
Co-chair, Acute Leukemia Working Committee CIBMTR	2005-Present
National Comprehensive Cancer Network (NCCN) Myeloid Growth Factor Panel	2006-Present

Eastern Cooperative Oncology Group:

Leukemia Committee, member	1989-Present
Bone Marrow Transplant Committee, member	1989-Present
Myeloma Committee, member	1989-Present
Cytogenetics Subcommittee, member	1991-Present
Leukemia Committee, Co-chairman	1993-1997
Bone Marrow Transplant Institutional Review Committee, member	1993-Present
Audit Team, member	1995-Present
Leukemia Committee, Chair	

F. HONORS AND AWARDS

Name of award	**Date awarded**
Medical Intern of the Year, Evanston Hospital, Northwestern University School Medical School	1981
Medical Resident of the Year, Northwestern University School Medical School	1983
Outstanding Teaching Attending, Northwestern Memorial Hospital	1989
John T. O'Connell Award, Chicago Medical Society 2-Chlorodeoxyadenosine (2-CdA): An Effective New Therapy for Hairy Cell Leukemia and Other Lymphoproliferative Disorders	1992
Woman's Board Compassionate Care Award, Northwestern Memorial Hospital	2002
Teaching Attending of the Year, Northwestern University Feinberg School of Medicine	2003-2004

G. INSTITUTIONAL/HOSPITAL AFFILIATION

Primary Hospital Affiliation: Memorial Hospital for Cancer and Allied Diseases
Other Hospital Affiliation: Weill Cornell Medical College

H. EMPLOYMENT STATUS

Name of Employer: Memorial Sloan-Kettering Cancer Center
Employment status: Full-time salaried attending

I. CURRENT AND PAST INSTITUTIONAL RESPONSIBILITIES AND EFFORT

1. Teaching/Mentoring	Dates
Northwestern University Medical School Department of Medicine Emergencies in Internal Medicine (oncologic emergencies)	1988-1995
Northwestern University Medical School Pathophysiology Course (hematology and oncology section)	1988-2010
Medical Resident Northwestern University, Medical School Independent Study Projects: -John Pandolfino, M.D."Hypocholesterolemia in Hairy Cell Leukemia: Marker for Proliferative Activity" -Richard Siegel, M.D. "Bone Marrow Scans After 2- Chlorodeoxyadenosine for Hairy Cell Leukemia"	1995
Moderator Problem-Based Learning Course for First Year Students Northwestern University Medical School	1997
Lecturer Scientific Basis of Medicine Course (for Sophomore Medical Students) -AML -CML	2002
Tutor, Physician Diagnosis (Sophomore Students)	2005
Mentor, Second year student Physical Diagnosis Course	2006
Attending Inpatient Service; 8weeks per year Team includes WCMC interns, residents, and students	2010-Present
Fellows Lecture; 2times per year	2010-Present

2. Clinical Care (duties)	Dates
Attending Physician In clinic 1 and 1/2 days per week	1988-2010
Outpatient Clinic Teaching; 2 half days per week	2010-Present

3. Administrative	Dates
Coordinator, Senior Student Elective in Hematology/Oncology Northwestern University Medical School, Chicago	1989-2010
Northwestern University Institutional Review Board, Chicago	1990-1998
Quality Assurance Committee Lakeside VA Medical Center, Chicago	1998-1990
Robert H. Lurie Comprehensive Cancer Center of Northwestern University:	
Co-chairman, Education Committee	1989-1993
Director, Clinical Leukemia Research Program	1990-2010
Assistant Director, Bone Marrow Transplant Program	1991-2000
Co-Director, Hematologic Malignancies Program	1996-2010

4. Research

*See section J.

Current % Effort		Does activity involve WMC students?	Does activity involve MSK Trainees or researchers?
Teaching/Mentoring	10%	Y	N
Clinical Care	40%	Y	N
Administration	20%	N	N
Research	30%	N	N
Total	100%		

EDITORIAL BOARDS

1992-present Medical Oncology and Tumor Pharmacotherapy
1995-2004 Section Editor, Leukemia
1995-1996 Associate Editor, Focus and Opinion: Oncology
1995-1998 Associate Editor, Yearbook of Oncology
1997-present Blood
1998-2000 Journal of Clinical Oncology
1998-present Leukemia Research
1998-present Communications in Clinical Cytometry
1998-present Bloodline
1999-present Evidence-Based Oncology
2000-present Annals of Hematology, Advisory Board
2000-present Associate Editor, Hematology
2001-present Blood Reviews
2001-present Bailliere's Best Practice & Research: Clinical Haematology
2002-present Associate Editor, Blood
2003-present Section Editor, The Hematology Journal
2006 Clinical Leukemia

Reviewer for:

Acta Haematologica
American Journal of Hematology
ASH Education Book (2006)
Annals of Internal Medicine
Annals of Oncology
BioDrugs
Blood
Bone Marrow Transplantation
Cancer
Cancer, Chemotherapy and Pharmacy
Cancer Research
European Journal of Haematology
Journal of Clinical Investigation
Journal of Clinical Oncology
Journal of Laboratory and Clinical Medicine
Leukemia
Leukemia and Lymphoma
Leukemia Research
New England Journal of Medicine
Proceedings of the National Academy of Science, USA
The Cancer Journal from Scientific American
Abstract submissions, American Society of Hematology Annual Meetings,
December 1994, 1995, 1998, 1999, 2000 (Coordinating Reviewer)
Abstract submissions, American Society of Clinical Oncology Annual Meetings,

New Developments in Induction and Postremission Therapy in AML

Martin S. Tallman

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Among younger patients (pts) (less than ages 55-60 years of age) with new AML an anthracycline and cytarabine results in CR in 60 to 80%. However, only approximately 40 to 45% of patients (pts) in CR are alive at 5 years. Among older pts the CR rate is 40-50% with only 10-15% alive at 5 years. Intensive consolidation including intermed- or high-dose cytarabine, is standard postremission therapy for younger pts, but is only effective for favorable- or intermed-cytogenetic risk disease and not for unfavorable-risk or older adults. Recent insights into molecular genetics have led to rapid drug discovery. The effectiveness ATRA and ATO with minimal or no chemotherapy in APL is a paradigm for targeted therapy. A randomized trial by ECOG tested daunorubicin (dauno) dose intensification in younger pts with new AML. Dauno 90 mg/m^2/day for 3 days was compared with 45 mg/m^2/day each with standard-dose cytarabine for 7 days. This led to a significantly better CR rate and survival in the 90 mg arm. The benefit was not observed in those pts with unfavorable-risk cytogenetics or *FLT3-ITD* mutations. The HOVON showed a benefit for high-dose dauno in pts up to age 65 years. These studies changed the standard of care. Three randomized studies have explored the addition of antibody directed chemotherapy with gemtuzumab ozogamicin (GO), a humanized anti-CD33 monoclonal antibody chemically linked to the toxin calicheamicin. The MRC, randomized 1,113 pts to dauno plus ara-C or dauno plus cytarabine and etoposide or FLAG-Ida, with or without GO at a dose of 3mg/m. There was a significant OS benefit for pts with favorable-risk cytogenetics. Due to toxicity and lack of sufficient efficacy in a second trial by the SWOG, S0106, the drug was removed from the market. However, the ALFA performed a randomized trial in pts ages 50-70 and showed a benefit for adding three doses of GO (total dose 9 mg/m2) to conventional induction for those with favorable-risk cytogenetics and to a lesser extent those with intermed-risk cytogenetics. Whether these studies establish GO as a new standard of care is not clear. Cladribine in younger pts and Losmutine in older pts have been added to standard induction regimens and may provide an advantage. The optimal drugs, dose, schedule and number of cycles of postremission chemotherapy are unknown. The MRC conducted a randomized trial of cytarabine 3 g/m^2 versus 1.5 g/m^2, following CR induced with 3-drug induction, and showed no benefit for the higher dose suggesting a new standard if additional studies confirm these results. Randomized trials by the HOVON and JALSG groups also suggest less cytarabine is as effective. New agents with unique mechanisms of action include CPX-351 (a liposomal formation of a fixed molar ratio of dauno and cytarabine), DOT1L inhibitor (histone H3K79 methyltransferase inhibitor) against *MLL*, *FLT3* inhibitors Sorafenib and AC220, novel purine analogs Clofarabine and Sapacitabine, elacytarabine [elaidic ester of cytarabine independent of the hENT1 (human equilibrative nucleoside transporter 1) transporter which facilitates transfer of cytarabine across the cell membrane] and Volasertib, a Polo-like kinase inhibitor. The heterogeneity of AML mandates close collaboration among clinical investigators and lab-based scientists to test new therapies directed at specific molecular targets.

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New Directions in Transplantation in AML

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Abstract

The role of allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia has experienced significant progress over the past decade with better understanding of leukemic molecular pathogenesis. Equally, improved supportive care, more accurate HLA-typing technology, widening the alternative donor options and reduced-intensity conditioning regimes have extended its applicability. Recently identified recurrent somatic mutations have refined prognostication thereby allowing a more informed decision-making. Current efforts have as a result focused on a more patient-specific integrated-risk profile approach tailored to the individual AML patient to optimize outcomes.

Keywords: Acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, genetic profiling, alternative donor, minimal residual disease, chimerism, donor lymphocyte infusion

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) has long been established as an integral part of treatment of acute myeloid leukemia (AML) given its curative potential. In fact AML is at present the most common indication for alloHSCT. An activity survey from the European Group for Blood and Marrow Transplantation (EBMT) indicated that AML accounted for a third of adult alloHSCT indications [1]. A similar trend was reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) with a steady increase in the number of AML alloHSCT in the past decade [2, 3] (figure 1). The curative potential of alloHSCT in AML is attributed not only to the conditioning chemotherapy +/- radiotherapy but also to the graft-versus-leukemia (GVL) effect [4]. GVL can promote durable remission and hinges in part on the ability of the donor-derived T lymphocytes to direct allo-reactive responses against residual or re-emerging host leukemic cells.

Better understanding of AML biology has lead to improved and more refined risk stratification for a more informed decision-making. In this review we evaluate the role of alloHSCT in AML patients in light of recent developments in the increasingly adopted integrated-risk adapted therapeutic approach.

AlloHSCT in first complete remission (CR1)

The current recommendation for alloHSCT in AML patients in CR1 is in those whose risk of relapse with standard chemotherapy outweighs the transplant-related mortality (TRM) and relapse with transplantation. Although more than 70% of AML patients< 60 years achieve complete remission (CR) with induction chemotherapy, the majority will subsequently relapse [5]. The role of alloHSCT in such patients in the context of an available HLA-matched sibling donor has been evaluated by a number of studies, the majority of which were non-randomized, non-controlled and did not evaluate outcomes on the basis of cytogenetic or molecular risk factors. In general, patients were treated on the basis of HLA matched sibling donor availability. A systematic review and meta-analysis of 24 prospective 'biologic' assignment trials based on donor availability in which 3638 patients in CR1 analyzed by cytogenetic risk revealed that alloHSCT resulted in significantly higher relapse-free survival (RFS) and overall survival (OS) rates for intermediate- and poor-risk AML but not for good-risk AML when compared with chemotherapy alone[6].

The majority of AML patients have been traditionally classified as intermediate risk majority on the

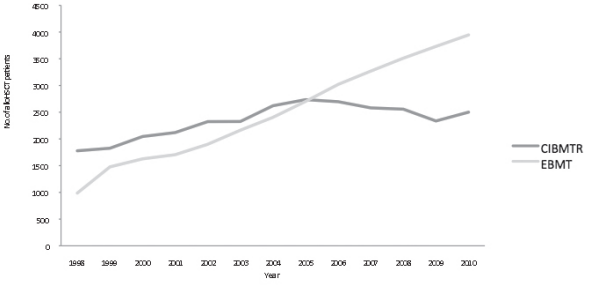

Figure 1. Adult AML alloHSCT activity: CIBMTR and EBMT registered cases data

basis of normal cytogenetics (CN-AML). Many of these patients have a poor outcome with standard chemotherapy. More recently identified molecular alterations have refined patient risk stratification of CN-AML; the most common being the FLT3-ITD mutation. An analysis of 4 prospective clinical trials conducted by Schlenk et al demonstrated that presence of FLT3-ITD mutation in combination with NPM1 or CEBPA mutations predicts outcome in CN-AML and identified those who will benefit from alloHSCT[7]. An intention to treat (ITT) analysis based on donor availability superior RFS was observed in those with a matched sibling donor amongst patients with CN-AML with genotypes other than mutated NPM1 without FLT3-ITD. Recent evidence suggests that the burden of mutated alleles in AML cells expressed as an allelic ratio also has prognostic implications. In a study by Ehninger et al of 257 FLT3-ITD mutated AML patients in CR1 a ratio of FLT3-ITD mutation to wild-type FLT3 allele of ≥ 0.8 at diagnosis (which defined a high-ratio) predicted superior disease free survival (DFS) and OS with alloHSCT when compared to either chemotherapy or autologous stem cell transplantation as consolidation [8]. The 3-year DFS in the low- and high-ratio groups who received alloHSCT was 58% and 50% versus 36% and 10% in the chemotherapy group, respectively (p<0.001). This supports the role of alloHSCT in FLT3-ITD mutated AML patients, specifically those with high-allelic ratio of FLT3-ITD mutation. A recent retrospective analysis from the EBMT-Acute Leukemia Working Party (EBMT-ALWP) of 206 CN-AML patients in CR1 showed that the post alloHSCT relapse incidence was higher (30% versus 16%; p=0.006) and LFS lower (58% versus 71%; p=0.04) in FLT3-ITD positive versus FLT3-ITD negative patients [9]. High-throughput sequencing has identified several other novel recurrent somatic mutations which appear to have prognostic relevance particularly when integrated genetic profiling was used for risk stratification of intermediate-risk AML [10]. DNMT3A, TET2 and MLL mutations were shown to be associated with adverse prognoses; in particular DNMT3A mutations which were independent of age and/or co-occurring FLT3-ITD mutation or NPM1 mutation [10, 11]. IDH mutations in conjunction with the aforementioned somatic mutations were found to be associated with poor prognosis. Despite this these results need further validation by other larger studies before using them for clinical decision-making as the data on the IDH1 and IDH2 prognostic values are controversial [12-14].

Patients with favorable risk cytogenetics, namely core binding factor (CBF)-AML or acute promyelocytic leukemia, who achieve CR1 are at a relatively low risk of relapse [15-17], have a DFS with chemotherapy alone at 60% [6, 18]and generally do not benefit from alloHSCT[6]. However, only 50% of patients with CBF-AML are alive at 5 years and 30% relapse [19]. Mutational studies have identified 2 common KIT mutations (mKIT) (mKIT exon 17 and mKIT exon 8) which appear to negate the otherwise favorable effect of CBF-AML though these data were not conclusive because of limited patient numbers and differences in treatment [19-22]. In a Cancer and Leukemia Group B (CALGB) study the 5-year relapse risk in patients with mKIT was 56% for those with inv(16) and 70% in those with t(8;21) versus 29% and 36% in those with wild type KIT, respectively [23]. Such relapse risk is almost similar to AML patients with unfavorable cytogenetics and therefore merits consideration of alloHSCT though to-date there are no randomized trial data to support this treatment recommendation. A recent prospective study by a French group showed minimal residual disease (MRD) response rather than KIT or FLT3 gene mutations identified CBF-AML patients at higher risk of relapse [24].

Is there a role for alternative donor alloHSCT in AML patients in CR1?

With only a minority of patients having a matched sibling donor, there is an increasing need for expanding donor options though at the expense of potentially higher non-relapse mortality (NRM) particularly with increasing number of HLA disparities. This is despite improved outcomes following the introduction of high-resolution HLA typing and hence more accurate donor-recipient matching [25-27].

Therefore, when making a decision to transplant using a graft from an alternative donor there is a need to assess whether the use of that donor will result in a higher NRM. In high-risk AML patients in CR1 there are several retrospective and only limited prospective studies [18, 28] that compared matched related and unrelated donor alloHSCT. For example, a prospective evaluation conducted by the German-Austrian AML Study Group showed no difference in outcomes including NRM in matched related and unrelated donor alloHSCT recipients with high-risk AML on multivariate analysis [28]. Researchers from the CIBMTR have demonstrated comparable leukemia free survival (LFS) and OS following HLA well-matched unrelated or matched sibling donor alloHSCT in AML patients in CR1 with unfavorable cytogenetics but significantly inferior survival for HLA mismatched unrelated donor recipients [29]. For intermediate-risk AML patients in CR1 data comparing outcomes of matched related and unrelated donor alloHSCT is scarce. Walter et al reported similar outcomes for the intermediate-risk subgroup

though sample size was modest [30]. A further retrospective study of 431 patients showed comparable 4-year OS and mortality rates in matched related and unrelated donor alloHSCT recipients [31]. For FLT-3/ITD mutated patients Brunet et al reported in a retrospective study similar LFS, relapse incidence and NRM with matched sibling and unrelated donor alloHSCT[9].

For patients with high-risk AML without a well matched related or unrelated donor, options include standard chemotherapy or use of an alternative donor source for transplant e.g. umbilical cord blood (UCB), haploidentical or mismatched-related donors. Despite the low cell dose of UCB the less stringent HLA-matching, rapid accessibility and lower acute and chronic graft-versus-host disease (GvHD) incidence makes it a more appealing choice. A comparative EBMT study of 682 acute leukemic adult patients showed similar outcomes in unrelated bone marrow and UCB recipients [32]. This conflicted with the data from CIBMTR which showed lower transplant-related mortality (TRM), treatment failure and overall mortality in HLA-matched bone marrow recipients but similar outcomes in mismatched-unrelated donor bone marrow and mismatched UCB recipients [33]. Eapen et al reported comparable LFS after UCB transplantation and 8/8 and 7/8 allele-matched peripheral blood or bone marrow alloHSCT recipients with acute leukemia though with higher TRM [34]. Interpretation of such studies is confounded by the inclusion all acute leukemic patients in the analysis. In a disease-specific comparative analysis conducted by Atsuta et al of AML patients in CR1 who underwent UCB and HLA-matched unrelated donor bone marrow alloHSCT inferior survival associated with higher TRM was observed in the UCB recipients [35]. A strategy to improve outcomes of UCB alloHSCT is to optimize unit selection, namely match and dose. Comparable LFS was observed after double UCB (dUCB) transplantation and matched related and unrelated donor transplantation but higher NRM in the dUCB recipients [36]. Data on use of haploidentical alloHSCT for high-risk AML patients in CR1 is limited. A survey by the EBMT reported outcomes of fully haploidentical alloHSCT in 266 adult high-risk acute leukemia patients in remission; 86 of these had AML with 25 being in CR1 [37]. The 2-year cumulative incidence of TRM, relapse and probability of LFS at 36%, 16% and 48%, respectively for those in CR1 and was inferior if in CR2 or advanced stage at transplant with much of the TRM attributed to infections. Researchers from the Thomas Jefferson Kimmel Cancer Center developed a 2-step approach to myeloablative haploidentical alloHSCT centered on optimizing T-cell dose in the context of cyclophosphamide tolerization to achieve prompt engraftment, little significant GvHD and prompt immunologic recovery [38]. The 3-year probability of OS for the whole cohort (which included 16 AML patients with 5 in CR1 at transplant) was 48% and 75% for those in remission at transplant. Cumulative incidences of grade II-IV GvHD, NRM and relapse-related mortality were 7.4%, 22.2% and 29.6%, respectively. Whilst encouraging, such approach will require further exploration in larger trials before extending its use to better-risk patients. Recently Brunstein et al conducted 2 parallel phase 2 trials comparing dUCB alloHSCT with haploidentical-alloHSCT using reduced-intensity conditioning (RIC) regimens in patients with leukemia or lymphoma and no suitable donors. Comparable LFS and OS were observed in the 2 trials [39]. A further viable donor option includes HLA-mismatched related donors. In a retrospective registry study single antigen mismatch was associated with increased mortality and lower 1-year OS (43% versus 52%) when compared to 8/8 HLA-matched donor alloHSCT in myeloablative setting [26]. In a comparative analysis by CIBMTR of mismatched related and matched unrelated donor alloHSCT no statistically significant difference was observed in OS, DFS, TRM or relapse [40]. In a further analysis focusing on mismatched unrelated donor alloHSCT no survival difference was noted between 7/8 and 8/8 HLA-matched donor recipients [41]. Kanda et al however observed higher overall mortality rates in HLA-1-antigen mismatched related donor recipients when compared with 8/8 HLA-matched unrelated donor recipients which was of statistical significance only in standard-risk and not in high-risk acute leukemia patients [42].

Current data is insufficient to guide decisions on using UCB, haploidentical or HLA-mismatched related donor alloHSCT. In the absence of a suitable HLA matched donor, a search for an alternative donor such as cord blood or haploidentical family member should be considered if high risk features of AML are identified either at diagnosis or following induction chemotherapy.

AlloHSCT beyond CR1

Treatment of AML following relapse is associated with relatively poor response rates [43] and outcomes following alloHSCT are inferior due to higher TRM and relapse rates. There are no prospective studies comparing outcome of alloHSCT in AML patients in second remission (CR2) with conventional therapy. Much of the available evidence is based on retrospective analysis and its interpretation is limited by the heterogeneity and selection bias of cohorts included. Breems et al devised a prognostic index

estimating the outcome of AML patients in first relapse from data on 667 AML (non-M3) [44]. This index was based on 4 clinically relevant parameters: length of remission after CR1, cytogenetics at diagnosis, age at relapse and prior stem cell transplant. Using this stratification system 3 risk groups were defined with the 5-year OS; favorable- (46%), intermediate- (18%) and poor-risk groups (4%). Only 249 (37%) patients achieved CR2 with only 109 (16%) proceeded to alloHSCT. For patients who achieved CR2 comparison of chemotherapy versus alloHSCT showed superior 5-year survival in those undergoing alloHSCT across all 3 risk groups. This was supported by 2 further studies that confirmed the beneficial effect of alloHSCT specifically in patients achieving CR2 [45, 46] were survival was significantly better (3-year survival in those in CR2 was 59% versus 21% for those not in remission) [45].

Refractory AML patients generally have a dismal prognosis and the utility of alloHSCT remains controversial partly as the current published data is confounded by small sample size and heterogeneity of cohorts included and publication bias. A CIBMTR study evaluated the outcome of 1673 AML patients not in remission at the time of myeloablativealloHSCT[47]. Three year survival was 19%. Five adverse pretransplantation variables significantly influenced survival; CR1 duration <6 months, circulating blasts, donor other than an HLA-identical sibling, Karnofsky performance score <90 and poor risk cytogenetics. Patients with none of these variables had a 3-year OS of 42% versus only 6% in those with ≥3. This delineates subgroups were alloHSCT may be a reasonable option.

The feasibility of a sequential chemoradiotherapy regimen ± donor lymphocyte infusions (DLI) in refractory AML was explored by Schmid et al in 103 refractory AML patients where 91% achieved a CR with an encouraging 4-year LFS of 30% [48].

AlloHSCT for the 'older' AML patient and patients with comorbidities

Management of the 'older' patients with AML remains a challenge considering that conventional chemotherapy alone is not curative in the majority of those ≥ 60 years [49]. A report from one of the most comprehensive acute leukemia registries indicated dramatically worse survival with increasing age owing to frequent co-morbidities, poorer performance status and different spectrum of genetic abnormalities but demonstrated lower early death rates with intensive chemotherapy that palliation [50]. In older patients, a high TRM limits the applicability of myeloablativealloHSCT[51]. RIC alloHSCT has extended the utility of alloHSCT to the 'older' and the 'less fit' patient given its lower TRM. Two large retrospective studies of older patients with AML showed improved outcomes with RIC alloHSCT compared to conventional therapy [52, 53]. EBMT reported in 2 different analyses reduced adjusted NRM but higher cumulative incidence of relapse with matched-related and unrelated donor RIC versus myeloablative alloHSCT resulting in comparable LFS to myeloablative matched-related and unrelated donor alloHSCT recipients [54, 55]. However a recent retrospective analysis by the CIBMTR reported no difference between RIC and myeloablative regimens [56]. A further study by the CIBMTR reported that age did not impact on the 2-year survival in 545 AML patients in CR1 undergoing RIC alloHSCT[57]. Only 1 prospective open-label phase 3 randomized study is reported to-date which compared RIC and myeloablative alloHSCT in 195 intermediate- and high-risk AML patients in CR1. RIC alloHSCT resulted in similar NRM without affecting survival outcomes and was associated with lower toxicity when compared to myeloablative conditioning [58].

Has MRD monitoring changed the concept AML therapy of "one size fits all'?

The association between MRD and disease relapse is well described in CML and acute lymphoblastic leukemia [59-62]. In AML this is less clear-cut partly due to its genetic heterogeneity. Over 85% of AML patients with normal cytogenetics harbor genetic alterations which have lately acquired great interest as target markers for MRD monitoring. The most frequently identified is NPM1 mutation ($NPM1^{mut}$) and which infers significantly higher CR rates and longer DFS [63, 64]provided it does not coexist with prognostically unfavorable mutations. Schnittger et al reported the prognostic value of $NPM1^{mut}$ level where an increase of at least 1 log or lack of reduction by < 3 log ranges predicted relapse[65]. A study from the German-Austrian AML Study Group demonstrated that $NPM1^{mut}$ monitoring at relevant time points during and after chemotherapy can reliably identify AML patients at high risk of relapse [66]. Patients with detectable $NPM1^{mut}$ transcript level after 2 courses of induction therapy or after completion of therapy had much higher cumulative incidence of relapse (53% versus 6.5%; p<0.001 and 66.5% versus 15.7% in those who were negative; p<0.001, respectively) and significantly lower OS (51% versus 90%; p=0.001). Bacher et al demonstrated in a retrospective study a correlation between persistence of NPM1 mutation and relapse post alloHSCT in 13 patients [67]. However the extremely short time interval between rising $NPM1^{mut}$ transcript level and disease recurrence (mean 24

days; range, 12-38 days) limits its clinical utility as it doesn't allow sufficient time for intervention. Flt3-ITD mutation is well recognized for its association with poor clinical outcome in patients receiving chemotherapy alone and therefore such patients should be considered for alloHSCT in CR1 [68, 69]. Its use as a molecular marker for MRD monitoring is dubious given its genomic instability [70] resulting in its loss in 20% of patients after relapse and technically for its requirement to have patient-specific primer for quantitative PCR monitoring [71]. Therefore it requires its combination with other markers. Scholl et al showed an association between FLT3-ITD and FLT3-TKD positivity by PCR and leukemic relapse but in only 4 patients [72]. Investigators from the UK Medical Research Council (MRC) AML-15 trial reported their prospective data on MRD monitoring in 278 CBF-AML patients [73]. At remission MRD monitoring by RQ-PCR at specific time points of RUNX1-RUNX1T1 transcripts in the marrow of t(8;21) patients and CBFB-MYH11 copy number in peripheral blood in inv(16) patients predicted reliably relapse risk on multivariate analysis. A recent prospective study by Jourdan et al of 198 CBF-AML patients reported that a < 3-log reduction in MRD after first consolidation was associated with higher risk of relapse as did high white cell count and KIT and/or FLT3-ITD/TKD mutations [24]. However MRD response was the only prognostic factor to significantly impact relapse rate on multivariate analysis. The cumulative incidence of relapse and RFS were 22% versus 54% and 73% versus 44% for those achieving a 3-log MRD reduction versus those who didn't, respectively. Buccisano et al demonstrated that an adjusted risk stratification based on pretreatment molecular markers/cytogenetics and post treatment MRD status distinguished 2 categories of patients: low-risk (which included favorable- (F-RK) and intermediate-risk (I-RK) karyotype) which were MRD negative after consolidation and high-risk (which included unfavorable-risk karyotpe (U-RK), FLT3-ITD mutated cases, F-RK and I-RK) which were MRD positive after consolidation [74]. The low-risk group had a significantly longer OS (73% versus 17%), RFS (58% versus 22%) and cumulative incidence of relapse (17% versus 77%); p<0.001.

Another molecular marker frequently expressed in AML patients is the Wilm's tumor 1 (WT1) gene. A study conducted by Candoni et al of 25 AML patients who underwent RIC alloHSCT WT1 gene expression was quantified sequentially pre- and at precise time points post-alloHSCT[75]. 18 patients were in complete cytogenetic remission (CcR) at transplant and had significantly lower WT1 gene expression levels compared to those with refractory disease. Of these 18, 17 maintained CcR and continued to have low level WT1 expression post transplant. 3 of the refractory patients achieved CcR post transplant with documented sustained decrease in WT1 levels. All patients who relapsed post transplant had high WT1 copy numbers prior to hematological relapse with 50% of them an increase in WT1 expression preceded a fall in molecular chimerism.

Walter et al reported the utility of multiparametric flow cytometry for MRD monitoring pre-myeloablative alloHSCT in 99 AML patients in CR1 [76]. 2-year estimate of OS was 30.2% and 76.6% for MRD-positive and MRD-negative patients and the 2-year estimate of relapse was 64.9% and 17.6%, respectively. After adjusting to other risk factors MRD-positive alloHSCT recipients had higher overall mortality (hazard ratio (HR) 4.05; 95% CI, 1.9-8.62) and relapse (HR 8.49; 95% CI, 3.67-19.65) compared to MRD-negative patients. In post transplant setting due to loss of the so-called 'leukemia-associated immunophenotypes' in about 25% of patients MRD monitoring using this technique will need to be interpreted with caution [77].

Based on current evidence, MRD monitoring after induction chemotherapy has further refined risk stratification such that it has allowed a more 'personalized' therapeutic approach and is being considered part of the AML treatment algorithm. In post transplant setting despite evidence that early MRD detection is associated with hematological relapse it is still unclear whether this can be utilized for clinical decision-making given the retrospective nature and small number of patients. It remains to be seen whether prospective studies can provide more informative data on the association of MRD kinetics and relapse post transplant.

Is there evidence of a role for post alloHSCT chimerism monitoring in AML?

Persistence or reappearance of recipient hematopoiesis termed as mixed chimerism noted in most patients following reduced intensity conditioned (RIC) alloHSCT may signal a risk of disease relapse. Whilst such risk is well established in CML patients the utility of chimerism in AML in predicting relapse risk is not as definitive. In a retrospective single center study by Mohty et al patients with full donor CD3+ T-cell chimerism at day 30 following fludarabine/busulfan/ATG or fludarabine/low-dose TBI conditioned alloHSCT had higher incidence of grade II-IV acute GvHD (61% versus 35%; p=0.01) [78]. Patients with mixed chimerism at day 90 had a higher risk of relapse (40% versus 0%; p=0.002) which resulted in poorer progression

free survival (PFS) (p=0.006). An earlier prospective study by Valcàrcel et al where 95% of patients who received fludarabine/ melphalan or busulfan conditioning achieved a state of full donor chimerism within the first 6 months post transplant and this did not influence the incidence of disease progression or acute GvHD[79]. Lange et al investigated the predictive value of marrow unsorted and CD34+ sorted donor chimerism in 89 patients who received 2Gy TBI +/- fludarabine conditioned alloHSCT[80]. Unsorted donor chimerism values did not predict accurately hematological relapse. However a decrease of >5% in CD34+ donor chimerism and an absolute level of ≤90% within 28 days post alloHSCT provided sensitive (sensitivity of 71% and 62%, respectively) and specific predictions of relapse. But it was the kinetics of CD34+ donor chimerism reduction rather than the absolute level that strongly predicted impending relapse, a finding that was unaltered following the exclusion of CD34- AML patients. When coupled with high WT1 transcript level in peripheral blood (defined as a cut-off of 10-fold > the highest level of WT1 expression in healthy volunteers within 28 days post transplant) 100% of patients with relapse were identified with a specificity of 84%. Conversely when both parameters were below the cut-offs (i.e. <5% decrease in CD34+ donor chimerism and WT1 $<24/10^4$ ABL1 transcripts) relapse within 28 days was excluded almost entirely (specificity 98%, sensitivity 57%). A recently published retrospective nested case control study by Rosenow et al showed that patients with stable donor cell chimerism had higher estimated 3-year RFS than those with incomplete CD34+ lineage specific donor cell chimerism (74% (95% CI 64-83%) versus 40% (95% CI 24-58%), respectively; p<0.05) and higher OS (79% (95% CI, 70-88%) versus 52% (95% CI, 35-69%), respectively; p<0.05) despite immune intervention in the latter group (i.e. rapid tapering of immunosuppressive treatment and/or DLI) [81]. Limitations of this study were its retrospective nature and lack of sufficient controls.

Despite the conflicting evidence of the role of chimerism analysis post alloHSCT, kinetics rather single time-point analysis of donor chimerism is likely to be a reasonable approach. In particular recent data show promising results on the utility of CD34+ lineage-specific donor chimerism to predict impending relapse though its sensitivity and specificity appears to improve when coupled with other disease-specific markers. Overall where a patient appears to show progressive loss of donor chimerism intervention either by immunosuppression tapering and/or the institution of DLI to promote conversion to full donor chimerism and possibly reduce risk of relapse ought to be considered.

Does DLI post alloHSCT for AML work?

There is clear evidence of a GvL effect in AML which is primarily driven by donor-derived lymphocytes that provide a better chance of long-term survival by reducing post transplant relapse. This has led to the notion of using DLI in 3 situations; treatment of hematological relapse, prophylactic in patients at high risk of post alloHSCT relapse and to promote full donor chimerism. Despite its established role in CML patients [82] the efficacy of DLI in AML particularly in the setting of frank hematological relapse is limited. OS was only 10-15% as remissions were less likely and not durable [83-86]. In a retrospective analysis from the EBMT Working Party of 399 AML patients in first hematological relapse post alloHSCT the estimated 2-year OS was 21% (± 3%) for patients receiving DLI (n=171) and 9% (± 2%) for those who didn't (n=228) [85]. Whilst this substantiates the evidence for a GvL effect induced by DLI the authors acknowledge that such clinical benefit is limited to selected patients; namely those in remission at the time of DLI or with a favorable karyotype where the 2-year survival was 56% and 15% if given in aplasia or with active disease [85]. In 2 independent prospective studies conducted by Levine et al [86] and Choi et al [87] an attempt at reducing tumor burden with chemotherapy followed by G-CSF-primed DLI for treatment of post alloHSCT relapse was evaluated. Remission was achievable and the overall survival was improved. In the former study the CR a 2-year OS rates were 42% and 19%, respectively. In the latter study the CR and 2-year OS was slightly superior at 63% and 31%, respectively with the 1-year OS of 55% in those with post alloHSCT remission of ≥ 6months versus 0% in those with remission < 6months (p=0.015) making post alloHSCT remission duration the only significant prognostic factor. Notably the incidence of overall and grades III-IV acute GvHD were high; 56% and 28% in the latter group [87] and 93% and 62% in the former [86]. Despite the prospective nature of both studies none were randomized. Yan et al adopted a risk stratification-directed DLI intervention based on MRD post alloHSCT in standard-risk acute leukemia patients [89]. In this prospective study 105 patients were MRD-positive and received either low dose IL-2 or modified (G-CSF-mobilized) DLI with or without low dose IL-2 based on donor availability. Patients who received DLI had significantly less 3-year cumulative risk of relapse (27.8% versus 64.4%; p=0.001) and better DFS (p=0.002) compared to those who received low dose IL-2. Despite the prospective nature of the study the lack of randomization confounds the outcome.

In summary with GvHD being the main complication of DLI the incidence and severity of which

is determined by the dose, donor type and timing post alloHSCT the benefit/risk ratio will need to be taken into account.

Relapse post alloHSCT

Relapse post alloHSCT is associated with extremely poor prognosis [90]. Treatment options vary from palliation to a second alloHSCT. Current data indicate limited efficacy of second alloHSCT[91-94]. Duration of remission after first alloHSCT appears to be the most relevant prognostic factor [93, 94]. The role of DLI has already been discussed both in the context of frank hematological and molecular relapse. Azacitidine, a DNA methylating agent, has been used with success in a small number of patients to reduce disease bulk before DLI/second alloHSCT[95]. More recently azacitidine was evaluated for treatment of imminent relapse determined by CD34+ donor chimerism analysis following alloHSCT[96]. 20 of a total 59 patients prospectively screened experienced a decrease in CD34+ donor chimerism to <80% whilst remaining in hematologic remission. These received 4 cycles of azacitidine. 16 patients responded either by stabilization or an increase in CD34+ donor chimerism. Hematologic relapse occurred in 13 patients but delayed by a median 231 days after the initial decrease in CD34+ donor chimerism.

Conclusion

The role of alloHSCT in AML patients will continue to grow with current more refined risk stratifications, expansion of donor options and improved supportive care. An integrated risk-adapted approach tailored to an individual patient is becoming the preferred strategy and should be prospectively evaluated.

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Multiple Myeloma

"It is my distinct pleasure to chair the **Multiple Myeloma : Provocative Diagnostics and Therapies** session at the 4th International Congress on Leukemia, Lymphoma and Myeloma. While tremendous advances in curative therapies have been achieved, significant work remains to ensure that all patients have the opportunity for the most beneficial outcomes. I look forward to presentations by our esteemed panel of experts and lively discussions focused on provocative diagnostics and therapies."

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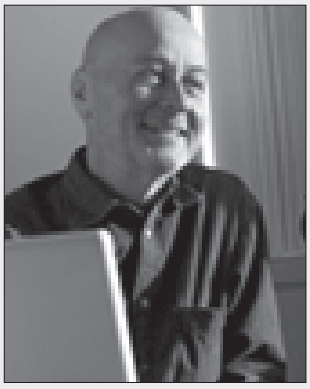

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Cell Kinetics Society - President - 1/85 to 1/86

International Myeloma Foundation - Member, Board of Directors - 7/1/92 to present

University of Arkansas for Medical Sciences
Research Advisory Committee 1993-1994

Multiple Myeloma Research Foundation (MMRF)
Scientific Advisory Board Member – 9/20/98 to present

UAMS Executive Committee Officer – 2004

Chair for the SWOG Myeloma Committee - 6/1/89 – Present

Serving as a member of the External Advisory Board for The University of Texas M.D. Anderson Cancer Center Multiple Myeloma SPORE

EDITORIAL BOARD:
Annals of Hematology
Blood
Clinical and Experimental Medicine
Clinical Cancer Research
Clinical Lymphoma & Myeloma
Current Cancer Therapy Reviews
Clinical Myeloma
International Journal of Oncology
Oncologie
The Oncologist
Journal of Clinical Oncology

HONORS AND AWARDS:
American Cancer Society Fellowship Award - 1976
Fellow, American College of Physicians - 1991
The Best Doctors in America - 1994
Distinguished Faculty Scholar Award – UAMS College of Medicine – 1995
Distinguished Faculty Award – UAMS College of Medicine - 1997
The Best Doctors in America – 1998
Distinguished Alumnus Award – UT M.D. Anderson Cancer Center – 1998
Jan Waldenström Award for Myeloma Research – 1999
American Society of Neuroradiology Award for Excellence (Scientific Exhibit) – 2002
Celgene Career Achievement Award in Hematolgy Research – 2002
The 2003 Francesca M. Thompson Outstanding Service Award – International Myeloma Foundation
The Robert A. Kyle Lifetime Achievement Award – 2004
Castle Connolly Medical Ltd., National Physician Award of the Year - 2006

SOCIETY MEMBERSHIPS:
American Association for Cancer Research
American Association for the Advancement of Science
Fellow, American College of Physicians
American Medical Association
American Society for Clinical Investigation
American Society of Clinical Oncology
American Society of Hematology
Association of American Physicians
Association of Subspecialty Professors
German Society of Hematology
International Society of Hematology
The American Society for Bone and Mineral Research

BIBLIOGRAPHY:
Peer reviewed publications: more than 500
Abstracts: more than 600
Book chapters: 75
Attended as *invited speaker*: more than 250

Provocative Diagnostics and Therapies for Multiple Myeloma

Genomics and Imaging

Bart Barlogie and John Crowley

Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
Cancer Research and Biostatistics, Seattle, Washington, USA

Clinical outcomes of patients with multiple myeloma (MM) have been advanced greatly over the past decade. Using our Total Therapy (TT) programs, aimed at maximizing MM cell kill also of high-risk tumor cell subpopulations from the outset and thus preventing relapse, data will be presented as they relate to stat-of-the-art genomics and imaging techniques. Special focus will be on the roles of immune-modulatory agents, thalidomide and lenalidomide, and proteasome inhibitor, bortezomib, employed successively in TT2 (-/+ thalidomide) and TT3 incorporating bortezomib and thalidomide upfront with VTD maintenance in TT3a and VRD maintenance in TT3b. Results will consider clinical outcomes in the context of gene expression profiling (GEP)-defined molecular subgroups and 70- and 80- as well as more recently defined 5- and 2-probe risk models. Data will be provided on the "clonal tiding" recognized by serial GEP examinations during protocol therapy until relapse. Imaging techniques included MRI and PET scanning at baseline and at defined steps during protocol therapies until relapse. In addition to clarifying genomics/imaging relationships, we will provide evidence for the powerful information gleaned from reduction in imaging-defined focal lesions early and later during therapies. These observations led to the conduct of TT4 for GEP-defined low-risk MM and TT5 for high risk MM, early results of which will be presented.

The audience will be informed of the major challenges facing MM therapies today: Identifying more effective treatments for GEP high-risk MM, especially recognizing that low-risk MM failures eventually end up with high-risk signature; Further individualization of treatment based on early follow-up data such as day-7 PET data, minimal residual disease (MRD) detection during pre-maintenance phases, GEP analysis of bone marrow biopsies in CR in context of normal donor data to determine whether "normalization" of bone marrow micro-environment can serve as an early cure surrogate and thus a clinical trial endpoint; Predicting t-MDS as an increasing sequel of MM therapy via SNP and CD34 GEP.

CURRICULUM VITAE

Name: Irene M. Ghobrial
Office Address: Dana-Farber Cancer Institute
4 Blackfan Circle, HIM building
Boston, MA 02115
Home Address: 1 Chatham Circle
Wellesley, MA 02481
Work Phone: 617-632-4198
Work Email: Irene_ghobrial@dfci.harvard.edu
Work FAX: 617-582-8608
Place of Birth: Egypt

Education

1995	MD	Medicine	Cairo University, Cairo, Egypt

Postdoctoral Training

Jan1996-Feb 1997	Internship	Internal Medicine	Cairo University Hospitals, Cairo, Egypt
March 1997	Externship	Internal Medicine	The Wellesley Hospital, University of Toronto, Toronto, Canada
April 1997-May 1998	Residency	Pediatrics	Cairo University Hospitals
Jun1998-Jun 2001	Residency	Internal Medicine	Wayne State University/ Sinai-Grace Hospital, Detroit, MI
Jul 2001-Jun 2004	Fellowship	Hematology/Oncology	Mayo Clinic, Rochester, MN

Faculty Academic Appointments

2002-2004	Instructor	Medicine and Oncology	Mayo Medical School, Rochester, MN
2004- 2005	Assistant Professor	Medicine	University of Pittsburgh, Pittsburgh, PA
2005- 2008	Instructor	Medicine	Harvard Medical School, Boston, MA
2008-2011	Assistant Professor		Medicine Harvard Medical School
2011-	Associate Professor	Medicine Harvard Medical School Boston, MA	

Appointments at Hospitals/Affiliated Institutions

Aug 2004-Sept 2005	Staff Physician	Hematology and Oncology	University of Pittsburgh Hospitals
October 2005 -	Active Staff	Medical Oncology	Dana-Farber Cancer Institute, Boston, MA
October 2005-	Associate Physician	Medical Oncology	Brigham and Women's Hospital, Boston, MA

Committee Service

Local

2002-2003	Hematology Education Board	MayoClinic, Rochester, MN Member
2003-2004	Hematology Research Board	Mayo Clinic Member
2004-2005	IRB Board	University of Pittsburgh Member
2004-2005	Data Safety Management Committee (DSMC)	University of Pittsburgh Member
2006-2010	Data Safety Monitoring Board	Dana Farber Cancer Institute Member
2010-	Laboratory Safety committee	Dana Farber Cancer Institute Member

National and International

2009	PhD dissertation review committee,	Trondheim, Norway member
2010- present	ASH development committee	Washington DC

Professional Societies

2002- present	Member American Society of Clinical Oncology (ASCO)
2003-2004	Member Iowa/Mayo Clinic Lymphoma SPORE
2004- present	Member American Association of Cancer Research (AACR)
2005-2006	Member Eastern Cooperative Oncology Group (ECOG)
2005- present	Member American Society of Hematology (ASH)
2007-present	Member Cancer and Leukemia Group B (CALGB)
2009-present	Member International Myeloma Society (IMS)

None

Report of Clinical Activities and Innovations

Current Licensure and Certification

1998 Michigan Medical License

2001 American Board of Internal Medicine Certificate
2001 Minnesota Medical License
2004 American Board of Internal Medicine, Hematology Certificate
2004 American Board of Internal Medicine, Oncology Certificate
2004 Pennsylvania Medical License
2005 Massachusetts Medical License

Practice Activities

Ambulatory Practice	Outpatient clinic Hematology/Oncology, Dana-Farber Cancer Institute	2 days per week
Inpatient Attending	Hospital Practice Hematology/Oncology, Brigham and Women's Hospital	4 weeks per year

Clinical Innovations:

- My clinical research focuses on designing innovative phase I and phase II investigator-initiated
- clinical trials that are translated from work that we perform in my laboratory.
- My studies are in plasma cell dyscrasias, in Multiple Myeloma and Waldenstrom
- Macroglobulinemia.
- We specifically focus on agents that regulate cell trafficking, specifically agents that inhibit
- adhesion of tumor cells to the bone marrow microenvironment.
- We specifically focused on the PI3K/Akt/mTOR pathway and CXCR4 signaling.
- Specific examples include the development of novel agents that target CXCR4 (plerixafor and
- BMS-936564), PI3K and mTOR inhibitors (RAD001 and CCI779) and novel targets of
- hypoxia (TH-302).
- Our data led to the exciting overall response of single agent RAD001 in patients with relapsed
- WM with over 70% of patients responding. This trial is currently being evaluated for possible
- FDA approval of RAD001 in Waldenstrom Macroglobulinemia.
- We have initiated multiple phase I/II clinical trials using the CXCR4 inhibitor plerixafor or BMS-936564 as chemosensitization modality in MM. This work is funded by NIHR01 grants

Narrative Report

My research focuses on understanding the regulation of cell trafficking and cell metastasis in malignancies that disseminate in the bone marrow such as Multiple Myeloma (MM) and Waldenstrom Macroglobulinemia (WM).

MM is a plasma cell dyscrasia characterized by the presence of multiple myelomatous "omas" throughout the skeleton indicating that there is continuous trafficking of tumor cells to multiple areas in the bone marrow niches. MM may therefore represent one of the best models to study cell trafficking or cell metastasis. Although the term "metastasis" is not commonly used to describe dissemination of hematological malignancies, my lab attempts to examine how MM can use a process of cell dissemination that is similar to cell trafficking of hematopoietic stem cell (HSCs) and cell metastasis in solid epithelial carcinomas. These studies can guide our understanding of the biological changes that occur during progression in MM.

The process of cell metastasis is described as a multistep process, the invasion-metastasis cascade. This involves cell invasion, intravasation into nearby blood vessels, passage into the circulation, followed by 44 homing into predetermined distant tissues, the formation of new foci of micrometastases, and finally the growth of micrometastasis into macroscopic tumors. This review discusses the significant advances that have been discovered in the complex process of invasion-metastasis in epithelial carcinomas and cell trafficking in hematopoietic stem cells and how this process relates to progression in MM. This progression is mediated by clonal intrinsic factors that mediate tumor invasiveness as well as factors present in the tumor microenvironment that are permissive to oncogenic proliferation. Therapeutic agents that target the different steps of cell dissemination and progression are discussed. Despite the significant advances in the treatment of MM, better therapeutic agents that target this metastatic cascade are urgently needed. We first used the chemokine SDF-1 and its receptor CXCR4 as a model of understanding migration, homing and egress of MM and WM cells into and out of the marrow. We examined mechanisms of cell trafficking through the CXCR4/SDF-1 axis and downstream signaling proteins including the PI3K/Akt axis and Rho/Rac signaling. In addition, we identified a critical role of integrins, selectins and cadherins in regulating MM cell trafficking in vitro and in vivo. Moreover, we showed for the first time that hypoxia regulates cell dissemination and metastasis in MM through activation of transcription factors that modulate epithelial-mesenchymal transition (EMT), a process similar to that observed in solid tumor metastasis.

To better examine in vivo localization of MM cells into the different niches of the bone marrow, we developed an imaging model to determine cell-cell interaction of tumor cells with the vascular niche or endosteal niche. Our group has shown that MM cells could be seen interacting with the endothelium of the calvarial bone marrow vasculature within minutes after intravenous injection into the tail vein of SCID mice using intravital confocal microscopy. We are also developing in vitro 3D model systems to examine interactions of stromal cells, endothelial cells and tumor cells.

Although preparation of the pre-metastatic niche has not been studied in MM, we recently showed that stromal cells present in contact with MM cells secrete exosomes that modulate the growth and dissemination potential of MM cells. Our study showed that MM derived bone marrow stromal cells release exosomes, which are transferred to tumor cells, thereby resulting in modulation of tumor growth
in vivo. Studies to define tumor derived exosomes and their role in preparing the pre-metastatic niche in MM are underway.

The lab is currently focusing on multiple aspects of cell metastasis or cell dissemination in MM and WM as tumor models for cell metastasis to the bone marrow niches: We are examining 1) mechanisms
of early cell dissemination such as EMT transition and its epigenetic regulation, 2) the role of circulating tumor cells in cell dissemination, 3) preparation of the metastatic niche, 4) factors regulator progression of micrometastasis in patients with MGUS to overt MM, 5) miRNA regulators of tumor dissemination and stromal/myeloma interaction for cell dissemination, 6) Mechanisms of cell dissemination in extramedullary MM, 7) the role of hypoxia in regulating cell dissemination and drug resistance in MM.

In addition, our laboratory research data has been rapidly translated to innovative investigator-initiated clinical trials. We have conducted over 10 phase I and II clinical trials. The phase II clinical trial of RAD001 in patients with WM is currently being considered for FDA approval for patients with WM. This would represent the first FDA approval of a drug in this orphan disease. Our studies on MM cell trafficking have been translated to the first chemosensitization trials in patients with Multiple Myeloma. In addition, we have the largest referral center for patients with Waldenstrom based on the clinical trials 45 and research studies that are being conducted in our group.

In support of the academic mission of Harvard Medical School, I am strongly involved in the teaching and training of our Internal Medicine Residents and Hematology/Oncology Fellows. I regularly give teaching lectures for Internal Medicine residents during their rotations on the Leukemia service and on morning teaching rounds. In addition, I am involved in the teaching of Hematology/Oncology fellows on regular basis and their academic career development. In addition, I am a mentor of Harvard Medical School/MIT students, The Continuing Umbrella of Research Experiences (CURE) program students as well as multiple postdoctoral fellows and students.

Myeloma Metastasis Model

Irene Ghobrial

Department of Medicine, Harvard Medical School Active Medical Staff, Myeloma Program, Dana-Farber Cancer Institute, USA

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by the presence of multiple myelomatous "omas" throughout the skeleton, indicating that there is continuous trafficking of tumor cells to multiple areas in the bone marrow niches. MM may therefore represent one of the best models to study cell trafficking or cell metastasis. The process of cell metastasis is described as a multistep process, the invasion-metastasis cascade. This involves cell invasion, intravasation into nearby blood vessels, passage into the circulation, followed by homing into predetermined distant tissues, the formation of new foci of micrometastases, and finally the growth of micrometastasis into macroscopic tumors. Here, I will discuss the significant advances that have been discovered in the complex process of invasion-metastasis in epithelial carcinomas and cell trafficking in hematopoietic stem cells and how this process relates to progression in MM. This progression is mediated by clonal intrinsic factors that mediate tumor invasiveness as well as factors present in the tumor microenvironment that are permissive to oncogenic proliferation. Therapeutic agents that target the different steps of cell dissemination and progression are discussed. Despite the significant advances in the treatment of MM, better therapeutic agents that target this metastatic cascade are urgently needed.

CURRICULUM VITAE

Saad Zafar Usmani, M.D., FACP is an Assistant Professor of Medicine at the University of Arkansas for Medical Sciences (UAMS) and also serves as the Director of Developmental Therapeutics at the Myeloma Institute for Research and Therapy at UAMS. Dr. Usmani received his medical education at Allama Iqbal Medical College Lahore, Pakistan. He completed a residency in Internal Medicine at Sinai-Grace Hospital/Wayne State University in Detroit, Michigan, and a fellowship in Hematology & Oncology at the University of Connecticut Health Center in Farmington, Connecticut. Dr. Usmani's clinical interest involves hematologic malignancies and stem cell transplantation. His academic focus is on research in the biology, pathogenesis and therapy of plasma cell disorders, with specific focus on clinical/translational investigations in high-risk myeloma (genomically-defined poor risk, plasma cell leukemia, extra-medullary disease, etc.). He is on the editorial review board of numerous medical journals, and has presented extensively at national and international meetings. Dr. Usmani is a member of the SWOG Myeloma Committee, International Myeloma Working Group, American College of Physicians, American Society of Hematology, the American Society of Clinical Oncology and the American Association for Cancer Research.

Saad Usmani, MD FACP
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Fax: (501) 526-2273
susmani@uams.edu

Education

Hematology & Medical Oncology Fellowship, University of Connecticut, Farmington,	CT 07/2007-06/2010
Internal Medicine Residency, Sinai-Grace Hospital/Wayne State University, Detroit, MI	07/2004-06/2007
Pathology Internship, Allama Iqbal Medical College & Jinnah Hospital, Pakistan	03/2003-08/2003
Radiology Internship, Punjab Medical College & Allied Hospital, Pakistan	06/2002-01/2003
M.B.B.S., Allama Iqbal Medical College, Lahore, Pakistan	01/1997-05/2002
B.Sc., University of Punjab, Lahore, Pakistan	01/1997-08/1999
HSSC, Crescent Model Higher Secondary School, Lahore, Pakistan	08/1994-08/1996

Current Position

Director of Developmental Therapeutics, Myeloma Institute for Research & Therapy, University of Arkansas for Medical Sciences, Little Rock, AR	07/2011-present
Assistant Professor of Medicine, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR	07/2010-present

Certifications & Licensure

Permanent ECFMG Certification	2003
Michigan Medical License (4301083810)	2006-present
American Board of Internal Medicine	2007-2017
American Board of Internal Medicine-Medical Oncology	2010-2020
American Board of Internal Medicine-Hematology	2010-2020
Arkansas Medical License (E-6470)	2010-present
Connecticut Medical License (50733)	2012-present

Professional Memberships and Activities
Fellow, American College of Physicians
Member, American Association for Cancer Research
Member, American Society of Hematology
Member, American Society of Clinical Oncology
Member, European Hematology Association
Member, European Society of Clinical Oncology
Member, American Medical Association
Member, Association of Physicians of Pakistani Descent of North America
Member, International Society of Laboratory Hematology
Member, Southwestern Oncology Group (SWOG) Myeloma Committee
Member, SWOG Imaging Committee
Member, International Myeloma Work Group
Member, International Myeloma Society
Member, Multiple Myeloma Committee, Bone Marrow Transplant-Clinical Trials Network
Member, Scientific Committee on Lymphoma and Plasma Cell Disorders, American Society of Clinical Oncology

Professional Experience/Academic Appointments
Director of Developmental Therapeutics, Myeloma Institute for Research & Therapy, 07/2011-present
University of Arkansas for Medical Sciences, Little Rock, AR
Assistant Professor of Medicine, Department of Medicine, 07/2010-present
University of Arkansas for Medical Sciences, Little Rock, AR
Attending Physician, Bone Marrow Transplant/Myeloma Service, 07/2010-present
University of Arkansas for Medical Sciences, Little Rock, AR
Chief Fellow, Division of Hematology-Oncology, 01/2010-06/2010
University of Connecticut Health Center, Farmington, CT
Fellow, Division of Hematology-Oncology, 07/2007-06/2010
University of Connecticut Health Center, Farmington, CT
Resident, Department of Internal Medicine, 07/2004-06/2007
Sinai-Grace Hospital/Wayne State University, Detroit, MI

Honors and Awards
Session Moderator, CLL Oral Abstract Presentations 2012
American Society of Hematology 2012 Annual Meeting
Member, Abstract Review Committee 2012
American Society of Hematology 2012 Annual Meeting
Member, Scientific Committee on Lymphoma and Plasma Cell Disorders 2012-2015
American Society of Clinical Oncology
Member, Grant Review Committee 2012
International Myeloma Foundation Brian D. Novis Research Award
Elected Fellow, American College of Physicians 2011
Member, International Myeloma Working Group 2010
Jo-Ann Smith Memorial Education and Research Fund 2010
Winner, University of Connecticut Health Center 2009
Multiple Myeloma Seed Grant Competition
AACR-ASCO Scholarship Award 2008
Workshop Molecular Biology in Clinical Oncology, Aspen, CO
Best Ambulatory Resident Award 2007
Sinai-Grace Hospital/Wayne State University, Detroit, MI
2nd Place Winner, 2007
ACP-Michigan Associates Case Report Competition
Joseph E. Johnson ACP Leadership Day Grant 2007
Finalist, National ACP Meeting Basic Science Research Competition 2007
San Deigo, CA
3rd Place Winner, ACP-Michigan Associates Case Report Competition 2006
Finalist, National ACP Meeting Case Report Presentation Competition 2006
Philadelphia, PA
3rd Place Winner, Basic Science Presentation 2006
Sinai-Grace Hospital/Wayne State University, Detroit, MI
Intern of the Year for Academic Excellence 2005
Sinai-Grace Hospital/Wayne State University, Detroit, MI
1st Place Winner, Case Report Presentation 2005
Sinai-Grace Hospital/Wayne State University, Detroit, MI
Other Positions & Employment
Clinical Research Assistant 06/2003-06/2004
Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan
House Officer, Department of Pathology 03/2003-08/2003
Allama Iqbal Medical College & Jinnah Hospital, Lahore, Pakistan
Additional House Officer, Department of Radiology 06/2002-01/2003
Punjab Medical College & Allied Hospital, Faisalabad, Pakistan

Committee Assignments and Administrative Services
Member, Abstract Review Committee, 2012
American Society of Hematology 2012 Annual Meeting
Member, Grant Review Committee 2012
International Myeloma Foundation Brian D. Novis Research Award
Member, Scientific Committee on Lymphoma and Plasma Cell Disorders 2012-2015
American Society of Clinical Oncology
Member, Editorial Board 2011-present
Journal of Hematologic Malignancies
Member, Editorial Board 2011-present
Experimental Hematology & Oncology
Co-Chair, Hematology & Medical Oncology 2011-present
Association of Physicians of Pakistani Descent of North America-Medical Education, Research & International Training program

Chair, Scholarly Activity Mentorship Project 2011-2012
Allama Iqbal Medical College Alumni Association of North America
Member, Medical Student Interview Committee 2011
UAMS School of Medicine Class of 2012
Member, Pathology Chair Search Committee, UAMS, Little Rock, AR 2010-2011
Member, Myeloma Translational Research Group, UAMS, Little Rock, AR 2010-present
Member, Cancer Committee, University of Connecticut Health Center 2008-2010
Member, Curriculum Committee, Hematology Oncology Fellowship program 2008-2010
University of Connecticut Health Center, CT
Representative, Wayne State University Resident's Council 2006-2007
Member, Residency Operations Committee 2004-2007
Sinai-Grace Hospital/Wayne State University, Detroit, MI
Member, Educational Curriculum Committee 2004-2007
Sinai-Grace Hospital/Wayne State University, Detroit, MI

Editorial Board Activities

Member, Editorial Review Board

Modern Chemotherapy	2012-present
Journal of Hematologic Malignancies	2011-present
Experimental Hematology & Oncology	2011-present
National ACP Associate Member Abstract Competition	2008-present
National ACP Medical Student Abstract Competition	2007-present

Ad-hoc Reviewer

Haematologica	2012-present
American Journal of Hematology	2012-present
Nature Blood Cancer Journal	2012-present
Nature Leukemia	2011-present
Nature Bone Marrow Transplant	2011-present
Biology of Bone Marrow Transplantation	2011-present
Journal of Clinical Oncology	2010-present
Nature Clinical Reviews Oncology	2010-present
European Journal of Hematology	2009-present
Cancer Letters	2009-present
Journal of Hematologic Oncology	2009-present
Journal of Invasive Fungal Infections	2009-present
Journal of Hepatology	2009-present
European Journal of Cancer Care	2008-present
Clinical and Translational Oncology	2008-present
Genes, Chromosomes & Cancer	2008-present
International Journal of Laboratory Hematology	2007-present

Long Term Sequela of Myeloma Therapy

Saad Z. Usmani MD, FACP.

Myeloma Institute for Research & Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA

The last decade has seen major advances in biologic understanding and drug development for multiple myeloma (MM), with improvements in median survival of patients improving from a dismal less than 2 years to over 6-7 years. Following the FDA/EMEA approval of carfilzomib and pomalidomide, several novel agents are on the road for commercial availability over the next 5 years. Such progress will make MM a chronic, manageable disease for the majority of patients in the near future. Living longer does come at a cost as both disease manifestations and cancer treatment can be associated with long-term adverse effects. Bone health problems, delayed immune system recovery, peripheral neuropathy, endocrine disorders, and therapy related neoplasms can occur in MM patients and impact their quality of life. It is, therefore, important to follow MM patients for these issues in the ambulatory setting so that care and counseling can be provided in a timely fashion. The current presentation will summarize the available data on each of these areas, with a special focus on the recent data regarding therapy related neoplasm.

ICLLM 2013

Diffuse Large B-Cell Lymphoma

CURRICULUM VITAE

Name: Laurence L. de LEVAL

Office Address: Institute of Pathology
University Hospital of Lausanne
25 rue du Bugnon
CH – 1011 Lausanne
Switzerland

Work Phone : +41 21 3147194
Work Fax: +41 21 3147205
Work E-mail: Laurence.deLeval@chuv.ch

Home address : 1 Chemin du Hameau
CH – 1052 Le Mont-sur-Lausanne
Switzerland

Place of birth: Liège, Belgium
Citizenship: Belgian

Education

1987 Certificate of secondary education
Lycée Saint-Jacques, Liège
1987 Certificate for access to Engineer School,
Faculty of Applied Sciences, University of Liège
1994 Medical Doctor, University of Liège
Summa cum laude plus Jury's congratulations
1998 PhD in Biomedical Sciences, University of Liège
Contribution à l'étude des interactions fonctionnelles entre lymphocytes B et lymphocytes T dans le syndrome murin d'immunodéficience acquise rétroviro-induit (MAIDS)
Summa cum laude plus Jury's congratulations
1999 United States Medical Licensing Examination
Certificate of the Educational Commission for Foreign Medical Graduates, Philadelphia, USA
2000 Board certified in Pathologic Anatomy and Cytology, Belgium
2007 Agrégation de l'Enseignement Supérieur, University of Liège
Contribution to the pathological study of human lymphomas
A l'unanimité

Post-doctoral training

July 1993 Rotation in Pediatric Pathology
Great Ormond Street Hospital for Sick Children, London, UK (Professor A. Risdon and Dr. M. Malone)
Research Fellow of the Belgian National Fund for Scientific Research (FNRS) and Resident in Pathology
Department of Pathology, CHU Sart Tilman, University of Liège (Professor J. Boniver)
Post-doctoral researcher of the FNRS,
Hematopathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA (Professors N.L. Harris and M. Shipp)
1999-2000 Resident in Pathology,
Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (Professor R. Colvin)

Faculty academic appointments

2001-2007 Permanent Research Associate of the FNRS
Department of Pathology, CHU Sart Tilman, University of Liège
2004-2009 Maître de Conférences, University of Liège
2007-2009 Permanent Research Associate of the FNRS
2008-2009 Professor of Clinics, University of Liège
2009- Full Professor of Pathology, University of Lausanne
2010- Invited Professor, University of Liège

Appointments at hospitals

2000-2009 Associate pathologist, Department of Pathology, CHU Sart Tilman
2002-2006 Chef de Laboratoire adjoint, Department of Pathology, CHU Sart Tilman
2004-2010 Consultant pathologist, Laboratory of Pathology, Hospital of Bastogne, Belgium
2006-2009 Chef de Laboratoire, Department of Pathology, CHU Sart Tilman
2009- Head of Clinical Pathology, University Institute of Pathology,
Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Professional Societies

Belgian Societies

2000-2010	Belgian Society of Pathology	member
2007-2009		secretary
2000-2009	Belgian Club of Digestive Pathology	member
2007-2009	Consilium Pathologicum Belgicum	member and treasurer

European Societies

1998-	European Association for Haematopathology	member
2003-	European Society of Pathology	member
2009-2013 : Executive committee member of the ESP		
2012-	: Education committee member of the ESP	
	European Molecular Pathology working group of the ESP	
	European Network of Uropathology	member
2008-	French Division of the International Academy of Pathology	member

2003-	British Division of the International Academy of Pathology	member
2000-2012	Groupe d'Etude des Lymphomes de L'Adulte (GELA)	member
2005-2010 : member of the scientific council of the GELA		
2010-2012 : member of the administrative board of the GELA		
2006-2012 : member of the GELA pathology group (GELA-P)		
2012-	Lymphoma Study Association (LYSA)	member
2012-	: member of the administrative board of the LYSA	
2012-	: member of the LYSA pathology group (LYSA-P)	
2009-	Swiss Society of Pathology	member
2011-	: executive board member	
2011-	: Carnet Officer	
2010-	Société Française de Pathologie	member

American Societies

1998-	United States and Canadian Association for Pathology	member
2000-	Society for Hematopathology	member
2000-2011	American Society of Hematology	member

International Working Groups

2010-	International Lymphoma Study Group (ILSG)	Selected member
2011-	ITMIG (International Thymic Malignancy Interest Group)	member

Editorial activities

Ad hoc reviewer

Annals of Hematology, APMIS, Blood, Cancer Genetics Cytogenetics, Clinical Cancer Research, Experimental and molecular pathology, Haematologica, Histopathology, Human Pathology, The Journal of Haematopathology, Leukemia, Leukemia and Lymphoma, Leukemia Research, Pathology Research and Practice

Other editorial roles

2008-	Editorial Manager for the Journal of Hematopathology
2008	Abstract reviewer for American Society of Hematology meeting
2010-2013	Associate Editor, Virchows Archives
2011-2013	Associate Editor, Leukemia, Lymphoma Section

Scientific awards

1994	Specia medical student award, first prize (600 euros)
2000	Prize of the Braconnier Lamarche foundation (7,500 euros)
2000	Award of the Belgian Society of Pathology for the best presentation at the winter meeting (500 euros)
2003	Prize Liliane Ruyters awarded by the Association for gastroenterologists of Liège for the best free paper presentation (1,500 euros)
2004	Prize of the Rotary Hannut Waremme (8,000 euros)
2007	Prize of the Foundation D and M Jaumain awarded for the thesis entitled "Contribution to the pathological study of human lymphomas" (12,500 euros)
2008	Benjamin Castleman award of the United States and Canadian Academy of Pathology, in recognition of the best paper published in the field of pathology (1,500 USD)
2009	Prize of the Inbev-Latour Foundation for clinical research (75,000 euros)

Biological Heterogeneity Of Diffuse Large B-Cell Lymphoma

Laurence de Leval, MD Ph.D

Department of Pathology, University Institute of Pathology, University Hospital of Lausanne, Lausanne, Switzerland

Diffuse large B-cell lymphoma (DLBCL) is the most frequent lymphoma type accounting for approximately one third of non-Hodgkin lymphomas. DLBCLs exhibit marked biological heterogeneity – with respect to histomorphology, immunophenotype, molecular and genetic features - and variable clinical presentation and clinical course. Although an increasing number of subtypes and entities have been recognized in the latest WHO classification (Table 1), the majority of cases fall into the category of DLBCL, not otherwise specified (DLBCL, NOS), which is the "usual" form of DLBCL and represents the diagnosis retained after exclusion of more "specific" categories.

Table 1. Classification of Diffuse Large B-cell lLymphomas (DLBCL)

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)
- Morphologic variants: centroblastic, immunoblastic, anaplastic
- Molecular subgroups
- Immunohistochemical subgroups

Diffuse large B-cell lymphoma subtypes
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL of the elderely

Diffuse large B-cell lymphoma entities
- Primary mediastinal (thymic) large B-cell lymphoma (PMLBCL)
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation (previously called pyothorax-associated lymphoma)
- Lymphomatoid granulomatosis
- Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ DLBCL)
- Plasmablastic lymphoma (PBL)
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (MCD)
- Primary effusion lymphoma (PEL)

i. Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)

DLBCL, NOS usually affects adults with a median age at presentation in the 7th decade, but also occurs in children and young adults. Up to one third of the cases present in extranodal sites. DLBCL, NOS may occur *de novo* or as a transformation of an underlying small B-cell lymphoma. By definition the disease is a neoplasm of large transformed B cells (with nuclear diameter more than twice that of a normal lymphocyte). By order of decreasing frequency, the centroblastic, immunoblastic and anaplastic variants are the most common morphologic variants. DLBCLs express CD45 and pan-B cell antigens, such as CD19, CD20, CD45RA, CD79a, and the nuclear transcription factor PAX5, but may lack one or more of these. Notably, treatment with rituximab can result in the loss of CD20 expression. The tumor cells usually express monotypic surface +/- cytoplasmic immunoglobulin (Ig), usually IgM. The proliferation fraction is is typically high (median 65%). Bone marrow involvement, seen in about 15% of the cases, may appear either as a large-cell infiltrate ("concordant"marrow involvement), associated with reduced overall survival, or as an infiltrate of predominantly small B cells ("discordant" marrow involvement); prognosis in the latter is not worse than cases without marrow involvement, but may confer a higher risk of late relapses.

Immunophenotypic variants

About 10% of *de novo* DLBCL cases express CD5, and are distinguished from blastoid mantle cell lymphoma by their negativity for cyclin D1. CD5-positive DLBCL tends to occur in older women, with a predilection for extranodal involvement, especially bone marrow and spleen; intravascular tumor cells are often present. CD5 expression in DLBCL is associated with a shorter survival and central nervous system recurrence.

Expression of CD30, characteristic of the anaplastic morphologic variant, may be seen occasionally in other morphologic types (overall about 15% of DLBCL cases), and appears to be associated with a good prognosis.

Genetic features

DLBCLs have clonally rearranged *IG* genes with somatic mutations in the variable regions, and hence are thought to derive from antigen-exposed B cells that have migrated to or passed through the germinal center (GC). No single genetic aberration typifies DLBCL. In addition to point mutations, gene amplifications and deletions that are common to many types of malignancies, chromosomal translocations and aberrant somatic hypermutation represent important mechanisms of oncogenesis in DLBCL. Recurrent translocations involving the *BCL6, BCL2* and *c-MYC* genes occur in about 50% of cases and induce deregulated expression of these protoconcogenes by promotor substitution as a result of their juxtaposition to *IG* genes. Somatic hypermutation activity not only affects "physiological" target genes such as the *IG* variable regions, but may also aberrantly targets multiple other protooncogenes, including *c-MYC, PIM1, PAX5* and *RhoH/TTF*. Hypermutation represents a powerful mechanism of transformation by facilitating translocations by the induction of DNA double-strand breaks. Recently, application of next generation sequencing technology has led to the identification of novel recurrent lesions for example *EZH2* mutations, and mutations and deletions of *CREBBP*.

Molecular Subtypes

Gene expression profiling studies have identified three distinct molecular DLBCL subgroups, namely the germinal center (GC) B cell-like DLBCL (GCB DLBCL) harboring a gene expression profile similar to that of GC B cells, and the activated B cell-like DLBCL (ABC DLBCL), with a gene expression profile similar to that of *in vitro* mitogenically activated peripheral blood cells, and primary mediastinal B-cell lymphoma (PMLBCL) described below. A subset of cases cannot be categorized as either GCB or ABC (so-called "type 3" tumors). The GCB and ABC subgroups of DLBCL differ in their oncogenic mechanisms and clinical outcome, validating the notion of pathogenetically distinct subgroups (**Table 2**). Importantly, patients with GCB DLBCL have significantly better outcomes than those with ABC DLBCL, a difference that remains significant with chemotherapy regimens that include rituximab. Analysis of the expression of a limited number of genes by real time RT-PCR can also predict outcome in DLBCL and may be more amenable to routine diagnostic use.

Both types harbor mutated *IG* genes, but ongoing somatic hypermutation is only a feature of GCB tumors. The t(14;18)(q32;q21) translocation involving *BCL2* ,and chromosomal amplifications of the *c-REL* locus at 2p occur predominantly if not exclusively in the GCB group, while *BCL6* translocations are three times more common in ABC than in GCB DLBCLs. GCB DLBCLs are characterized by recurrent abnormalities affecting the tumor suppressor *PTEN* leading to constitutive activation of the PI3K/AKT signaling pathway. DNA sequencing studies have recently evidenced aberrations in a number of chromatin modifying genes with a higher prevalence in GCB than in ABC subtypes. Somatic mutations of the histone methyltransferase *EZH2* in about 20% of GCB DLBCLs. Genetic aberrations affecting CREBBP and EP300, two related histone and non-histone methyltransferases that act as transcriptional coactivators of several pathways, have been identified in about

Table 2. Characteristics Of The Gcb And Abc Dlbcl Molecular Subgroups

	Germinal Center B-cell (GCB) DLBCL	Activated B-cell (ABC) DLBCL
Overexpressed genes	*CD10, BCL6, HGAL, LMO2*	*MUM1/IRF4, XBP1, CD44, FOXP1*
Postulated cell of origin	Germinal center B cell	Post-germinal center B cell that is blocked during plasmacytic differentiation
Ongoing *IG* mutations	Yes	No
Genetic alterations and oncogenic mechanisms	*BCL2* translocation (35%) cMYC translocation (15%) Deletion of *PTEN* tumor suppressor (10%) leading to constitutive activation of PI3/AKT signaling pathway *c-REL* amplification at 2p (30%) *MDM2* amplification *EZH2* mutations Genetic aberrations of *CREBBP* and *EP300*	*BCL6* translocations *PRDM1/BLIMP1* inactivation Trisomy 3, trisomy 18 Deletion 6q Constitutive NFkappaB activation Deletion of the *INK4a/ARF* locus Mutations of *CARD11*, *CD79A, CD79B, MYD88*
Morphology	Centroblastic	Immunoblastic-rich
Immunophenotype	CD10+ BCL6+/- MUM1+/- or CD10- BCL6+ MUM-1-	All other combinations
Clinical outcome	Favorable	Unfavorable
CHOP-like	60% 5-year survival	35% 5-year survival
R-CHOP	75% 5-year survival	50% 5-year survival

one third of GCB DLBCL cases and a lesser proportion of ABC tumors. Activation of the nuclear factor-kappaB signalling pathway relying upon the CARD11/MALT1/BCL10 (CBM) signaling complex, is the pathogenic hallmark of the ABC subgroup, and interference with this pathway selectively kills ABC-type DLBCL tumor cells. The CBM complex is activated by different genetic aberrrations in ABC DLBCL, including mutations in *CARD11*, mutations in *CD79A* or *CD79B.* Other mechanisms of NF-kappaB activation include biallelic mutations/deletions of *A20* (in avbout 30% of the cases) which encodes a ubiquitin-modifying protein acting as a negative regulator of NF-kappaB, and mutations of *MYD88*. ABC DLBCLs are characterized by amplifications and consecutive overexpression of *BCL2* as well as deletions affecting the *INK4a/ARF* locus.

The ABC and GCB molecular signatures are reflected at the protein level by differential expression of antigens normally related to physiological B-cell differentiation, including GC markers such as CD10 and BCL6 and post-GC markers such as MUM1, VS38c, and CD44. Different algorithms have been developed that variably correlate with the gene expression profiling classification, although the concordance is imperfect.

II. PRIMARY MEDIASTINAL (THYMIC) LARGE B-CELL LYMPHOMA

Primary mediastinal large B-cell lymphoma (PMLBCL) is a distinct DLBCL entity arising in the mediastinum, thought to be derived from thymic B cells. PMLBCL tends to occur in young patients (median age about 35 years), and affects women more commonly than men. Patients present with an often bulky anterior mediastinal mass and symptoms related to impingement of local anatomic structures. The disease is usually localized at presentation, but progression can be characterized by dissemination to other extranodal sites, including lung, liver, kidneys, adrenals, ovaries, brain, and the gastrointestinal tract. Patients with PMLBCL have a survival similar to those with GCB DLBCL, NOS.

Histologically, PMBCL is a diffuse proliferation of medium to large cells. Particular (but not entirely specific) morphologic features include the presence of fine compartimentalizing sclerosis, the presence of cells with abundant clear cytoplasm and/or multilobated nuclei, and the presence of large cells with Reed-Sternberg-like morphology. The tumor cells express the B-cell-associated antigens CD19, CD20, and CD79a, but often lack surface Ig, despite expression of the IG-associated transcription factors BOB.1, Oct-2 and PU.1. Most cases express BCL6, MUM1/IRF4, BCL2, and CD23 and a variable proportion of cases also expresses CD30. Expression of MAL, FIG1 (the product of the interleulin-4-induced gene 1), and TNF-receptor-associated factor 1 (TRAF-1) are characteristic of PMLBCL, especially when combined with nuclear c-REL localization.

By gene expression profiling, PMLBCL has a molecular signature distinct from that of both GCB and ABC DLBCL, NOS, characterized by low levels of expression of multiple B-cell signalling components and coreceptors and high expression of cytokine pathway components, tumor necrosis factor (TNF) family members, and extracellular matrix elements. Interestingly the PMBCL signature partly overlaps with that of Hodgkin lymphoma cell lines. Altered JAK/STAT signaling, manifested by constitutive activation of STAT5 and STAT6, represents another alteration common to both PMLBCL and cHL and may cause defective suppressor of cytokine signalling. Aberrant tyrosine kinase activities and activation of the PI3K/AKT pathway were recently identified as a further shared pathogenic mechanism between PMLBCL and cHL.

PMLBCL only exhibit *BCL2* or *BCL6* rearrangements. The most frequent genetic abnormalities are gains in chromosomes 9p24 (including the *JAK2* locus) in up to 75% of cases, and gain of *REL* on chromosome 2p in about 50% of cases. Recently the MHC class II transactivator CIITA has been implicated in the pathogenesis of PMLBCL as *CIITA* translocations, associated with downregulation of surface HLA class II expression, are highly recurrent in PMLBCL (occurring in about 40% of the cases).

III. OTHER DLBCL ENTITIES AND SUBTYPES

T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA (THRLBCL)

In THRLBCL, there are few large neoplastic B-cells scattered in a background of non-neoplastic T cells with or without histiocytes. THRLBCL usually presents in middle-aged or older male adults, often with advanced-stage disease and frequent involvement of spleen (with a typical micronodular pattern of involvement of the white pulp), liver, and bone marrow. The neoplastic cells may resemble centroblasts, immunoblasts, lymphocyte predominant Hodgkin cells or classic Reed-Sternberg cells. They express B-cell antigens, are strongly positive for BCL6, variably express BCL2 and EMA, are negative for CD30 and CD15, and do not harbor EBV.

BCL2 gene rearrangement is present in a s subset of the cases. The reactive cells comprise CD68+ histiocytes and variable proportions of CD4+ and CD8+ T cells. THRLBCL may develop an increasing density of neoplastic cells with progression or relapse and exhibit an appearance indistinguishable from DLBCL, NOS. By molecular profiling, most THRLBCL cases fall into a subset of DLBCL characterized by "host inflammatory response" genes.

PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

Primary DLBCL of the central nervous system comprises all primary intracerebral (PCNSL) or intraocular (PIOL) DLBCL, and do not apply to patients with immunodeficiency conditions. PCNSL usually affects elderly individuals with a slight male predominance PCNSL can present as solitary (75%) or multiple (25%) supratentorial masses. The tumor cells usually infiltrate perivascular spaces and adjacent brain parenchyma. In addition to CD20, the tumor cells are virtually always MUM1+ and are positive for BCL6 in the majority of cases while CD10 expression is infrequent. Chromosomal translocations involving *BCL6* are frequent (30-4% of cases), often involve non-*IG* partners, and are associated with poor outcome. Conversely, rearrangements of *BCL2* and *cMYC* are virtually never found in PCNSL. By gene expression profiling, the molecular signature of PCNSL includes both GCB and (more commonly) the ABC subtypes, PCNSL shows a distinct differential gene expression pattern from non-CNS DLBCL, but the identified "CNS signature" might in fact reflect the non-neoplastic brain microenvironment. Activation of the IL4 pathway in endothelial cells may account for the angiotropism typically encountered in PCNSL.

PRIMARY CUTANEOUS DLBCL, LEG TYPE

This primary cutaneous DLBCL is a tumor-forming non-epidermotropic neoplasm that preferentially affects the lower limb, frequently disseminates to non-cutaneous sites and has an aggressive course. It usually affects elderly women. It is composed of large B cells with a striking round cell morphology. The tumor cells express CD20, BCL6, and MUM1, cytoplasmic IgM and are usually CD10-negative. BCL2 is overexpressed in most cases as a consequence of *BCL2* amplification. The gene expression profile is that of the ABC DLBCL subtype.

INTRAVASCULAR LARGE B-CELL LYMPHOMA

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of DLBCL characterized by the selective growth of lymphoma cells within small blood vessels, with occasional limited infiltration of perivascular tissue, but without an obvious extravascular tumor mass or leukemia. Involvement of sinuses of the bone marrow, liver, and spleen are frequent, while lymph nodes are usually spared. IVLBCL predominantly affects elderly patients and presents as disseminated and aggressive malignancies eventually resulting in multiorgan failure. A "cutaneous variant" of IVLBCL is limited to the skin at presentation, and has a more favorable clinical behavior. The neoplastic cells in IVLBCL are large CD20+ B cells, which may CD5. Many cases are BCL2+ without harboring the t(14;18) translocation. The selective localization of the tumor cells within the vessels has been ascribed to defective expression of specific surface molecules, such as CD29 and CD54, that are necessary for transvascular migration.

EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMAS

Many EBV-associated lymphoid proliferations in immunocompromised individuals manifest histologically asproliferations of EBV+ large B cells categorized as DLBCL, otherwise similar to the common form of EBV-negative DLBCL encountered in immunocompetent patients. Moreover several DLBCL subtypes/entities are defined at least by their association with EBV (plasmablastic lymphoma, DLBCL associated with chronic inflammation, lymphomatoid granulomatosis, EBV-positive DLBCL of the elderly) or with dual EBV/HHV8 coinfection (primary effusion lymphoma) (**Table 3**).

EBV+ DLBCL of the elderly comprises per definition EBV+ DLBCL in patients over 50 years, without HIV infection and without any known immune deficiency syndrome. It is believed to be related to the altered immune function caused by immune senescence. Median age is 70 years. The disease often involves extranodal sites (skin, tonsil, lung, stomach), with or without lymph node involvement. On histology, the tumor resembles a monomorphous large-cell lymphoma or a polymorphous large cell infiltrate with a variable inflammatory background. Angiocentricity and extensive necrosis are frequent. Reed-Sternberg-like cells may be numerous, raising the differential diagnosis with classical Hodgkin lymphoma.

Plasmablastic lymphoma (PBL) designates a group of tumors that morphologically resemble DLBCL (immunoblastic +/- plasmacytic differentiation) but have an immunophenotypic profile of plasma cells (absent or weak expression of CD45 and B-cell antigens and strong expression of CD138 and MUM-1, +/- expression of cytoplasmic Ig (usually IgG or IgA)). PBL usually exhibits a high

Table 3. EBV-positive large B-cell lymphoid proliferations		
Type of lymphoid proliferation	Clinical setting	Presentation
EBV+ DLBCL	Associated with primary immune disorders Associated with HIV infection Post-transplant lymphoid proliferation Iatrogenic immunodeficiency-associated lymphoproliferation (methotrexate, TNFa antagonists) With no known predisposing conditions, <50 years	Nodal or extranodal
Plasmablastic lymphoma	HIV infection Less often : HIV-negative indivisuals	Extranodal (oral cavity or other), less commonly nodal
Primary effusion lymphoma *	HIV infection Less often : post-transplant, elderly mediterranean individuals	Body cavity effusion Solid extracavitary
Lymphomatoid granulomatosis	Congenital immunodeficiency syndromes HIV infection Post-transplant	Lung, brain, skin ; angicentric multifocal involvement
DLBCL associated with chronic inflammation	Chronic pyothorax or chronic infection	Pleural-based mass, bone or joint tumor
EBV+ DLBCL of the elderly	>50-year old, immune senescence	Extranodal, less commonly nodal
* coinfection by EBV and HHV8		

proliferation rate with frequent apoptotic cells +/- starry-sky pattern. Virtually all cases are positive for EBER, and HHV8 is consistently absent. Since the original description as a rare variant of DLBCL occurring in the oral cavity in HIV-infected patients, its spectrum has been expanded to include similar lesions in immunocompetent patients and in other extranodal sites such as the anorectal region, nasopharynx, intestine, and in lymph nodes. PBL has a highly aggressive clinical behavior, but improved survival outcomes have been reported in HIV-infected patients in the era of highly active anti-retroviral therapy.

Pyothorax-associated lymphoma (PAL) is the prototypic form of ***DLBCL occurring in the context of chronic inflammation*** and associated with EBV. This rare disease (more frequent in Japan) develops in the pleural cavity of elderly male patients with a history of longstanding pyothorax, usually resulting from artificial pneumothorax for treatment of tuberculosis. PAL presents as a pleural-based tumor mass, often with direct invasion to the chest wall and lung. Occasional cases of EBV-positive lymphomas complicating long-standing chronic suppuration in other extranodal sites (such as bone or joint lymphomas occurring in the setting of chronic osteomyelitis or in association with metallic implants and skin lymphomas in patients with chronic venous ulcers) are also considered part of the disease spectrum.

Lymphomatoid granulomatosis (LYG) is a rare angiocentric and angiodestructive lymphoproliferative process in the lungs, comprising a proliferation of EBV-positive large B cells (CD20+ and may weakly express CD30) associated with an exuberant reactive polymorphous cellular infiltrate (T lymphocytes, histiocytes, plasma cells.). Patients typically present with multinodular bilateral lung involvement +/- infarct-type necrosis and respiratory symptoms. The central nervous system, kidneys, and skin are also commonly involved. Lymphoid organs are usually spared. LYG often occurs in the setting of HIV or iatrogenetic immunosuppression due to organ transplant or autoimmune diseases. LYG encompasses a spectrum of histological grades (from 1 to 3) related to the proportion of EBV-positive large B cells with grade 3 lesions resembling EBV-positive DLBCL.

Primary effusion lymphoma (PEL) originally identified in AIDS as a neoplasm of large pleomorphic B cells usually presenting as effusions in serous cavities (pleural, pricardial or peritoneal) without tumor masses, may in some cases may have concomitant or subsequent solid tissue involvement of adjacent structures. PEL affects AIDS patients at a stage of profound immunodeficiency, often with previous history of or cocomitant Kaposi sarcoma; it also affects post-transplant patients and elderly Mediterranean individuals in zones of HHV8 endemy. The tumor cells are imunoblastic, plasmablastic or pleomorphic, characteristically coinfected by EBV and HHV8 which likely plays a major role in lymphomagenesis. Rare cases may present as extranodal or less commonly nodal masses with no associated effusions. These “extra-cavity PELs”

Table 4. Lymphomas with plasmablastic features				
	PBL	**PE**	**Large B-cell lymphoma in HHV8+ MCD**	**ALK+ DLBCL**
Clinical presentation	Oral cavity, other extranodal sites, less commonly lymph nodes	Body cavity effusion Extracavitary solid PEL	Lymph nodes and spleen, diffuse	Lymph nodes, sinusoidal pattern
Association with HIV	yes	yes	yes	no
Morphology	Immunoblastic to plasmablastic +/- plasma cells	Pleomorphic with immunoblastic +/- plasmablastic +/- anaplastic features	Plasmablastic	Immunoblastic to plasmablastic
Viruses				
EBV	+	+	-	-
HHV8	-	+	+	-
Immunophenotype				
CD45	-/+	+	+	-
CD20	-/+	-	+/-	-
CD79a	+/-	-	-	-
BCL6	-	-	-	-
MUM1	+	+	+	+
CD138	+	+	-	+
cIg	+/- (IgG)	-	IgMl	+/- (IgA)
CD30	+/-	+	-	-
EMA	+/-	+	-	+
ALK	-	-	-	+
Ig variable regions	Unmutated or mutated	Mutated	unmutated	NA
Cell of origin	Plasmablast	Post-GC B cell	Naïve B cell	Post-GC B cell
Clinical course	Aggressive	Very aggressive	Very aggressive	Usually aggressive

exhibit clinicopathologic features similar to those of PEL except for a somewhat more frequent expression of B-cell antigens and Ig.

DIFFUSE LARGE B-CELL LYMPHOMAS WITH PLASMABLASTIC FEATURES

In addition to PBL and PEL described above, other DLBCL entities present plasmablastic characteristics (summarized in **Table 4**).

Anaplastic lymphoma kinase (ALK)-positive DLBCL is s a very rare neoplasm is composed of large immunoblast-like cells with abundant cytoplasm and occasional plasmablastic differentiation that shows a prominent intrasinusoidal growth pattern in lymph nodes. Tumor cells bear *ALK* gene rearrangement; most cases express clathrin-ALK fusion protein. The tumor cells are negative for CD20, CD79a, and CD30, but are positive for EMA and CD138, and express cytoplasmic IgA. A subset of cases may also express CD4 and CD57. The disease affects mostly adult males and is often disseminated at presentation, with a poor prognosis.

Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (MCD) is composed of monoclonal HHV8+ large B cells resembling plasmablasts that express cytoplasmic IgMLambda in the setting of HHV8-associated MCD. The majority of cases occur in HIV-infected patients. The disease involves lymph nodes and spleen, can evolve towards a leukemic phase and has a short median survival. The neoplastic cells are HHV8-infected EBV-negative naïve, unmutated B cells that usually express CD20, but are negative for CD138. Precursor lesions to this lymphoma can manifest as clusters or aggregates of large IgMLambda positive, HHV8+ B cells with a plasmablastic appearance in the mantle zones of lymph nodes involved by MCH ("microlymphomas").

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1992-1995 Member, Institutional Review Board, NCI
1995-2008 Member, Protocol Review and Monitoring Committee, DCS, NCI
1995-2002 Chairman, Institutional Review Board, NCI
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1997 Teacher of the Year Award, Medicine Branch and Division of
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1998 Director's Award, National Institutes of Health
2000 Director's Award, Division of Clinical Sciences, NCI
2010 Director Award, National Institutes of Health
2010 Director Award, National Caner Institute

Editorial Boards
1999-2011 Clinical Lymphoma
2000-2003 Journal of Clinical Oncology
2012-Present
2002-Present The Oncologist

2006-2011 Leukemia and Lymphoma, Associate Editor
2007-Present Blood
2008-Present Advances in Hematology
2013-Present Biomed Central Hematology

Extramural Activities
2000-Present Member, CALGB Cooperative Group
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First Line Treatment of Diffuse Large B-cell Lymphoma: Do We need to Adapt Treatment to Subtypes?

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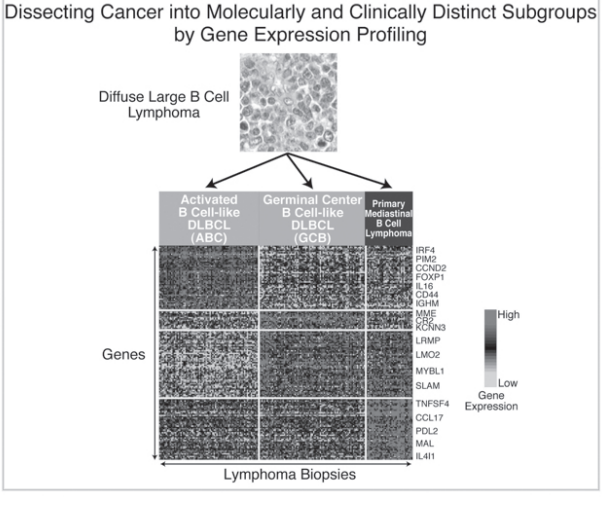
The last 30 years have seen a plethora of treatments for diffuse large B-cell lymphoma (DLBCL) but none proved better than CHOP, the first curative treatment. In the recent immunochemotherarpy era, however, there is convincing evidence for superior chemotherapy platforms. A randomized study from GELA showed R-ACVBP was superior to R-CHOP in patients under 60 years, but toxicity limits its use to younger patients. Studies also suggest Dose-Adjusted EPOCH-R represents an advance in some subtypes of DLBCL with a randomized comparison with R-CHOP now nearing completion. The simplicity and safety of R-CHOP and long history of failed contenders, however, has set a lofty bar for other approaches.

We have now entered the era of targeted therapy, propelled by a rapidly increasing knowledge of tumor biology, driver pathways and clinical successes. The first targeted treatment, rituximab, has been an unqualified albeit empirical success. Rational drug discovery now leverages our understanding of tumor pathogenesis and tumor-host interactions. The discovery of new signaling pathways through gene expression profiling (GEP), transcriptome sequencing, RNA interference screens and DNA sequencing has identified an array of new targets for DLBCL. The division of DLBCL into at least three distinct molecular diseases, germinal center B-cell (GCB), activated B-cell (ABC) and primary mediastinal B-cell (PMBL) DLBCL, is essential for advancing treatment (Figure 1). Proof of principal studies have now shown that targeted treatment against NFKappaB and Bruton's Tyrosine Kinase (BTK) have activity in ABC but not GCB DLBCL, which is consistent with the molecular findings that chronic active B-cell receptor signaling and activation of NFKappaB are driver events in ABC but not GCB DLBCL.

Figure 1. GEP showing molecular GCB, ABC and PMBL DLBCL have distinct molecular profiles.



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Dr Gisselbrecht has been lead investigator of several major phase II and phase III clinical trials, which investigated the place of autologous stem cell transplantation in the treatment of lymphoma. Currently, he is chair of the international CORAL study on relapsed diffuse large B-cell lymphoma. His research interests include clinico-pathologic correlative studies in lymphoma, the pharmacology of novel antineoplastic agents, and stem cell transplantation.

Dr Gisselbrecht is an active member of several European and American scientific societies and has served as an expert with the French Agency for the Safety of Healthcare Products, as well as several cancer research agencies. He has published over 300 peer-reviewed papers and several book chapters and is on the editorial board of a number of highly respected journals.

Treatment Options for Relapsed Diffuse Large B cell Lymphoma in the Rituximab Era

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Abstract

Salvage chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) is the standard of treatment for chemosensitive relapses in diffuse large B-cell lymphoma (DLBCL). The addition of rituximab to chemotherapy has improved the response rate and failure-free survival following first-line treatment and relapses. Fewer relapses are expected, although there is no consensus on the best salvage regimen. The intergroup CORAL trial set the limits for this standard of treatment after first comparing two salvage regimens: rituximab, ifosfamide, etoposide, and carboplatin (R-ICE); and rituximab, dexamethasone aracytine and cisplatin (R-DHAP). There was no difference in response rates or survivals between these salvage regimens. Several factors affected survival: prior treatment with rituximab, early relapse (< 12 months), and secondary IPI 2-3. Moreover, patients with an ABC subtype or c-MYC translocation responded poorly to treatment. Over 70% of patients will not benefit from standard salvage therapy, and continued progress is needed. Studies evaluating immunotherapy post-transplantation, including allotransplantation, new conditioning regimens with radioimmunotherapy and other combinations of chemotherapy based on DLBCL subtypes, are discussed. Early relapses and/or patients refractory to upfront rituximab-based chemotherapy have a poor response rate and prognosis. A better biological understanding of these patients and new approaches are warranted.

Introduction

The development of rituximab, a chimeric anti-CD20 antibody, represented a revolutionary advance in the therapy of hematologic malignancies. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has produced significant survival benefits in elderly patients with untreated diffuse large B-cell lymphoma (DLCBL) compared with CHOP alone [1]. The same immunochemotherapy regimen has resulted in an improved outcome in young, low-risk patients as defined by the age-adjusted

International Prognostic Index (aaIPI) [2]. Despite these major advances, a proportion of patients will either experience early treatment failure, a partial response or a relapse after the initial chemotherapy. In this context, treatment is a major challenge. The initial approach to relapsed DLBCL management is to determine whether a patient is a candidate for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). In 1995, the PARMA trial evaluated salvage chemotherapy with a platinum- and cytarabine-based (DHAP) regimen alone or in combination with ASCT [3]. Both EFS and OS were significantly superior in the transplant group versus patients receiving chemotherapy alone. Based on these results, HDT/ASCT has become the standard of care in younger patients with chemosensitive relapsed or primary refractory aggressive lymphoma. However, in the rituximab era, the impact of chemotherapy on the final therapeutic results must be determined along with other prognostic factors. How many patients require salvage treatments, and is salvage with ASCT an efficient treatment?

Rate of relapse or failure according to aaIPI after first-line treatment with rituximab.

In young patients (less than 60 years old) with no adverse prognostic factors, the expected relapse rate is 10% [2]. In the case of only one IPI factor, the rate of relapse varies from 20% to 30% depending on whether the patient has received treatment with dose-intensive R-ACVBP (adriamycin, cyclophosphamide, vindesine and prednisone) or R-CHOP [4]. Fewer data are available for patients with 2 or 3 aaIPI factors, but the relapse rate is estimated between 25% and 35% following generally intensive treatment and ASCT [5, 6]. Finally, in patients between 60 and 70 years of age, the relapse rate was 40% in the R-CHOP study. Despite major progress, the number of patients eligible for salvage treatment and ASCT remains significant.

Salvage regimens before HDT/ASCT.

Only patients identified with a disease responsive to salvage regimens are eligible for HDT/ASCT. The addition of rituximab was expected to improve the complete remission and partial remission (CR/PR) rates and allow more patients to access HDT/ASCT. The initial studies incorporating rituximab in salvage regimens, mostly in rituximab-naïve patients, were encouraging [7, 8, 9, 10].

A clear demonstration of the impact of rituximab is provided by a prospective randomized trial exploring the potential benefits associated with the addition of rituximab to platinum-based salvage regimens. In a study conducted by the HOVON group, 239 patients with relapsed or refractory DLBCL received a salvage regimen consisting of DHAP-VIM-DHAP ± rituximab followed by ASCT [9]. The analysis of the 225 evaluable patients showed that after two courses of chemotherapy, PR/CR was obtained in 54% of the patients in the DHAP arm and 75% in the R-DHAP arm ($p \leq .01$). A marked difference in favor of the R–DHAP arm was observed at 24 months for failure-free survival, at 50% vs. 24% ($p < .001$), respectively, but not for overall survival (OS), at 52% vs. 59% ($p = .15$), respectively. However, less than 5% of the patients had previously been exposed to rituximab, in this study.

Choice of the salvage chemotherapy regimen.

The CORAL intergroup trial compared a combination therapy consisting of rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) with rituximab, dexamethasone, aracytine and cisplatin (R-DHAP). Patients who were DLBCL CD20+ at the time of the first relapse and patients remaining refractory after first-line therapy were randomized between the R-DHAP and R-ICE groups. Responding patients received BEAM and ASCT and were randomized between observation and rituximab maintenance for 1 year. An analysis was conducted on the first 396 randomized patients (R ICE: 202; R DHAP: 194) [11]. The median age was 55 years. The overall response rate was 63%; 38% of patients achieved CR. There was no difference between the response rates in the R-ICE (63.5%; CI: 56-70%) and R-DHAP (62.8%; CI: 55-69%) groups. The factors that significantly affected the response ($p < .0001$) were as follows: refractory/relapse at < 12 months, with response rates of 46 % vs. 88 %; secondary IPI >1 (52% vs. 71%); and prior exposure to rituximab (51% vs. 83%). There were no statistically significant differences between the patients achieving complete and partial remission just prior to ASCT. Patients with prior exposure to rituximab had more refractory disease and adverse prognostic factors.

Based on this first randomized study on relapses, there was no difference in the response rates and the ability to mobilize stem cells between the two commonly used regimens. A similar study under the NCIC sponsorship has been completed, comparing R-GDP (Gemcitabine, dexamethasone, platinum) to R-DHAP and results confirmed that there was no difference between GDP less toxic and RDHAP. There is obviously a need to incorporate new agents to improve the response rates of salvage regimens. Several Phase I/II clinical trials are currently under

way. For example, one trial has combined inotuzumab ozogamicin, a humanized anti-CD22 antibody conjugated to cytotoxic calicheamicin, with rituximab, gemcitabine and oxaliplatin (R Gem Ox) [12] and a other trial has added lenalidomide to various regimens, such as R-DHAP.

Relapses post autologous transplantation.

Only 206 ASCTs were performed in the CORAL study, with an dropout rate of 50%, mainly due to tumor progression [11]. Despite salvage therapy only about half of patients actually proceed to transplant, a figure that identifies one of the key limitations to current salvage practice. There was no significant difference between the R-ICE and R-DHAP groups with respect to 3-year event-free survival (EFS, 26% vs. 35%, respectively; p=.6) or overall survival (OS, 47% vs. 51%, respectively; p=.5). The three-year EFS was affected by the following factors: prior treatment with rituximab (21%) vs. none (47%; p<.0001); early relapse at < 12 months (20%) vs. >12 months (45%; p <.0001); secondary IPI 2-3 (18%) vs. 0-1 (40%; p=.0001). In the Cox model, all of these parameters were significant (p<.0001) for EFS, PFS and OS but not the treatment arm. As an early relapse (<12 months) was the main prognostic factor, we more closely examined the population with a relapse at >12 months to determine whether prior exposure to rituximab affected the outcome. At the other end of the spectrum, the population of relapsed patients with prior rituximab exposure and relapse at < 12 months had a 46% response rate with a 3-year PFS rate of 23% and a median PFS of 5 months. The same negative impact of rituximab was found in other nonrandomized studies [10].

Due to the introduction to the armamentarium of a very efficient monoclonal antibody for first-line treatment, we are now observing patients with early relapse that are more refractory to any available treatment. Currently, salvage therapy using HDT/ASCT is inefficient and requires improvement. One may even question whether it is helpful for the patients, as no randomized study has been modeled after the PARMA trial. In the EBMT registry, we found 470 relapsed DLBCL patients, but only those in complete remission after salvage and pre-ASCT were evaluated[13]. The 5-year OS rate was 63%, and the 5-year PFS rate was 48%. The duration of post-ASCT PFS was longer than that prior to ASCT in 289 patients. When each patient was used as his/her own control, PFS after ASCT was longer than PFS prior to ASCT (p<.001). This difference in favor of post-ASCT remission was significant for patients with or without rituximab exposure. In patients responding to a salvage regimen, even those in good partial remission, HDT/ASCT remains the best choice of treatment [14].

Biological characteristics of relapsing patients.

Among the 394 patients included in the CORAL study, histological material was available for a total of 249 patients at the time of diagnosis (n= 189 cases) and/or relapse (n= 147 cases). The cases were analyzed by immunohistochemistry to establish cell of origin using for CD10, BCL6, MUM1, FOXP1, and BCL2 expression and by FISH for *BCL2*, *BCL6* and *c-MYC* breakpoints [15].

When treatment interaction was tested, the GCB-like DLBCL based on Hans's algorithm was significantly associated with a better PFS in the R-DHAP arm [16]. In a univariate analysis, the presence of c-*MYC* gene rearrangement was the only parameter significantly correlated with both a worse PFS (p= .02) and a worse OS (p =.04). Of the 161 patients analyzed, 28 (17%) presented with a MYC^+ DLBCL [17]. The outcomes of patients with MYC^+ DLBCL were significantly worse than those with MYC^- DLBCL, with the 4-y PFS rate at 18% vs. 42% (p = .0322), respectively, and the 4-year OS rate at 29% vs. 62% (p = .0113), respectively. These findings underline the need to study the effects of new treatments according to DLBCL subtypes.

Post-transplantation maintenance/consolidation

After transplantation, the rate of progression in the CORAL study was 39% at 3 years. Progress should be made to prevent relapses. Post-ASCT rituximab maintenance has been evaluated as a means to reduce minimal residual disease. Two institutions have independently reported improvements in DFS and OS rates with the use of rituximab post-ASCT. [18] [19] It should be noted that there was an increased risk of prolonged neutropenia complicated by infection and hypogammaglobulinemia.

A clear answer is given in the CORAL study. Patients were randomized after transplantation to observation or rituximab given at a dose of 375 mg/m² every two months for one year [20]. The 4-year post-ASCT EFS rates were 52% and 53% for the 122 patients with rituximab and the 120 patients in the observation group, respectively (p=.7). However, the Cox model revealed that only an saaIPI of 2-3 remained significant (p<.001) for EFS, PFS, and OS. The relapse rate post-transplantation remains 40% despite adjuvant treatment with anti-CD20. The introduction of other immunomodulatory agents

constitutes an alternative that remains to be established in a randomized study.

Radio immunotherapy associated conditioning regimen.

A further attempt to develop a more effective therapeutic strategy for relapsed DLBCL patients consists of the combination of radioimmunotherapy (RIT) with standard chemotherapy regimens. After an initial report of the use of high-dose iodine-131 and ASCT [21], several studies have used myeloablative RIT with promising results. The development of radiolabeled immunotherapies such as ^{90}Y-ibritumomab tiuxetan has capitalized on the targeting ability of antibodies to deliver therapeutic doses of radiation to disseminated tumor sites with limited radioprotection. In a Phase II study, ^{90}Y-ibritumomab tiuxetan combined with BEAM was superior to a historical control in the salvage of patients with high IPI scores [22]. To further increase the therapeutic potential of RIT, a dose escalation study for ^{90}Y-ibritumomab tiuxetan with BEAM and ASCT has been performed [23]. The delivered RIT dose could safely reach 70 mCi, twice the standard dose, in 44 patients. More recently, a randomized study compared ^{90}Y-ibritumomab tiuxetan and BEAM chemotherapy versus BEAM alone in 22 and 21 patients, respectively, followed by ASCT. The two-year overall survival rates were 91% and 62% after the Z-BEAM and BEAM treatments, respectively (p=.05) [24]. The authors concluded that Z-BEAM was safe and possibly more effective than BEAM alone in the era of rituximab. Almost simultaneously, the results of the randomized comparison between two conditioning regimens were reported: rituximab BEAM versus iodine-131-tositumomab BEAM followed by ASCT [25]. For the 113 patients treated with rituxan-BEAM, the 2-year progression-free survival rate was 49%, which was similar to the 2-year PFS rate (48%) of the 111 patients treated with 131-iodine tositumomab BEAM. If new developments are to be made in this field, a regimen with a higher RIT dose or with other noncompeting antigens such as CD22 should be implemented.

Is there a place for reduced-intensity allografts?

Unlike ASCT, allogeneic SCT (alloSCT) generates an allogeneic graft-versus-lymphoma effect that reduces the likelihood of disease relapse following transplantation. It needs to be pointed out that previous studies, including the large CIBMTR report [26], suggested a very modest GvL effect (if any) in aggressive histology lymphomas. Standard myeloablative conditioning regimens were associated to unacceptable treatment related deaths and age limitations. The advent of reduced-intensity conditioning (RIC) regimens has renewed interest in alloSCT, which reduces non-relapse mortality while maintaining a graft-versus-lymphoma effect and therefore allows the treatment of elderly patients and/or patients with co-morbidities. Currently, the major role of reduced-intensity conditioning allogeneic transplantation (RIC-allo) is in the treatment of patients who have failed an autograft or in whom an autograft is not possible. Although RIC-allo has only been used for a few DLBCL patients, the results suggest that it may be beneficial. In previously published studies of RIC- allo, the rates of relapse at 2 or 3 years ranged from 33 to 79 % [27]; the stringency of patient selection is likely to be a major reason for such discrepancies. The use of RIC-allo in 48 consecutive patients with DLBCL (18 transformed from follicular lymphoma), 69% of whom had failed a previous autograft, was also reported [28], with an overall survival rate of 47% at 4 years. The French Society of Marrow Transplantation and Cellular Therapy reported 68 patients [29] who had received a median of 2 regimens of therapy prior to RIC-allo, and 54 (79%) had previously undergone ASCT. Prior to allotransplantation, 32 patients (47%) were in complete remission. With a median follow up of 49 months, the estimated 2-year OS, PFS and cumulative incidence of relapse rates were 49%, 44%, and 41%, respectively. The 1-year cumulative incidence of non-relapse mortality was 23%. Given the poor prognosis of this subset of patients when treated with conventional therapy, these results suggest that RIC-allo is an attractive therapeutic option for patients with high-risk DLBCL. The results of all of these studies can be considered encouraging and are confirmed by EBMT registry data [30]. In this study, including 101 patients who had relapsed after ASCT, the 3-year PFS and OS rates post-transplantation were 41% and 52%, respectively. A comparison of RIC and myeloablative conditioning regimens prior to alloSCT revealed no significant differences in PFS or OS. However, there was a trend of lower unrelated mortality with RIC-allo. The two main factors affecting outcome were relapses less than 12 months after ASCT and the quality of response before the transplant. Improvement of the response remains the key issue [31]. The introduction of radioimmunotherapy in a nonmyeloablative conditioning regimen has been proposed in Phase II studies [32, 33] to improve the antitumor effect without significantly increasing toxicity.

With a better definition of the prognostic factors and the poor results obtained with HDT/ASCT in early relapse, high secondary IPI, and the ABC subtype, we can now discuss whether, in the case of

a response, these patients should be transplanted directly with RIC-allo or ASCT or treated with a tandem approach of ASCT followed by RIC-allo. Nevertheless, it should be pointed out again, that RIC-allo should not be proposed to refractory patients. The evaluation of such an approach remains an unsolved challenge.

Conclusions

If the introduction of rituximab represents major progress in the treatment of B-cell lymphoma, patients failing to respond early on to rituximab combination chemotherapy generally have a poor prognosis and may be candidates for more experimental and innovative treatments or trials testing significant improvements of the existing tools. In total, only 30% of relapsed patients will benefit from HDT/ASCT. Identifying an efficient second-line treatment for DLBCL remains a key issue. Most regimens yield the same response rate, and there are no differences between the two most widely used salvage treatments, R-ICE and R-DHAP. Based on the main prognostic factors, two prognostic groups can be identified. A good-prognosis group, with an 80% response rate and a 60% PFS rate, remains accessible to standard salvage HDT/ASCT. In the second group, patients with poor prognoses, i.e., a 40% response rate and a 25% PFS rate, are candidates for alternative approaches. Any progress can be readily detected in a poor-prognosis patient. Improvements in salvage therapy will require the introduction of new drug combinations targeting the pathways involved in the biology of the different subtypes of DLCBL. Improvements in the existing situation may be directed toward the prevention of post-ASCT relapses utilizing new immunomodulators or RIC–allo, which remains experimental. Enrollment in large, randomized studies will be more problematic in the absence of significant progress in response rates.

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Chronic Myeloproliferative Disorders

Summary of presentation

"The session on myeloproliferative neoplasms (MPN) aspires to update the audience with the most recent advances in the science, prognostication and treatment of MPN as well as provide an overview on disease classification and contemporary diagnosis."

Ayalew Tefferi

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1978	B.S. Mathematics	M.I.T.
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1984-86	Internal Medicine	Brigham & Women's Hospital, Boston
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Licensure and Certification:

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1984-present	Massachusetts Medical License #56147
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PROFESSIONAL APPOINTMENTS:

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1989-1991	Instructor in Medicine	Harvard Medical School
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1998-2003	Associate Prof. of Genetics	Harvard Medical School
2003-present	Professor of Medicine	Tufts University School of Medicine
2003-2007	Leader, Hematologic Malignancies Program	Molecular Oncology Research Institute Tufts Cancer Center
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1989-2003	Physician	Hematology Division, Department of Medicine, Brigham & Women's Hospital
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1988-1991	Visiting Scientist	Whitehead Institute for Biomedical Research
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2007-present	Scientific Advisory Board	Cephalon Oncology
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AWARDS AND HONORS:

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1978	Phi Beta Kappa
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REPORT OF RESEARCH:

Major Research Interests

Function and regulation of the c-ABL protein; mechanisms of leukemogenesis by BCR-ABL and other tyrosine kinases; identification of novel therapeutic strategies for human Philadelphia-positive leukemia; molecular pathogenesis of myeloproliferative diseases; preclinical assessment of targeted therapeutic agents for hematologic malignancies

Narrative Description of Research

The Van Etten laboratory studies the pathogenesis and therapy of human blood cancers, with particular emphasis on myeloid and lymphoid neoplasms that are associated with dysregulated tyrosine kinases. Their original focus was on the pathogenesis of chronic myeloid leukemia (CML), which is caused by the product of the Philadelphia (Ph) chromosome, the BCR-ABL fusion tyrosine kinase. Two major approaches were taken: (1) the study of the c-*ABL* gene products, their functional roles, localization, and regulation; (2) expression of oncogenic *ABL* genes in the hematopoietic system of mice.

c-ABL is a non-receptor protein-tyrosine kinase localized to the nucleus and cytoskeleton whose normal function is unknown. For c-ABL, we characterized its nuclear localization signals (Wen et al., 1996) and actin-binding domains (Van Etten et al., 1994), and identified novel oncogenic ABL mutations that suggested a Src-like autoinhibitory regulatory mechanism (Brasher et al., 2001), which was confirmed by biochemical studies of purified ABL (Brasher and Van Etten, 2000). We demonstrated that c-ABL was dysregulated by a chemical dimerizer (Smith and Van Etten, 2001), identified the peroxiredoxin Prdx1 as a potential cellular inhibitor of ABL (Wen and Van Etten, 1997), and showed that Prdx1-deficient mice developed hemolytic anemia and multiple malignant cancers (Neumann et al., 2003). We discovered that a mutation in the ABL P-loop dysregulated c-ABL and conferred intermediate resistance of c-ABL and BCR-ABL to the kinase inhibitor imatinib (Roumiantsev et al., 2002). Our current work focuses on elucidating the functional roles of ABL and Prdx1 and the regulatory mechanisms involved, employing both a direct biochemical approach with purified proteins and genetic approaches with mutants and knockout mice and cells.

In parallel studies, we developed methods for the expression of BCR-ABL in bone marrow of mice by *ex vivo* retroviral gene transfer and bone marrow transplantation, demonstrated efficient induction of CML-like leukemia in recipient mice, and compared the leukemogenic activity of the three principal isoforms of BCR-ABL, p190, p210, and p230 (Li et al., 1999). We utilized the model to characterize signaling pathways required for BCR-ABL leukemogenesis in vivo, including the ABL SH2 domain (Roumiantsev et al., 2001), myeloid cytokines (Li et al., 2001b), and Stat5. We defined a BCR Tyr177-Grb2-Gab2 pathway (Li et al., 2001a; Million and Van Etten, 2000), leading to activation of SHP2 and Akt, which is absolutely required for CML pathogenesis (Sattler et al., 2002). We showed that BCR-ABL, like c-ABL, was autoinhibited through its SH3 domain (Smith et al., 2003). We demonstrated that Src kinases contributed to BCR-ABL-induced B-lymphoid leukemia but not CML (Hu et al., 2004). In other studies, we developed a mouse model of adoptive immunotherapy for CML (Krause and Van Etten, 2004), and investigated pathways of CML leukemic stem cell homing and engraftment, implicating donor CD44 and recipient E-selectin in this process (Krause et al., 2006). Parallel studies of leukemia pathogenesis were carried out on TEL-ABL (Million et al., 2002; Million et al., 2004) and FGFR1 fusion proteins (Roumiantsev et al., 2004), and on the JAK2 V617F mutant kinase found in non-CML myeloproliferative diseases (Zaleskas et al., 2006). We are currently utilizing this system and other technology such as transgenic mice to develop a molecular understanding of the leukemias induced by these genes, to identify signaling pathways and potential drug targets critical for leukemogenesis, and as a platform for the development and preclinical testing of new treatments, including immune therapies and molecularly targeted drugs.

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Molecular Pathogenesis of the Ph-negative Myeloproliferative Neoplasms: An Update

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Abstract

Since the discovery of somatic mutations in JAK2 in 2005, the subsequent eight years have witnessed substantial and rapid progress in our understanding of the molecular pathogenesis of the *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs). Dysregulated JAK2 signaling has emerged as a central pathognomonic feature of these diseases, but genetic analysis has revealed unexpected complexity as well. Mouse models of the MPNs have been useful in dissecting the critical signaling pathways underlying the MPNs. Future progress in this area should lead to improvements in diagnosis and therapy of the Ph^- MPNs.

Introduction

The cardinal features of the MPNs, as first formulated by William Dameshek [1] and subsequently by many others, include clonal hematopoiesis involving the hematopoietic stem cell, cytokine hypersensitivity leading to overproduction of mature myeloerythroid cells, variable tendency to progress to acute myeloid leukemia, and abnormalities of hemostasis and thrombosis. This review will highlight our current understanding of the molecular underpinnings of the MPNs, with the majority of the focus on polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis. It has been know for many years that patients can develop myelofibrosis (MF) following PV or ET, and to date there is no strong clinicopathological evidence that this condition differs significantly from patients presenting de novo with MF, so they will be discussed together here.

JAK2 mutations and JAK2 signaling in MPNs

The cardinal pathophysiological feature underlying the MPNs appears to be dysregulated JAK2 signaling. We now understand that this dyregulation can be either due to direct, activating mutations in JAK2 itself, or though other mechanisms. The majority of patients with PV, and about half of those with ET and MF, have the canonical mutation in exon 14 of the *JAK2* gene that leads to substitution of Phe for Val at position 617 in the pseudokinase (JH2) domain [2]. Of those PV patients without the $JAK2^{V617F}$ mutation, about half have mutations in exon 12 of *JAK2* [3], and often present with isolated erythrocytosis. Hence, virtually every patient with PV has mutant JAK2.

Although a complete structure of the JAK2 kinase is lacking, molecular modeling based on other JAK kinases indicates that the Val617 is located at a point of contact between the pseudokinase domain and the catalytic (JH1) domain, and the substitution of Phe is presumed to relieve the negative regulation of phosphotransferase activity imposed by this interaction. Recent studies have also shown that the JAK2 pseudokinase domain has intrinsic dual-specificity autokinase activity and contributes to negative regulation of the JH1 domain through phosphorylation of JAK2 Ser523 and Tyr570 [4]. Tyr570 phosphorylation is reduced in the $JAK2^{V617F}$ mutant, suggesting that the catalytic activity of JH2 functions in part to control basal activity of JAK2.

For those MPN patients who lack JAK2 mutations, the evidence that dysregulated cytokine signaling mediated by JAK2 is critical to disease pathogenesis comes from genetic, cell biological, and clinical studies. The genetic evidence emerged from discovery of activating mutations of MPL, the receptor for thrombopoietin, in a small number (5-7%) of patients with ET and MF (but not PV). Mutation of Trp515 to several amino acids, including Leu, Lys or Ala, disrupts an autoinhibitory juxtamembrane domain of MPL and causes constitutive signaling, mediated by JAK2 [5]. The cellular evidence comes from the observation that many MPN patients lacking JAK2 mutations nonetheless have endogenous erythroid colonies (EEC), defined as erythroid colonies that grow in methylcellulose in the absence of exogenous erythropoietin (EPO). These EEC are

prima facie evidence of autonomous erythropoiesis and of cytokine signaling dysregulation. The clinical evidence originates from the observation that MF patients without JAK2 mutation nonetheless responded to JAK2 inhibitors [6]. Collectively, these findings emphasize the concept that the cytokine signaling pathway through JAK2 is universally activated in the MPNs.

What then is the pathophysiological basis of the remaining MPNs that are not defined by *JAK2* or *MPL* mutations? There are a significant number of gene products involved in the regulation of the cytokine receptor-JAK-STAT signaling pathway, and through multiple studies virtually all the relevant candidate genes have sequenced and assessed for mutations. The overall yield of this effort has been disappointingly low. Inactivating mutations have been identified mutations in LNK and CBL, both negative regulators of JAK2 signaling, in small numbers of MPN patients [7,8]. However, mutations in other JAK family kinases, STAT transcription factors, or other cytokine receptors are not found. It is anticipated that whole genome sequencing of these MPN patients may provide some insights into this question.

Mutations in epigenetic regulators in MPNs

Epigenetic changes are heritable alterations in gene expression that are not associated with changes in the DNA sequence of the respective genes. Epigenetic regulation of gene expression occurs either through methylation of CpG dinucleotides, or modification of nucleosomal histones, principally histone H3. A major emerging story in MPN pathogenesis is the discovery of mutations in genes implicated in epigenetic regulation. *TET2* is a gene encoding an enzyme that converts 5-methylcytosine to 5-OH-methylcytosine, part of a metabolic pathway of cytosine methylation whose precise physiological role is as yet unknown. Heterozygous loss-of-function mutations in *TET2* are found in MPNs and other myeloid and lymphoid neoplasms [9,10]. Inactivation of *Tet2* in mouse bone marrow leads to increased hematopoietic stem cell (HSC) self-renewal and myeloid transformation [11,12]. Interestingly, somatic mutations in *TET2* are also found at significant frequency in older healthy adults with clonal hematopoiesis [13], further supporting the hypothesis that loss of TET2 confers a competitive advantage to HSC without causing overt transformation or disease.

Mutations in several other epigenetic regulators have also been described in MPNs. *DNMT3a* mutations are most frequent in AML (12–22%) and post-MPN AML (8–15%), but are also found in chronic-phase MPNs, including in 10–15% of MF patients and 5–7% of PV patients [14]. *Dnmt3a* knockout mice have a striking expansion of HSC number and function as assessed by serial transplantation [15]. Inactivating mutations in ASXL1 and EZH2 [17] are also found in MPNs, predominantly in MF. EZH2 is a catalytic component of the polycomb repressor complex 2, a histone methyltransferase that modulates expression of homeotic genes in development and hematopoiesis, while ASXL1 is a chromatin modifier whose function is not clear.

Direct connections between JAK2 signaling and epigenetic regulation in MPN have also emerged from two different experimental directions. A fraction of JAK2 is nuclear and directly phosphorylates Tyr41 on histone H3, blocking the binding of the chromatin regulator HIP1alpha [18]. JAK2 also phosphorylates PRMT5, an arginine methyltransferase, impairing its ability to methylate histones. Knockdown of PRMT5 in human $CD34^+$ cells increased colony formation in methylcellulose and erythroid differentiation in liquid culture, while overexpression of wild-type PRMT5 decreased hematopoietic colony formation [19].

While mutations in epigenetic regulators are found with considerable frequency in the MPNs, their precise role in the pathogenesis of these diseases and in other myeloid neoplasms is as yet unclear [20,21]. The mutations tend to be mutually exclusive and associated with inferior clinical prognosis. Studies in mutant mice suggest a common effect on HSC self-renewal and perturbation of myeloid differentiation, but the fact that most mutations are loss of function suggests that this will be a challenging area for targeted therapies.

Genetic and clonal analysis in MPNs indicates a complex pathogenesis

Expression of the $JAK2^{V617F}$ allele in mouse bone marrow recapitulates the entire spectrum of PV, including erythrocytosis, increased red cell mass, progression to MF, and abnormalities of platelet function [22,23], strongly suggesting that it is the direct cause of PV in patients. However, analysis of individual hematopoietic colonies from MPN patients has shown that the clonal hierarchy of the disease can be highly diverse between individual patients, with no strict temporal order in the acquisition of mutations. *TET2* mutations and deletions of chromosome 20q have been found to often precede *JAK2* mutation, but the opposite order is also observed [24,25]. Furthermore, some $JAK2^{V617F}$–positive patients transform to AML that

is *JAK2*^{V617F}–negative. Studies of numerous families where two or more members develop diverse MPNs have provided strong evidence for a gene or genes that predispose individuals to develop MPN [26], but the *JAK2*^{V617F}–positive mutation has not been found in the germline (although several other mutant *JAK2* alleles can be inherited in families with hereditary thrombocytosis [27]). To date, linkage analysis has not identified any candidate predisposition genes in these pedigrees. Finally, there is a remarkable effect of a common polymorphism in the non-coding region of the JAK2 gene, denoted 46/1 or GGCC, such that acquisition of the JAK2 mutation in MPN patients preferentially occurs on this allele [28,29]. The overall penetrance of this effect is, of course, very low, and the mechanism involved is unclear, although most evidence favors a functional difference that confers a selective advantage when JAK2 is mutated ("fertile ground").

Determinants of phenotype in *JAK2*^{V617F}-positive MPNs

One of the major unresolved questions in the MPN field is reason that some V617F-positive patients develop PV whereas others develop ET or other myeloid disorders. There is clear evidence that has emerged from human and mouse modeling studies that one determinant appears to be the strength of JAK2 signaling, as homozygosity for the JAK2 V617F mutation is common in PV and MF but uncommon in ET, an effect that is even more pronounced upon clonal analysis of single hematopoietic colonies [30,31]. In *JAK2*^{V617F} transgenic mice, there is also some correlation between JAK2 expression level and MPN phenotype, with higher levels favoring PV-like and lower levels favoring ET-like disease (reviewed in [32]). However, this cannot be the only determinant, as many PV patients have lower allele burdens than patients with clinical ET. Presumably, differences in genetic background or other somatic mutations may contribute. Recent studies have also suggested that interferon signaling in hematopoietic progenitors may affect the MPN phenotype, with the ratio of STAT1 to STAT5 activation playing a key role [33]. It is not clear whether these differences in STAT activation are acquired or partially inherited.

Molecular basis for response to JAK2 inhibitor therapy in MPNs

One of the central questions in contemporary MPN research is why JAK2 inhibitors are so different from ABL1 inhibitors, which are very effective at decreasing the *BCR-ABL1* allele burden in CML patients and in mouse models. Levine and colleagues recently described heterodimeric JAK1-JAK2 and TYK2-JAK2 complexes in cell lines selected for cross-resistance to multiple JAK2 inhibitors and in granulocytes from patients treated chronically with ruxolitinib on clinical trials [34]. For unclear reasons, although ruxolitinib is a potent JAK1 inhibitor, inhibition of the JAK1-JAK2 complex by ruxolitinib *in vitro* was inefficient, and the authors proposed that such heterodimeric JAK complexes may contribute to persistence of *JAK2*^{V617F}–positive cells in treated patients.

Although interesting, several features of this model are difficult to reconcile. First, it is clear that JAK2 inhibitors dramatically reduce the total burden of *JAK2*^{V617F}–positive cells in both mice and patients, as the spleens are returned to near normal size, but some physiologic response prevents further specific reduction in the malignant cells with continued treatment. Calling this persistence may beg the question, as the production of *JAK2*^{V617F}–positive neutrophils in ruxolitinib-treated patients is nearly normal and represents an enormous and ongoing proliferation of malignant cells in the marrow. Second, it is unclear what stimulus triggers formation of the active heterodimeric JAK complexes, as no difference in total JAK1-JAK2 heterodimers is observed in treated patients, only an increase of phospho-JAK2 in the complex [34]. As an alternative view, the difference between JAK2 and ABL1 as TKI targets might lie in the fact that ABL1 is not required for myelopoiesis [35] while JAK2 is absolutely required for both erythropoiesis and platelet production. Of interest is the fact that none of the current JAK2 inhibitors is selective for JAK2^{V617F} over endogenous JAK2, and that the IC_{50} of these inhibitors against erythroid progenitors is dependent on the ambient EPO concentration. Hence, one possibility is that, as cytoreduction occurs in response to JAK2 inhibitor therapy, a compensatory increase in EPO and EPOR signaling limits any further reduction in the *JAK2*^{V617F} malignant clone.

Conclusions and future directions

The Ph-negative MPNs have served as a paradigm for our understanding of hematologic malignancies, and as an example of how this understanding can lead to improved treatments. However, the unexpected genetic and epigenetic complexity of MPNs may account, along with other factors, to the relatively modest clinical efficacy of JAK2 inhibitors compared with targeted therapy in CML (see discussion by Dr. Tefferi later in this session). We can expect that additional mutations will be identified

in these MPNs, including perhaps novel disease-initiating mutations through whole genome sequencing of patients and MPN pedigrees. The challenge for the future will be to develop a better molecular understanding of how these genetic and epigenetic abnormalities interplay to determine MPN phenotype and prognosis, and leverage this information toward improved treatment for our MPN patients.

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International Prognostic Scores models (IPSET) in Essential Thrombocythemia Diagnosed by WHO Criteria

Tiziano Barbui, MD

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Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) are chronic myeloproliferative neoplasms (MPN) characterized by clonal expansion of an abnormal hematopoietic stem/progenitor cell. The natural history of these chronic myeloproliferative neoplasms (MPN) is marked by thrombo-hemorrhagic complications and a propensity to transform into myelofibrosis and acute leukaemia. Understanding their pathophysiology dramatically improved following the description in 2005 the V617F mutation in *JAK2* exon 14 that is the most frequent and involves >95% of PV and ≅60-70% of ET and PMF patients. It is to be recalled that previous prognostic studies had relied on the Polycythemia Vera Study Group (PVSG) criteria for diagnosis and did not distinguish true ET from prefibrotic MF, as established by the WHO diagnostic criteria for MPN.[1] Furthermore, current conventional risk factors for thrombosis are based on relative risk estimates such as odds ratio, risk ratio, or hazard ratio (HR) so that no direct meaning or relevance to prognostication of thrombosis in individual patient can be drawn.

Background for a new Prognostic Score in Essential Thrombocythemia

It is widely accepted that in ET age and previous thrombosis are independent single risk factors for new major vascular events and on this basis, patients are now stratified in low-risk and high-risk of events.[2]

In contrast, there is still much controversy about the role played by other possible predictors, such as leukocytosis, JAK2V617F mutation status and generic vascular risk factors (diabetes, hypertension, smoking).[2] Given the variability among ET patients in the clinical and hematologic presentation and treatment of the disease, a single predictor or variable, rarely gives an adequate estimate of thrombotic prediction in individual patient or groups. In contrast, a more reliable and consistent prediction of thrombotic risk may be provided by combining multiple variables in prognostic models. However, to show that a prognostic model is valuable, it is not sufficient to show that it successfully predicts outcome in the initial development data. Validation of prognostic models, either internally (using the same data) or externally (using different

data), is essential to understand the reliability of the model. Clearly, these validation cohorts should be comparable with the training cohort in terms of diagnosis, demographic characteristics, treatments and the sample size should be powered enough to allow a sufficient number of events for the analysis. Notably, the predictive performance or accuracy of a model may be adversely affected by poor methodological choices or weaknesses in the data.[3]

The IPSET-thrombosis model

The main objective of IPSET-thrombosis model[4] is to determine the probability of major vascular complications in a well-defined population of WHO-defined ET patients. It is to be recalled that previous prognostic studies had relied on the PVSG criteria for diagnosis and did not distinguish true ET from prefibrotic MF. Furthermore, current conventional risk factors for thrombosis are based on relative risk estimates such as odds ratio, risk ratio, or hazard ratio (HR) so that no direct meaning or relevance to prognostication of thrombosis in individual patient can be drawn. Accordingly, the aim of IPSET-thrombosis score was to construct an accurate prediction model for thrombosis, from multiple variables predicting thrombosis in an inception multicenter cohort of 891 strictly WHO- defined ET patients, and to validate its performance internally and externally in new cohorts of comparable patients. Under the auspices of the International Working Group for MPN Research and Treatment (IWG-MRT) we have addressed the prognostic relevance of distinguishing early/prefibrotic PMF associated with thrombocytosis from ET. A clinicopathologic database of patients previously diagnosed as having ET (*n*=1104) and for whom treatment-naïve BM specimens obtained within one year of diagnosis were available, underwent a central re-review.[5] Diagnosis was confirmed as ET in 891 patients (81%) and revised to early/prefibrotic PMF in 180 (16%); 33 cases were not evaluable. Ten/15-year survival (76%/59% vs. 89%/80%), leukemic transformation (5.8%/11.7% vs. 0.7%/2.1%) and progression to overt myelofibrosis (12.3%/16.9% vs. 0.8%/9.3%) rates were significantly worse in early/prefibrotic PMF vs. ET; the respective death, leukemia and overt myelofibrosis incidence rates per 100 patient-years were 2.7% vs. 1.3% (RR=2.1, p=0.0002), 0.6% vs. 0.1% (RR=5.2, p=0.001) and 1% vs. 0.5% (RR=2.0, p=0.04). Multivariable analysis confirmed these findings and also identified age >60 years (HR=6.7), leukocyte count >11x10^9/L (HR=2.01), anemia (HR=2.95), and thrombosis history (HR=2.81) as additional risk factors for survival. Thrombosis and *JAK2*V617F incidence rates were similar between

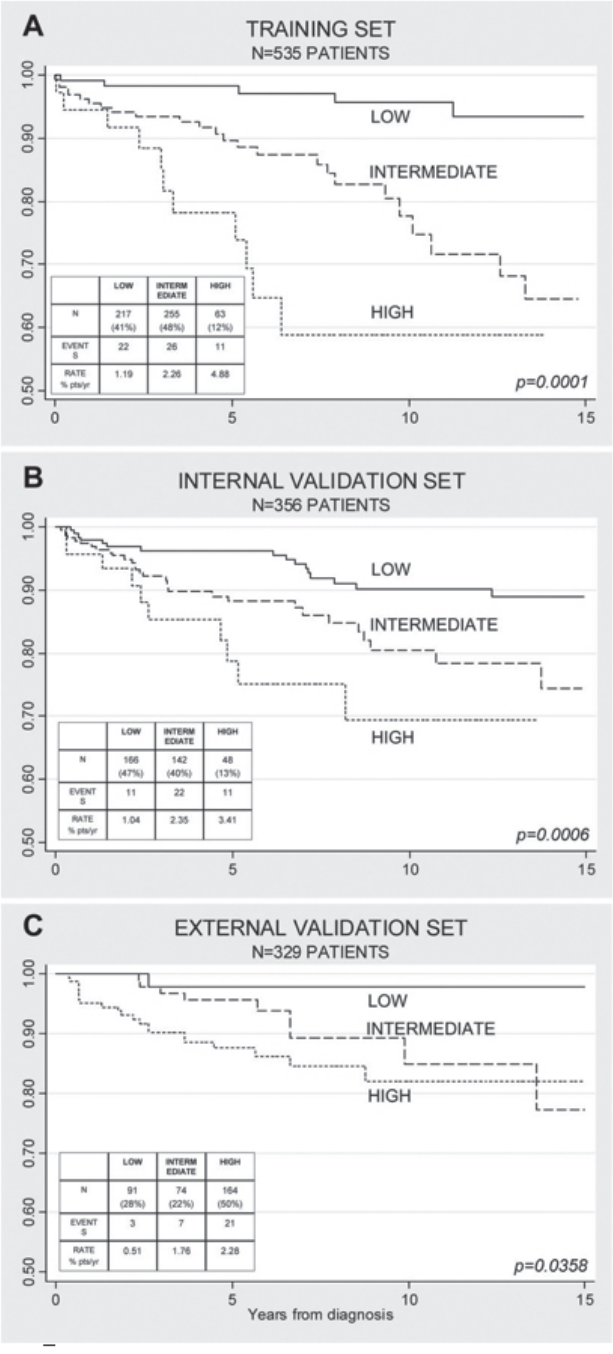

Figure 1. Thrombosis-free survival curves. Shown are survival curves according to the International Prognostic Score for Essential Thrombocytopenia (IPSET) thrombosis model in the training set (A), internal validation set (B) and external validation set (C).

the two groups. Survival in ET was similar to sex- and age-standardized European population while it was worse in early-PMF.

In multivariable Cox regression analysis, predictors of total major thrombotic events of IPSET cohort included age more than 60 years (P=0.049;

hazard ratio [HR]=1.5), thrombosis history (P=0.002; HR=1.93), cardiovascular risk factors (including tobacco use, hypertension, or diabetes mellitus (P=0.038; HR=1.56) and presence of JAK2V617F (P=0.009; HR=2.04).4 To each of these factors, an integer weight close to the corresponding HR resulting from the analysis was assigned . On the basis of these score values, patients were divided in low (sum of score=0), intermediate (sum of score=1-2) and high (sum of score=>3) risk category. Kaplan-Meier analysis of thrombosis-free survival showed a significant different pattern (p=0.0001). Low-risk patients (25%) (younger than 60 years, asymptomatic, without CV risk factors and JAK2V617F negative) had a probability of thrombosis free survival approaching to 90% and a rate of events of 0.43% pts/year. The majority of patients (63%) presented a sum of scores of 1-2 and an intermediate rate of events of 1.9% per year. In contrast, the high risk group (12%) including patients with a score of ³3, had the highest rate of events calculated 4,88%/ patients per year, a figure comparable to the average rate of patients with Polycythemia Vera. (Figure 1). The predictive accuracy of the training set was validated in internal and external new data set patients, allowing to confirm its generalisability. Practical implications of adopting this model need consensus and impact studies

The IPSET-survival model

The IPSET-survival model[6] is based on three parameters: age equal to or greater than 60 years, history of thrombosis and leukocyte count equal to or higher than 11 x 10^9/L. Age over 60 years was recognized as a risk factor for survival in large cohorts of ET patients. This study confirms previous observations on the association between leukocytosis and worse survival in ET.[10,12,16] Although all these factors should ideally be assessed in a prospective study, the IPSET model undoubtedly states that leukocytosis higher than 11 x10^9/L is a predictor of survival as well as history of thrombosis. The IPSET database also allowed to study the predictive role of *JAK2* (V617F) mutation in 690 WHO-ET with assessed mutational status (61% V617F-positive). Concerning survival, we did not find any association between the presence of the mutation and outcome: although *JAK2* (V617F) is a risk factor for thrombosis, thrombosis accounts only for half of the causes of death; other causes have likely a lower association with the presence of the mutation.

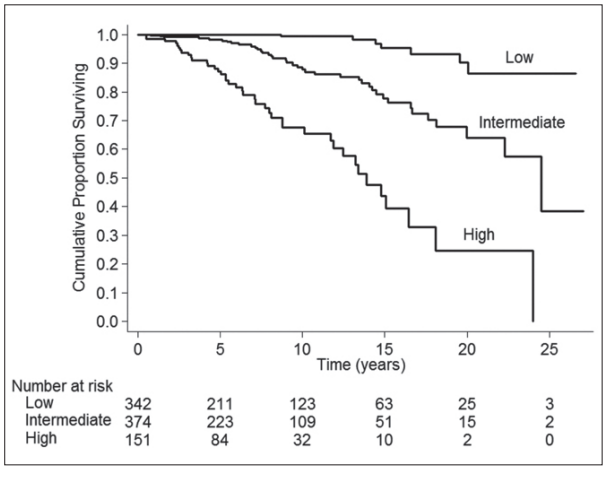

Figure 2. Estimate of survival of 867 patients with essential thrombocythemia, by IPSET score. Three risk factors were taken into account: age ≥ 60 years (2 points), leukocyte count ≥ 11 × 109/L (1 point) and prior thrombosis (1 point). The resulting risk categories were low (sum of scores = 0), intermediate (sum of scores = 1 or 2), and high (sum of scores = 3 or 4) with significantly different survivals: not reached in low-risk patients, 24.5 years (95% CI: 22.3-NR) in intermediate risk, and 14.7 years (95% CI: 11.9-18) in high-risk patients.

IPSET-survival model was validated in two independent samples of patients from Europe. One set (Cologne cohort) included patients with ET strictly diagnosed according to the WHO criteria and we found that IPSET-survival stratifies patients into three risk categories with different survivals (Figure 2). This finding demonstrates that IPSET is useful in survival prediction of WHO-ET patients and may be applied in the case of diagnosis made according to WHO. The difference in terms of median survival between the IPSET and the Cologne cohort might be explained by the different sample of patients. A further external validation in a second set (Dijon cohort) included patients with diagnosis of ET performed outside of the WHO criteria. Median survivals of these patients are lower than those of the IPSET database, probably due to the inclusion of patients with early phase PMF, known to have worse survival. Hence, the validation process showed that the IPSET-survival model stratifies all patients with ET independently from the type of diagnostic classification applied. All this makes the IPSET model universally applicable in all patients phenotypically presenting as ET.The international database used for the IPSET model reflects the current clinic practice in the EU and US and defines what doctors may expect from current treatments in WHO-ET. Most patients who are at low and intermediate risk at diagnosis have a long survival especially if cardiovascular risk factors are absent or controlled. Patients at high risk, i.e. patients aged over 60 years with leukocytosis or with history of thrombosis, have a median survival of 14.7 years. Defining survival in diseases known to be long lasting as ET is clinically relevant for patient-doctor communication, for treatment strategy and for enrollment criteria of clinical trials.

Progression to acute leukemia (AML) in WHO-ET

Reassuring data from the IPSET international data base, are the low prevalence of AML calculated around 1%.[6] Baseline leukocytosis had a borderline impact on AML occurrence as the consequence of the "myeloproliferative phenotype" that may expose patients to higher risk of evolution and probably more prescription of therapy. However, the IPSET database did not show any relationship with cytotoxic therapy use, indicating a relative safety of current therapies at least in the short term (median time of observation: 6.2 years). evolution,

Risk factors for bleeding in essential thrombocythemia or prefibrotic myelofibrosis

In the same IWG.MRT data base of 1,104 patients with essential thrombocythemia (ET), risk factors for major bleeding were determined and compared in the categories of patients classified as ET(n= 891) and early-PMF(n=180) respectively.[7] Major bleeding during follow-up occurred in 55 (6%) WHO-ET and 21 (12%) PMF patients (p=0.009), with a rate of 0.79 and 1.39% patient-years, respectively (p=0.039). In multivariable analysis, predictors of bleeding included diagnosis of PMF (p=0.05; HR 1.74), leukocytosis (p=0.04; HR 1.74), previous hemorrhage (p=0.025; HR 2.35) and aspirin therapy (p=0.001; HR 3.16). The analysis restricted to patients with WHO-ET confirmed previous hemorrhage (p=0.043; HR 1.92) and aspirin (p=0.027; HR 2.24) as independent risk factors. The current study reveals that major bleeding associated with thrombocytosis might be relatively specific to PMF, as opposed to WHO-defined ET. Furthermore, it shows that low-dose aspirin exacerbates these hemorrhagic events of PMF. In contrast thrombocytosis *per se* was not a risk factor for bleeding: however, low-dose aspirin had a synergistic hemorrhagic effect unmasking the bleeding tendency of patients with extreme thrombocytosis. These observations carry significant therapeutic implications in these two WHO entities.

Conclusion

By combining novel risk factors selected on the basis of their independent value to predict events, IPSET models have been constructed and have shown accuracy in the prediction of thrombosis and survival in WHO-ET patients. Clinical implications refer to make clinical decisions for individual patients and to create clinical risk groups by disease severity in clinical trials.

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4. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood. 2012;120(26):5128-33.
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CURRICULUM VITAE

Ayalew Tefferi, MD

PERSONAL INFORMATION

Work Address:

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PRESENT ACADEMIC RANK AND POSITION

Consultant - Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota	07/01/1989 - Present
Professor of Medicine - College of Medicine, Mayo Clinic	07/01/2001 - Present

EDUCATION

University of Athens Medical School MD, Medicine	1975 - 1982
St. Joseph Hospital, Chicago, IL Residency, Internal Medicine	1983 - 1986
Mayo Graduate School, College of Medicine, Mayo Clinic Fellowship, Hematology	1986 - 1989

BOARD CERTIFICATION(S)

American Board of Internal Medicine (ABIM) Diplomate in Internal Medicine	1987
Diplomate in Internal Medicine	1988

LICENSURE

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HONORS/AWARDS

William Summerskill Award - Mayo Medical Center, Mayo Clinic Rochester Centers	01/1989
Dean's Recognition Award - Mayo Medical School	01/1999

PREVIOUS PROFESSIONAL POSITIONS AND MAJOR APPOINTMENTS

Assistant Professor of Medicine - College of Medicine, Mayo Clinic	07/01/1989 - 06/30/1997
Associate Professor of Medicine - College of Medicine, Mayo Clinic	07/01/1997 - 07/01/2001

PROFESSIONAL & COMMUNITY MEMBERSHIPS, SOCIETIES AND SERVICES

Professional Memberships & ServicesAmerican Federation for Clinical Research	Member
American Medical Association	Member
American Society of Hematology	Member
Central Society for Clinical Research	Member
Eastern Cooperative Oncology Group	Member
Minnesota Medical Association	Member
North Central Cancer Treatment Group	Member
Zumbro Valley Medical Society	Member

JOURNAL RESPONSIBILITIES

Journal Other Responsibilities

American Journal of Hematology	Reviewer
Blood	Reviewer
European Journal of Haematology	Reviewer
Experimental Hematology	Reviewer

EDUCATIONAL ACTIVITIES

Curriculum/Course Development

First year Hematopoietic Course Mayo Medical School Rochester, Minnesota	01/1991 - Present

Teaching

1st Year Hematopoietic Course Chairman Mayo Medical School Rochester, Minnesota	01/1989 - Present
Chronic Lymphocytic Leukemia-1992:Diagnosis, Prognosis, Treatment Medical Grand Rounds Mayo Clinic Rochester, Minnesota	03/1992
Porphyria Clinical Chemistry Seminar Mayo Clinic	

Rochester, Minnesota 09/1993

The Management of Chronic Granulocytic Leukemia
International Symposium of Myeloproliferative Disorders
Rochester, Minnesota 10/1994

Proliferative Disorders of Large Granular Lymphocytes: T-LGL, NK-LGL, TCUS?
Medical Grand Rounds
Mayo Clinic
Rochester, Minnesota 04/1995

Vitamin B12 Deficiency: a new look at an old problam
Practice of Internal Medicine - 1996
Rochester, Minnesota 04/1996

Pulmonary Complications of Bone Marrow Transplantation
Cardiothoracic Transplant Conference
Mayo Clinic
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CLL - - Is it now Curable?
Practice of Internal Medicine -- 1997
Rochester, Minnesota 05/1997

Chronic Myelogenous Leukemia: Recent Advances in Diagnosis and Treatment
Medical Grand Rounds
Mayo Clinic
Rochester, Minnesota 07/1997

Pulmonary Complications of Bone Marrow Transplantation
Mayo Alumni Association
Mayo Clinic
Rochester, Minnesota 10/1997

Chronic Leukemias
CRA/Nurse workshop
North Central Cancer Treatment Group
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Current Therapeutic Approaches for Myeloproliferative Disorders
Oncology Society
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Erythromcytosis and Polycythemia Vera
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Erythrocytosis and Polycythemia Vera
Practice of Internal Medicine-1998
Mayo Clinic
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Therapeutic approaches in the myeloproliferative diseases
Practical Diagnostic Hematopathology: Peripheral blood and bone marrow
Mayo Clinic
Rochester, Minnesota 06/1998

Thrombopoietin: Clinical Usage
Fourth Annual Mayo Multidisciplinary Symposium on Platelets, Blood Vessels, and Extracorporeal Medicine
Mayo Clinic
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New Therapeutic Approaches For CLL
Practice of Internal Medicine, 1999
Mayo Clinic
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Acute Respiratory Distress Syndrome After Bone Marrow Transplantation
Mayo Thoracic Society Lecture
Mayo Clinic
Rochester, Minnesota 11/1999

Iron Overload Disorders: When and how to screen
Practice of Internal Medicine-2000
Mayo Clinic
Rochester, Minnesota 05/2000

Thrombocytosis and Essential Thrombocythemia
Mayo Regional Visiting Faculty Program
Grand Rapids, Michigan 05/2000

Porphyrias
Practical Diagnostic Hematopathology: Non-neoplastic hematologic diseases with emphasis on red blood cell disorders
Mayo Clinic
Rochester, Minnesota 06/2000

Secondary thrombocytosis
Practical Diagnostic Hematopathology: Non-neoplastic hematologic diseases with emphasis on red blood cell disorders
Mayo Clinic
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Porphyrias
Practical Diagnostic Hematopathology: non-neoplastic hematologic diseases with emphasis on red blood cell disorders
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Secondary thrombocytosis
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Honors and Awards for Education

Teacher of the Year - Department of Internal Medicine, Mayo Clinic 01/1992

Teacher of the Year - Mayo Medical School 01/1992

Teacher of the Year - Department of Internal Medicine, Mayo Clinic 01/1994

Teacher of the Year - Department of Internal Medicine, Mayo Clinic 01/1995

Teacher of the Year Hall of Fame - Department of Internal Medicine, Mayo Clinic 01/1995

Distinguished Mayo Medical School Service Award - Mayo Medical School 01/1996

Teacher of the Year - Mayo Medical School 01/1996

Department of Medicine Medical School Education Award - Mayo Medical Center, Mayo Clinic Rochester Centers 01/2000

Teacher of the Year - Mayo Medical School 01/2001

INSTITUTIONAL/DEPARTMENTAL ADMINISTRATIVE RESPONSIBILITIES, COMMITTEE MEMBERSHIPS AND OTHER ACTIVITIES

Mayo Clinic
Department of Education Services
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Mayo Medical School
Organ Unit Curriculum Committee
Member 01/1992 - Present

Mayo Clinic Committees

Acute Leukemia Study Group
Member 01/1989 - Present

Bone Marrow Transplant Committee
Member 01/1990 - Present

Chronic Lymphocytic Leukemia Study Group
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Mayo Clinic in Rochester

Department of Internal Medicine
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Education Committee
Member 01/1989 - Present

Resident Evaluation Committee
Member 01/1994 - Present

Mayo Medical Center
Human Genomics Education Committee
Member 01/2000 - Present

William J von Liebig Transplant Center
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Myeloproliferative Neoplasms 2014

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Introduction

BCR-ABL1-negative myeloproliferative neoplasms include primary myelofibrosis (PMF), polycythemia vera (PV) and essential thrombocythemia (ET) and are characterized by stem cell-derived clonal myeloproliferation. PMF is associated with abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis (EMH), constitutional symptoms, leukemic progression and shortened survival. PV and ET are respectively associated with erythrocytosis and thrombocytosis while other disease features include leukocytosis, splenomegaly, thrombohemorrhagic complications, vasomotor disturbances, pruritus and a small risk of leukemia or fibrotic progression.

Contemporary diagnosis

i. PMF:
The presence of bone marrow fibrosis, *JAK2/MPL* mutation or +9/13q- cytogenetic abnormality is supportive but not essential for diagnosis. Differential diagnosis includes chronic myeloid leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia and acute myeloid leukemia.

ii. PV and ET
The presence of a *JAK2* mutation is highly suggestive of PV diagnosis and its absence, combined with normal or increased serum erythropoietin level, excludes the diagnosis. Differential diagnosis of ET includes reactive thrombocytosis, chronic myeloid leukemia and prefibrotic myelofibrosis. A *JAK2* mutation is found in 50-70% of patients with ET and is capable of distinguishing reactive from clonal thrombocytosis

Current risk stratification

i. PMF
The Dynamic International Prognostic Scoring System-plus (DIPSS-plus) prognostic model for PMF can be applied at any point during the disease course and uses eight independent predictors of inferior survival: age >65 years, hemoglobin <10 g/dL, leukocytes >25 x 10^9/L, circulating blasts 1%, constitutional symptoms, red cell transfusion dependency, platelet count <100 x 10^9/L and unfavorable karyotype. The presence of 0, 1, "2 or 3" and 4 adverse factors defines low, intermediate-1, intermediate-2 and high-risk disease with median survivals of approximately 15.4, 6.5, 2.9 and 1.3 years, respectively.

ii. PV and ET
Current risk stratification in PV and ET is designed to estimate the likelihood of thrombotic complications: high-risk is defined by the presence of age >60 years or presence of thrombosis history; low-risk is defined by the absence of both of these two risk factors. Recent data considers *JAK2*V617F and cardiovascular (CV) risk factors as additional risk factors for thrombosis.

Risk-adapted therapy

i PMF
Observation alone is adequate for asymptomatic *low/intermediate-1 risk* disease. Allogeneic stem cell transplantation is often considered for *high risk* disease. Experimental drug therapy is reasonable for symptomatic *intermediate-1* or *intermediate-2* risk disease. Splenectomy and low-dose radiotherapy are used for drug-refractory splenomegaly. Radiotherapy is also used for the treatment of non-hepatosplenic EMH, PMF-associated pulmonary hypertension and extremity bone pain.

ii. PV and ET
The 10-year risk of leukemic/fibrotic transformation is <1%/1% in ET and <3%/10% in PV. In contrast, the risk of thrombosis exceeds 20%. The main goal of therapy is therefore to prevent thrombohemorrhagic complications. In low risk patients, this is effectively and safely accomplished by the use of low-dose aspirin in both PV and ET and phlebotomy (hematocrit target of <45%) in PV. In high risk patients, treatment with hydroxyurea is additionally recommended. Treatment with busulfan or interferon-α is usually effective in hydroxyurea failures.

ICLLM 2013

Acute Lymphoblastic Leukemia

Outcome of acute lymphoblastic leukemia (ALL) has improved in the past decade in some studies from 35% to 50% overall survival and more. This progress is mainly due to optimised chemotherapy based on pediatric approaches, risk adapted therapy including stem cell transplantation, individualised treatment according to minimal residual disease and targeted therapy.

ALL is a rare disease and therefore it is essential to stay up to date regarding treatment approaches in order to offer patients an optimal chance of cure. This includes younger patients and even older patients who can reach reasonable survival rates with moderate intensity therapy.

Complete diagnostic characterisation of the disease is the basis for risk stratification and for the use of targeted therapies such as antibody therapy or molecular therapies such as tyrosine kinase inhibitors. At diagnosis parameters for risk stratification are identified. This is particularly important for the decision making on stem cell transplantation. Therefore the first presentation of the session by Herve Dombret covers the topic, **Conventional and molecular prognostic factors in adult ALL**'.

The general treatment approach to ALL became more and more complex in the past decade. Risk adapted and individualised treatment approaches based on conventional prognostic factors and individual response to treatment and available targets for specific therapies are the basis for treatment optimisation. Promising approaches for future optimised management will be discussed by Nicola Gökbuget in the topic,**How to improve outcome of adult ALL**'

Targeted therapy has contributed to the improved overall outcome of ALL. The use of tyrosine kinase inhibitors in Ph/bcr-abl positive ALL led to an increase of survival rates from less than 20% to more than 50% in this formerly unfavorable subgroup of ALL and is a model for causal molecular therapy of acute leukemias. The second presentation by Renato Bassan will cover the topic ,**Current and Future Management of Ph/BCR-ABL positive ALL**,

Participants of the session will get a complete overview on state of the art management of ALL starting from diagnosis to subgroup adjusted therapy.

Nicola Gökbuget

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2007/11: Head of the Leukemia Unit and Head of the Clinical Haematology Immunology Department, Hôpital Saint-Louis, Paris
20011/present: Head of the Leukemia Unit and Head of the Clinical Haematology Immunology Oncology Department (209 beds + 78 out-patient beds), Hôpital Saint-Louis, Paris

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  - Acute Lymphoblastic Leukemia
  - Myelodysplastic Syndromes
  - Chronic Myeloid Leukemia

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Member of the French Bone Marrow Transplantation and Cell Therapy Society
Member of the European Haematology Association
Member of the European Bone Marrow Transplantation Society
Member of the American Society of Haematology
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Member of the International Association for Comparative Research on Leukemia and Related Diseases (IACRLRD)
President of the Acute Leukemia French Association (ALFA)
Chairman of the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)
Member of the European Acute Promyelocytic Leukemia (APL) group
Member of the Groupe Français des Myélodysplasies (GFM)
Member of the French LMC Intergroup (FILMC)
Member of the French MPD Intergroup (FIM)
President of the Acute Leukemia and Myeloid Disorders Clinical Research Committee (French National Cancer Institut, INCa)
Expert for the French PHRC Clinical Research Program
Member of the French Association Contre le Cancer (ARC) Committee
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Conventional and molecular prognostic factors in adult ALL

Herve Dombret

University Institute of Hematology, University Hospital Saint-Louis

Paris Alliance of Cancer Research Institutes

Adult acute lymphoblastic leukemia (ALL) is currently divided in three distinct disease subsets, namely T-cell ALL (T-ALL), Philadelphia chromosome (Ph)-negative B-cell precursor (BCP) ALL, and Ph-positive (Ph+) ALL, which all required specific risk evaluation. At the present time, patients with Ph+ ALL are treated according to specific protocols combining chemotherapy with tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib, while patients with Ph-negative ALL are treated with similar chemotherapy schemes, whatever they have T- or BCP-ALL. In these three subsets, conventional risk factors may comprise: 1) patient-related factors, including age, ECOG performance status, and presence of comorbidities; 2) leukemia-related factors, including white blood cell count, central nervous system involvement, immunophenotype, cytogenetics and ploidy; and 3) response-related factors, including the pediatric-inspired assessment of corticosteroid sensitivity in the peripheral blood, followed by chemosensitivity assessment in the bone marrow during and after first induction course. Of importance, it does not appear that patient-related factors govern more than the occurrence of toxic events, such as tolerance of L-asparaginase or steroids, induction-related toxic deaths, or transplant-related mortality after allogeneic stem cell transplantation (SCT), while leukemia- and response-related factors clearly influence the risk of remission induction failure or disease recurrence.

Apart from these conventional risk factors, two major advances in the diagnosis and monitoring of ALL patients have been demonstrated to be associated with strong prognostic significance in adults as well as in children with the disease. First, gene expression profiling, SNP- or CGH-array, and next generation sequencing (NGS) technologies allowed deeply refining ALL molecular genetics and leukemia-related risk subsets. Multiple genomic anomalies or gene mutations have been discovered, some of them (like *NOTCH1/FBXW7* gene mutations in T-ALL or *IKZF1* gene deletions in BCP-ALL) being of great importance due to their incidence and specific prognostic value. In addition, some relatively rare molecular events (such as *ABL* gene amplification or *JAK* or *FLT3* gene mutations) may justify specific therapeutic TKI evaluations. Secondly, the level of minimal residual disease (MRD) after induction and/or consolidation has been reported as the most powerful response-related risk factor in adult as in childhood ALL. MRD levels may be evaluated by molecular clone-specific Ig-TCR probes, fusion transcript amplification, or aberrant immunophenotype detection by flow cytometry.

In the same time, recent chemotherapy intensification using pediatric or pediatric-inspired protocols in adults allowed significant improvement in the outcome of adult ALL patients. This may affect the prognostic significance of some conventional risk factors. This may also affect the place of allogeneic SCT in first remission in adult patients. Actually, the main treatment-stratification decision is to indicate or not indicate allogeneic SCT, based on patient-related, leukemia-related, and response-related individual risk assessment. Given the number of risk factors mentioned above that could enter this process, systematic (but also pragmatic) hierarchical evaluations are needed, in order to standardize adult ALL risk classification, as it is currently done for instance in patients with acute myeloid leukemia.

CURRICULUM VITAE

Dr. Nicola Gökbuget

Nicola Gökbuget is since 1990 member of the Department for Internal Medicine II, Hematology/Oncology of the University Hospital in Frankfurt and is head of the Study Center of the department. Since 20 years she serves as Coordinator of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) with more than 140 participating hospitals all over Germany. She is coordinating or principal investigator of various academic or industry sponsored trials in adult ALL. The GMALL currently conducts a number of Investigator-initiated trials in adult ALL and related diseases such as lymphoblastic lymphoma or Burkitt's lymphoma. Furthermore the GMALL conducts a nation-wide registry for newly diagnosed and relapsed ALL in adults
Nicola Gökbuget is founding and board member of the German Network for Acute and Chronic Leukemias supported by the German Ministery of Research and Education and more recently by the German Jose Carreras Foundation. The network coordinates all major German multicenter trials in leukemia, projects on leukemia diagnosis, supportive care and basic research. Nicola Gökbuget is the head of the Information Center for Leukemias. Furthermore she is founding member of the European Leukemia Network which was funded in the 6th framework programme of the European Union. Within the European Network she leads a project named "European Leukemia Information Center" and is board member and coordinator of the European Working Group for Adult ALL (EWALL). EWALL is a collaborative group of all large national study groups for adult ALL in Europe.

Recently she has been appointed as head of the Study Center Network of the University Cancer Center (UCT), the Comprehensive Cancer Center of the University of Frankfurt. She is also member of the Board of Directors of the UCT.

Her scientific interest focuses on clinical research in the field of adult acute lymphoblastic leukemia including diagnosis, therapy, late effects, quality of life, management of relapsed/resistant disease and evaluation of new drugs. Furthermore she is involved in management, organization and logistical development of clinical studies in the field of leukemias and public health. She has published review articles, chapters for national and international textbooks and original articles on acute lymphoblastic leukemia on behalf of the GMALL study group and acted as invited speaker at various international meetings.

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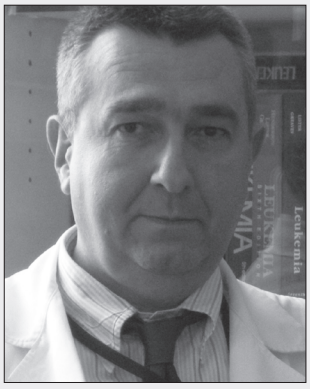
How to improve outcome of adult ALL

Nicola Gökbuget
J.W. Goethe University Hospital, Frankfurt, Germany



CURRICULUM VITAE

Dr Renato Bassan

Dr Renato Bassan obtained his degree in Medicine and completed his postdoctoral fellowship in Hematology at Padua University (Italy), then started his work as full-time hematologist at Bergamo Hospital where he set up the leukemia diagnostic section, the autologous bone marrow transplantation section and the leukemia clinics. He was trained in Onco-hematology at St. Bartholomew's Hospital (London, UK), lately reaching the position of honorary consultant. Since 2011 he is the Director of the Hematology Unit at Venice Hospitals. His main professional interest is in acute lymphoblastic leukemia and acute myeloid leukemia therapy. He has been leading for the Northern Italy Leukemia Group (NILG) several prospective phase II and III trials, as well as new collaborations with GIMEMA and the European Working Group on Adult ALL.

Current and Future Management of Ph/BCR-ABL Positive ALL

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Abstract

With the introduction of tyrosine kinase inhibitors at the beginning of the past decade the outcome of Ph+ ALL has steadily improved in adult patients. Nowadays, refined programs with second generation inhibitors together with a careful choice of chemotherapy elements and an improved, wider transplantation platform allows some forty to fifty per cent of the patients to achieve cure, which represent a massive improvement over results obtainable in the pre-imatinib era. Further progress is expected exploiting ponatinib which may overcome resistance caused by T315I point mutation, other small molecules targeting relevant pathways in Ph+ cells, autologous transplantation that is seemingly effective in PCR-negative patients, highly active monoclonals like inotuzumab ozogamicin and blinatumomab, and chimeric antigen receptor-modified T cells. These innovations could transform Ph+ ALL into a curable disease, allowing at the same time to spare allogeneic stem cell transplantation to many patients, minimizing the risk of therapy-related death and greatly improving the quality of life.

Ph+ ALL: making a diagnosis

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) is traditionally diagnosed through standard cytogenetic analysis which demonstrates, in an otherwise unremarkable case of B-cell precursor (BCP) ALL, the typical translocation between chromosomes 9 and 22 (Figure 1). Other chromosomal aberrations may be present, to aggravate the prognosis. The blast cell population is rather homogeneous on immunophenotypic

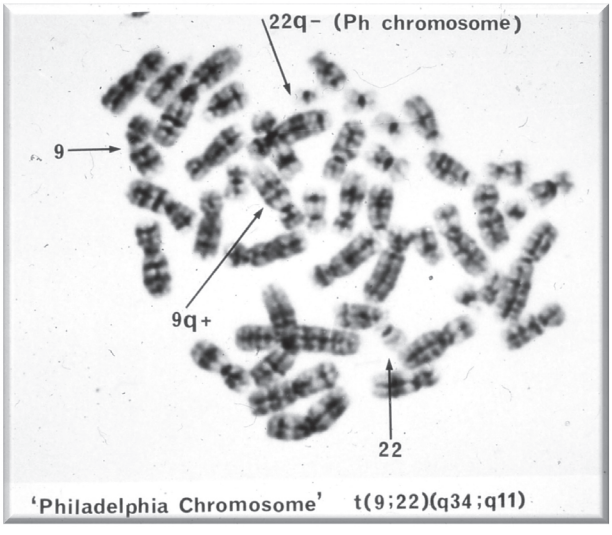


Figure 1. The Philadelphia translocation.

analysis (TdT+, CD19+, CD79a+, cCD22+) and may variably express CD20, CD25 and stem/myeloid cell markers (CD34, CD13, CD33). The Ph chromosome is a shorter 22q- chromosome, in which the unbalanced exchange of genetic material with chromosome 9 creates a new fusion gene, BCR-ABL1, encoding for an abnormal tyrosine-kinase (TK) directly implicated in the pathogenesis of Ph+ ALL. The BCR-ABL1 gene rearrangement is easily detectable by RQ-PCR methodology, hence this assay is highly recommended as a most rapid and sensitive means to identify Ph+ ALL with a minimum of delay from patient referral (24-48 hours). In contrast the cytogenetic analysis takes longer and may fail in some instances. There are two distinct BCR-ABL1 rearrangements resulting in mRNA's and TK's of slightly different structure, named P190 and P210. Although the P190 subtype is more common and the P210 subtype is similar to that found in Ph+ chronic myelogenous leukemia (CML), there is no way to differentiate *de novo* ALL from the lymphoid blast crisis of CML solely on this basis, nor is it required for therapeutic decisions. Other gene lesions may be present, like IKZF1 deletions, conferring a bad outlook, and a variety of other gene up- and down-regulations were described as specific pattern on microarray analysis. Altogether, the molecular identification of BCR-ABL1 rearrangements is a must, to be immediately applied to every new case of BCP ALL before treatment. Subsequently, quantitative variations of the transcript reflect treatment efficacy or suggest growth of sub-clones with TK point mutations leading to therapy resistance.

The patients

Although observed at any age, even in childhood (where it is a rare illness), Ph+ ALL becomes more frequent with ageing. The incidence of ALL is roughly 0.9/100.000 per year in Western countries, and Ph+ ALL is the more common subset with recurrent cytogenetic abnormality, representing at least 20% of all cases. In older patients (>50 years), up to 40-50% of all cases are constituted by Ph+ ALL. The higher incidence in the older age group is an additional problem, because of frequently associated comorbidity and poor performance status, making treatment more difficult overall, especially when facing the most intensive phases (transplantation).

Treatment results before targeted therapy (TKI)

The advent of TKI's in the early 2000's marks a totally new era in the therapeutic history of Ph+ ALL. Before that, the disease was initially sensitive to standard chemotherapy combinations, although the complete remission (CR) rate could be lower than in Ph- ALL, but the major problem was

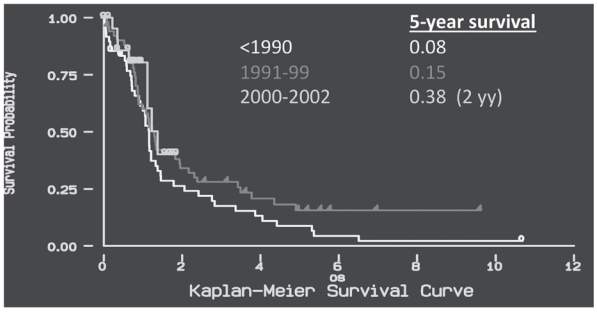


Figure 2. Pre-TKI survival of adult Ph+ ALL patients, from the NILG database.

recurrence despite intensive consolidation, so that all series reported dismal median disease-free and overall survival (DFS, OS) results. Attempts to improve outcome were only partly successful with allogeneic stem-cell transplantation (SCT), which became the treatment of choice once in CR. However bot the paucity of donors (until the development of unrelated-donor [URD] SCT and other stem cell sources in recent years) and SCT-related toxicities with high mortality prevented this procedure to exert a great impact on overall results, and the disease remained a most feared one among oncohematologists. Incresing treatment intensity with autologous SCT, high-dose cycles, and intensification therapy with anthracyclines (found of interest in a subset of Ph+ ALL in a large retrospective NILG analysis) were almost unremarkable, so that median and long-term DFS and OS rates were no greater than 1-1.5 years and 15-25%, respectively (Figure 2). The majority of long-term survivors belonged to the group of patients undergoing allogeneic SCT.

Progress at last: a decade of TKI-based therapy

The therapeutic progress obtained with imatinib in Ph+ CML was soon translated into Ph+ ALL, first in patients with refractory/relapsed disease and eventually in chemotherapy-naïve patients, with clear improvements in terms of CR rate (very close or even up to 100% in many series) and DFS/OS (close or even up to 40-50% at 3-5 years in some series). Results were generally more positive on shorter follow-up (1-2 years), but progress was undeniable, not only for the ability to bring into remission more patients but also, thanks to the longer duration of these remissions and the favorable changes in the allogeneic SCT area (URD, cordblood, haploidentical SCT programs; reduced mortality), to an increased transplantability rate and a better transplantation outcome.

Progress generated discussion, raising questions about the preferred induction schedule and optimal therapeutic associations (how much imatinib?

Table 1. Time to peripheral blast cell clearance after start of imatinib therapy in patients with relapsed/refractory Ph+ leukemias. The shorter course to response was observed in Ph+ ALL. Adapted from Karamlou et al, Blood 2001;98:590a.

Ph+ subtype	BM blasts <5%	Time to response (days), median (range)	
		WBC <10x109/L	PB blasts 0%
CML myeloid blast crisis (n=14)	9 (64%)	8.5 (1-38)	16 (8-28)
CML lymphoid blast crisis (n=5)	3 (60%)	4.5 (2-7)	8 (4-10)
Relapsed/refractory ALL (n=13)	6 (46%)	3 (2-5)	6.5 (1-14)

BM, bone marrow; WBC, white blood cells; PB, peripheral blood

How long for? How much chemotherapy? Which one preferably?), which continues to these days and reflects the opinion and treatment design of different investigators and studies, respectively, which in the end is beneficial allowing to explore at one time several therapeutic possibilities.

With regard to induction and early consolidation phase, imatinib was confirmed effective in association with chemotherapy, from 600 mg/d for 7 days during each chemotherapy cycle (first NILG trial), 600 mg/d for 14 days (first MDACC trial, others), and 600-800 mg/d for longer periods (most recent NILG, GMALL, GRAALL, PETHEMA, MRC trials in Europe, other trials in US and far East). The Italian GIMEMA group investigated with success an induction schema in the elderly with imatinib alone except for a short initial prednisone course. Tolerance was excellent and the induction response 100%. Because of these early results, newer imatinib-based induction schedules considered longer exposure to the drug and reduction, or abolishment in the case of GIMEMA studies, of associated chemotherapy elements to warrant an excellent induction outcome without any risk of toxic death by intensive chemotherapy. This approach proved effective in a second GIMEMA trial with dasatinib and is further explored rotating imatinib and nilotinib. The concept of extensive TKI-based therapy with concurrent de-intensification of chemotherapy is certainly worthy of consideration. Among the positive aspects, the notion that TKI therapy alone can induce gently (to be read: without chemotherapy-related toxicity) a clinical and hematological remission in most/all patients with Ph+ ALL; among the negative ones, the fact that chemotherapy may be synergistic with TKI (as demonstrated *in vitro*: imatinib restored apoptosis sensitivity to chemotherapy) and increase the PCR negativity rate (see below), which is a prerequisite for achieving longer survival and cure. Far from being points of attrition, these issues should be intelli(gently) developed to obtain the highest possible CR rate (100% is the target) with the highest possible molecular remission rate and the lowest possible induction death rate (0% is the target).

Second generation TKI's dasatinib and nilotinib were and are being evaluated in more recent studies, confirming induction success and improved survival in both adult and elderly patients (EWALL dasatinib trial in the elderly), with and without associated chemotherapy, in line with prior imatinib studies. The benefit these new drugs can confer is related to their different spectrum of toxicity making them suitable alternatives to imatinib-intolerant patients (and vice-versa), to a more powerful inhibition of the abnormal TK, which renders them more effective therapeutically improving the rates of molecular response, and to their ability to overcome imatinib resistance to some TK point mutations (however not T315I). Bosutinib is another new compound of the TKI family, for which there is very little information as yet. With the advent of second generation TKI's, it has in part become difficult to interpret outcome results of imatinib-based studies, because many of these patients were given dasatinib or nilotinib at time of molecular recurrence, especially following transplantation. These patients should be clearly identified in scientific publications, to avoid an interpretative bias.

Lately, ponatinib emerged as the most potent pan BCR-ABL1 inhibitor so far available, showing promising therapeutic activity even in Ph+ ALL carrying T315I and resistant to all other TKI's. In the international PACE trial, 37% of refractory patients with T315I achieved a major hematological and cytogenetic response with ponatinib, and some patients entered a major molecular response. Assessing the role of ponatinib in first line therapy of Ph+ ALL is now a central therapeutic question.

To exemplify the impact TKI therapy can have in Ph+ ALL, Table 1 reports the results of an exploratory study performed by the Portland team (Oregon, USA) on response kinetics to imatinib in different types of Ph+ leukemias, Figure 3 reports the course of peripheral blood counts following exposure to imatinib alone in an elderly patient with Ph+ ALL, and Table 2 reports improved outcome results of a large GMALL patient series treated with chemotherapy-imatinib-SCT programs.

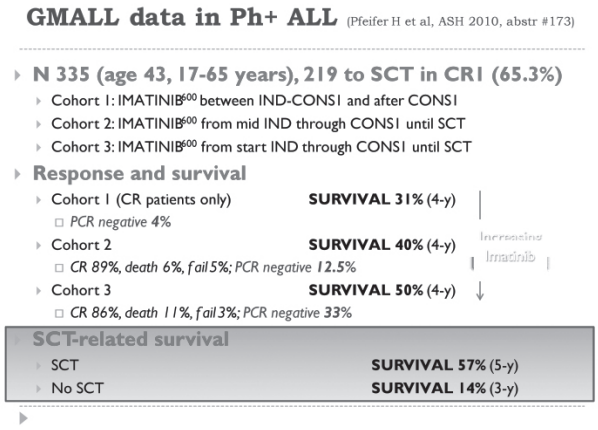
Molecular response and remission

While obtaining a CR is mandatory, the real curative potential of Ph+ ALL is accurately reflected by the concept of complete molecular remission (CMR), which is a durable disappearance from bone marrow and peripheral blood of the RQ-PCR signal related to the BCR-ABL1 fusion gene with a sensitivity of 10^{-5}. Several studies documented the prognostic significance of CMR, both pre- and post-transplantation. The early post-transplantation phase seems particularly critical, as those losing the CMR status are at greatest risk of disease progression when not receiving supplemental therapy. Others considered inferior PCR thresholds, like 10^{-3}, that is between a two-three log decrease of the molecular signal, still associated with an improved outcome. However, to harmonize response definitions, the CMR appears the best way to define optimal treatment response, because of its powerful association with long-term cure rates (virtually all patients surviving disease-free at 5 years fall within this category) and its therapeutic implications during postgraft monitoring. Although there is no agreement on what represents a good CMR rate following induction/early consolidation (pre-transplantation), looking at published data it seems that a figure close to 30% could be realistically used to define the effectiveness of a chemotherapy-TKI program, while the objective of post-transplantation assessment and associated treatment is the highest possible rate. Of note, TKI only programs with either imatinib or dasatinib yielded lower CMR rates of about 15% (GIMEMA studies).

TK mutations and resistance mechanisms

TKI resistance mechanisms range from defective intracellular drug transport and accumulation (P-gp) to increased drug metabolism, higher than usual BCR-ABL1 levels, presence of growth signals by-passing the TK inhibition, and TK domain mutations altering the drug ability to irreversibly bind the protein. Modern cloning and sequencing techniques allow to identify minor cell clones harboring resistance mutations at diagnosis. The majority of patients relapsing after imatinib-based therapy carry imatinib-resistant mutations like T315I, E255K/V, Y253H, Q252H, F317L and few othersh, but at least one third of the cases are mutation-free and develop resistance on account of other mechanisms. Because of its high incidence at relapse and insensitivity to second generation TKI's including dasatinib, T315I mutation is the most frequent resistance mechanism associated with treatment failure in Ph+ ALL.

Table 2. Improving outcome of Ph+ ALL in adult patients: GMALL studies. Adapted from *Pfeifer et al, Blood 2010;116:79a.*



Allogeneic stem cell transplantation (SCT)

In patients achieving CR following chemotherapy/TKI or TKI alone, allogeneic SCT is still the preferred consolidative option (see Table 2 for example). The increased SCT rates obtained in recent years (60-80%), in parallel with the improved CR rates (90-100%), was thus partly responsible for therapeutic advancement. In patients excluded from allogeneic SCT, long-term survival is only occasionally seen, perhaps with the exception of autologous SCT (see below). A minority of patients may maintain a good clinical and molecular response to maintenance chemotherapy plus imatinib/other TKI with/without alpha-interferon, and benefit from a prolonged remission phase even without achieving a CMR, an approach to be prescribed to elderly/frail patients only.

The therapeutic objective of allogeneic SCT is to cure the disease by inducing a stable post-transplantation CMR negative status without the need to continue chemotherapy/TKI treatments (unless indicated in the specific situation of an incomplete molecular response) and without excess transplant-related mortality (TRM). Given the expanded access to SCT and the higher median age of Ph+ patients, the issue of TRM has become crucial, because expected TRM is still high (20% on the average and increasing with age). The other serious problem with allogeneic SCT is post-transplantation relapse, which is common in patients who remain or become PCR positive afterwards. Thus quantitative, close post-transplantation PCR monitoring is necessary for the early identification of cases at high risk of relapse, in whom an early therapeutic intervention is mandatory again with TKI therapy (also depending on underlying TK domain mutations), donor lymphocyte infusions, or other experimental

therapies. A recent GMALL study randomized SCT patients between re-start of TKI therapy (imatinib) at time of molecular recurrence or as early as possible after SCT. Results were excellent in both arms with a very low rate of post-transplantation relapse, suggesting that additional post-SCT TKI therapy is useful to clear off the Ph+ clone. At present, and until clear evidence to the contrary will emerge from new clinical trials, allogeneic SCT must be viewed as a necessary component of curative-intent therapy in the age of TKI's.

Autologous SCT

Although the demonstration that Ph-negative stem cells could be obtained for auto-transplantation dates back of several years (chemotherapy alone can induce a PCR negative status in a fraction of patients), the issue of autologous SCT was only recently revived by trials offering this treatment, most often followed by TKI-based maintenance, to patients deemed unable to proceed to allogeneic SCT for their advanced age or other medical reasons. Rather surprisingly, several independent observers (NILG, GRAALL, CALGB, EBMT review) reported favorable results in patients auto-grafted at time of CMR, in whom long-term DFS and OS rates were not inferior (and occasionally better) to what obtainable with an allograft. One central question comparing the two procedures concerns TRM, which is almost nil with autograft. These observations prompted further clinical studies, like a comparative North-American Intergroup study, the results of which are awaited with interest.

Entering a new age: new drugs, less transplants?

Ten years and more into the TKI era, the survival of adult patients with Ph+ ALL has doubled compared to historical series and may continue to improve due to other advancements. Thus, the challenge is to render it a curable disease and maybe simplify therapy, first excluding SCT which remains the most dangerous and toxic treatment phase. While the nature of this short writing precludes an accurate analysis of the several new compounds under scrutiny, it is worth mentioning that small molecules acting at critical steps of the cellular metabolism could open the way to dual targeted therapies and multi-targeted therapies, like in the case of hedgehog inhibitors, PI3K/AKT/mTOR inhibitors, Aurora kinase inhibitors etc. Another promising area regards the use of cytotoxic monoclonal antibodies, which by virtue of their different mechanism of action and are ideal companion to TKI's and other inhibitors. Among them, owing to the immunophenotypic profile of BCP ALL, rituximab could be used in cases of CD20+ Ph+ ALL, but the greatest attention must be paid to the highly effective anti-CD22 inotuzumab ozogamicin (conjugated to calecheamicin) and the newest anti-CD3/CD19 construct blinatumomab that recruits autologous cytotoxic T-cells against CD19+ blast cells. Studies with these new drugs were conducted in relapsed patients and patients with high levels of molecular disease, including some cases with Ph+ ALL, showing a very high rate of response even after failure of second generation TKI's. Lastly, on the same way, chimeric antigen receptor T-cells (CART) could be obtained to directly target Ph+ ALL cell via the CD19 antigen. Combining new drugs with the best TKI's is the current challenge for new clinical studies, aiming to move progressively from the field of chemotherapy/SCT to multi-targeted therapy, with a much lower toxicity burden and an increased potential for cure.

Selected readings

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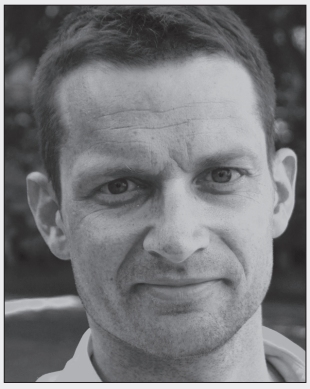
ICLLM 2013

Hodgkin Lymphoma

Herewith I welcome you all to this very interesting session on Hodgkin lymphoma. There will be a total of three presentations covering PET (Martin Hutchings), early stages (Anton Hagenbeek), advanced stages and relapsed HL (Andreas Engert).

Andreas Engert



CURRICULUM VITAE

Martin Hutchings

Martin Hutchings is a clinical oncologist and staff specialist from the Department of Haematology, Rigshospitalet, Copenhagen University Hospital.

After obtaining his master's degree (2000), he trained in nuclear medicine until pursuing his current specialisation in clinical oncology. In 2006, he defended his PhD on PET and PET/CT in Hodgkin lymphoma.

Dr. Hutchings acts as chairman of the EORTC Lymphoma Group's Scientific Steering Committee and as a consultant to various other research groups. He is currently involved in a number of observational clinical studies of PET/CT in lymphoma and is the principal investigator for the EORTC H11 randomised trial on very early PET-response adapted therapy of advanced stage Hodgkin lymphoma.

He has written numerous journal articles and book chapters on the role of PET/CT in Hodgkin and non-Hodgkin lymphomas, and is engaged in a range of clinical research activities centred around his specialisation in lymphoma treatment and research.

Prognostic factors and the role of PET/CT in Hodgkin lymphoma

Martin Hutchings

Copenhagen University Hospital, Copenhagen, Denmark

Abstract

Selection of treatment for Hodgkin lymphoma is based on clinical staging, on well-established clinical prognostic factors, and on the age and general state of the patient. A number of biologic markers and cytokines have prognostic abilities, but they have yet no proven therapeutic value for the patients.

PET/CT has emerged as the most accurate tool for staging, treatment monitoring and response evaluation in Hodgkin lymphoma (HL). While accurate staging and restaging are very important for the optimal management of HL, we are only beginning to understand how to use PET/CT to improve our patients' treatment outcomes. More precise determination of disease extent may result in more precise pre-treatment risk stratification, and is also essential to the minimal and highly individualized radiotherapy volumes of the present era. A number of trials currently investigate the use of PET/CT for early response-adapted therapy, with therapeutic stratification based on interim PET/CT results. Post-treatment PET/CT is a cornerstone of the revised response criteria and enables selection of advanced stage patient without need for consolidation radiotherapy. PET/CT looks promising for selection of therapy in relapsed and refractory disease.

Introduction

Optimal management of Hodgkin lymphoma (HL) demands a careful balance between high treatment efficacy and acceptable acute and late treatment-related toxicity. With modern therapy, overall long-term survival from Hodgkin lymphoma (HL) exceeds 80%(1), but there are serious long-term adverse effects of the treatment, including heart and lung disease, and secondary malignancies. HL patients have an excessive mortality directly related to these late treatment effects(2). At 15 years following treatment, the risk of death from HL is overtaken by the risk of death from other causes, and in early-stage HL, treatment related illness accounts for more deaths than HL itself(3). In order to reduce the long-term effects of treatment, therapeutic strategies are becoming more tailored to the individual patient's disease profile and other clinical characteristics. The aim is to maintain and improve the high cure rates while reducing therapy-related morbidity and mortality.

A more patient-tailored treatment approach demands precise determination of the initial disease extent, optimal knowledge about other prognostic factors, and also an accurate and preferably early assessment of the responsiveness to therapy.

Table 1. Clinical prognostic factors in Hodgkin lymphoma.	
Early stage disease	Advanced stage disease
Large mediastinal mass	Large mediastinal mass
Tumor burden	Tumor burden
B-symptoms	B-symptoms
Age	Age
Sex	Sex
Erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Hemoglobin	Hemoglobin
Low serum Albumin	Low serum Albumin
Extranodal involvement	Stage IV disease
	Leukocytosis
	Lymphocytopenia
	High lactic dehydrogenase (LDH)

Prognostic factors

Decisions on first-line treatment strategy for HL patients rely on determination of histology, on accurate staging of the disease, and on identification of risk factors for early stage disease or the individual parameters of the International Prognostic Score (IPS) for advanced stage disease(4). Clinical stage is by far the most important determinant for the choice of up-front treatment strategy. The clinical factors used for prognostication in early and advanced stage disease (table 1) are derived from studies of large patient cohorts(5). They are used as a supplement to staging, for therapy selection and for patient counseling, but they offer rather uncertain prediction of outcome for the individual patient. A number of biologic factors and cytokine markers have shown prognostic properties and will probably in the future play a role in more tailored therapeutic approaches.

The true prognostic factors are pre-therapeutic factors, i.e. available before the start of treatment. These factors are either tumor-related, host-related or environment-related. In the individual patient, the response to treatment is generally more predictive of outcome, and thus more prognostic, than the true prognostic factors.

In relapsed disease, most of the prognostic factors for first-line treatment are still valid. However, at this point the most important prognostic pre-therapeutic factors are the depth and duration of remission after first-line therapy(6;7).

Clinical factors and the prognostic scoring systems for early and advanced stage disease

Combined-modality treatment of early stage disease is often tailored according to prognostic subgroups. This grouping is based on prognostic scoring systems (table 2) which include factors that mainly reflect the patient's tumor burden. Patients with advanced disease are often risk stratified according to the IPS (table 3), which is also mainly a reflection of the tumor burden and dissemination of disease. Despite its prognostic properties, the IPS has no clear role in the selection of therapy. Age, poor performance status, and to a lesser extent male sex, are adverse patient-related prognostic factors in both early and advanced stage disease.

Biologic markers

In recent years, the importance of the microenvironment in HL has become increasingly clear, and a number of biologic markers have shown correlation with treatment outcome. A selection of these biomarkers are summarized in table 4. It has long been recognized that high levels of regulatory T cells and also of benign B cells in the microenvironment correlate with a favorable prognosis. An adverse prognosis has been associated with the presence of tumor-infiltrating macrophages. Steidl *et al.* analyzed 130 frozen samples from patients with classic HL during diagnostic lymph node biopsy using gene expression profiling(8). This identified a gene signature of tumor associated macrophages which was associated with primary treatment failure. Further, using immunohistochemical analysis in an independent cohort of 166 patients, an increased number of CD68+ macrophages was correlated with reduced progression free survival (PFS),

Table 2. Prognostic scoring systems for early stage disease.			
Risk factor	GHSG	EORTC	NCIC
Age		≥ 50 years	≥ 40 years
ESR and B-symptoms	> 50 if A or > 30 if B	> 50 if A or > 30 if B	> 50 or any B symptoms
Mediastinal mass	MMR > 0.33	MMR > 0.35	MMR > 0.33 or > 10 cm
Number of nodal sites	> 2	> 3	> 3
Extranodal lesions	Any		

Abbreviations: GHSG = German Hodgkin Study Group. EORTC = European Organisation for the Research and Treatment of Cancer. NCIC = National Cancer Institute of Canada. ESR = Erythocyte sedimentation rate. MMR = Mediastinal Mass Ratio = maximum width of mass/maximum intrathoracic diameter.

Table 3. International Prognostic Index for advanced stage disease.

Albumin < 4 g/dL
Hemoglobin < 10.5 g/dL
Male sex
Age ≥ 45 years
Stage IV disease
Leukocyte (WBC) count > 15,000/μL
Lymphocyte count < 8% of WBC count and/or absolute lymphocyte count < 600 cells/μL

increased relapse after relapse therapy, and shortened HL-specific survival. Interestingly, in patients with early stage HL, the absence of CD-68+ macrophages was correlated with 10-year disease-specific survival of 100% with current standard therapies.

Cytokine markers

Soluble CD30 and serum Interleukin-10 (IL-10) have both been associated with poor outcome in HL(9;10). The thymus and activation related chemokine (TARC) is a chemokine secreted by Hodgkin Reed-Sternberg (HRS) cells and its chemotactic properties may explain the infiltration of reactive T lymphocytes in HL. Elevated TARC levels have been seen in the majority of patients with HL. TARC is specifically secreted by HRS cells in more than 90% of cases and can be used as a tumor cell specific marker for disease activity. Data have shown that serum levels correlate with tumor extensiveness and that plasma TARC during and after treatment correlate with clinical response(11). Recent data showed that TARC levels after one cycle of chemotherapy could already predict final treatment response with high positive predictive value(12).

The role of PET/CT

Positron emission tomography (PET) using 2-[18] fluoro-2-deoxyglucose (FDG) has gained widespread use in most lymphoma subtypes. State-of-the-art FDG-PET is carried out in combined scanners, with FDG-PET and computed tomography (CT) performed in one scanning session, resulting in fusion PET/CT images. The National Comprehensive Cancer Network guidelines recommend the use of PET/CT for primary staging and final response evaluation in patients with HL(13). Interim PET/CT during chemotherapy is still considered investigational, as well as PET/CT in relapsed/refractory disease. Since PET/CT seems to be the most accurate staging tool in HL and provides the most reliable response assessment during and after therapy, the method plays an important role in current efforts to optimize therapy.

Staging PET/CT and selection of first-line therapy

The first reports on FDG-PET for lymphoma imaging were published 25 years ago(14). Studies of HL patients showed a very high sensitivity of FDG-PET for nodal staging, especially for the detection of peripheral and thoracic lymph nodes. When performed as PET/CT, the increased sensitivity does not come at the expense of a decreased specificity(15). PET/CT also detects extranodal disease more sensitively than conventional methods, both in the bone marrow and in other organs and seems to be at least as sensitive as blind bone marrow biopsy (BMB)(15;16). A recent study of 454 HL patients with staging BMB and PET/CT showed no value of routine BMB in the era of PET/CT staging(17).

PET/CT has a consistent, large influence on the

Table 4. Selected biomarkers and gene expression profiles with prognostic value in Hodgkin lymphoma. Adapted from Steidl et al.(52)

Immunohistochemistry			
Marker	Expressed on	Function	Outcome correlation
Granzyme B	Cytotoxic T cells	Target cell lysis	Adverse
FoxP3	Regulatory T cells	Transcriptional regulation	Favorable
CD20	Background B cells	B cell differentiation	Favorable
CD68, PNA	Macrophages	Scavenger receptor	Adverse
STAT1	Macrophages	Transriptional activation	Adverse
EBV-enc. small RNAs	HRS cells	Activation of NFκB?	Adv/Fav in elderly/young
Gene expression profiling			
Signature	Gene components		Outcome correlation
B-cell signature	BCL11A, BANK1, STAP1, BLNK, FCER2, CD24, CCL21		Favorable
Cytotoxic T cell signature	CD3D, CD8B1, CTSL, CD26, SH2D1A, IFI16, RGS13, CR2, ELL3, CCDC23, PPM1L, TRAα, PIK2CA		Adverse
Plasmacytoid dendritic cells	ITM2A, SRPX, CTSB, APP		Adverse
Macrophage signature	ALDH1A1, LYZ, STAT1, ITGA4, CCL13, MS4A4A, CCL23, VCAN, HSP90AB3P, CFL1, JMJD6, MAPK7, IKBKG, RAB7A, RXRA, MAPK13		Adverse

Table 5. Studies of early PET-response adapted Hodgkin lymphoma therapy.

Study title/description	Study group	Patients	Main PET-driven intervention	Study type
HD16 for Early Stage Hodgkin Lymphoma	German Hodgkin Study Group	Early stage HL	No radiotherapy in experimental arm if PET-negative after 2xABVD	Phase III
FDG-PET Guided Therapy or Standard Therapy in Stage I-II Hodgkin's Lymphoma (H10 trial)	EORTC/GELA/FIL	Early stage HL	No radiotherapy in experimental arm if PET-negative after 2xABVD	Phase III
RAPID trial	UK NCRI lymphoma group	Early stage HL	If PET-negative after 3xABVD randomization to RT vs. no RT	Phase III
PET-adapted Chemotherapy in Advanced Hodgkin lymphoma	GITIL	Advanced HL	Intensification to BEACOPPesc if PET-positive after 2xABVD	Phase II
FDG-PET response-adapted therapy in advanced-stage Hodgkin lymphoma (RATHL)	UK NCRI lymphoma group	Advanced HL	Intensification to BEACOPP if PET-positive after 2xABVD	Phase III*
HD+ASCT in patients PET-positive after 2xABVD and RT Versus no RT in PET-negative patients (HD0801)	IIL	Advanced HL	Salvage regimen if PET-positive after 2xABVD	Phase III*
HD18 for Advanced Stage Hodgkin Lymphoma	German Hodgkin Study Group	Advanced HL	4 vs. 8 x BEACOPPesc in exper. arm if PET-negative after 2 cycles	Phase III
Study of a treatment driven by early PET response to a treatment not monitored by early PET in patients with stage 2B-4 HL (AHL 2011)	GELA/LYSA	Advanced HL	De-escalation from BEACOPPesc to ABVD in exper. arm in case of a neg. PET after 2 and 4 cycles. Standard arm: 6 x BEACOPPesc.	Phase III
H11 trial for advanced Hodgkin lymphoma	EORTC/PLRG	Advanced HL	Experimental arm: Intensification to BEACOPPesc if PET-positive after 1xABVD. Standard arm: 6 x BEACOPPesc.	Phase III

Abbreviations: DLBCL = diffuse large B-cell lymphoma. HD+ASCT = high-dose chemotherapy with autologous stem cell transplantation. R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, vincristine, prednisone. GELA = Groupe d'Etudes des Lymphomes de l'Adulte. R-ICE = Rituximab, Ifosfamide, Carboplatin, Etoposide. UK NCRI = United Kingdom National Cancer Research Institute. ABVD = Doxorubicin, Bleomycin, Vinblastin, Dacarbazine. EORTC = European Organisation for the Research and Treatment of Cancer. FIL = Fondazione Italiana Linfomi. GITIL = Gruppo Italiano Terapie Innovative nei Linfomi. PLRG = Polish Lymphoma Research Group. *No randomization regarding PET-response adapted therapy.

staging in classical HL, with upstaging of approximately 15-25% of patients, and downstaging in only a small minority of patients. This leads to a shift to a more advanced treatment group in approximately 10-15% of patients(15;18;19). A single showed a similar pattern in nodular lymphocyte predominant HL (NLP HL), where staging FDG-PET resulted in changes of stage in nine out of 31 patients (seven upstagings and two downstagings)(20). The tendency towards upward stage migration is important, since early and advanced disease stages are treated very differently. However, early stage HL patients have an excellent prognosis and are prone to serious treatment-related late morbidity and mortality. With this in mind, the use of FDG-PET/CT for staging of HL should be accompanied by steps to reduce the intensity of therapy; otherwise the net effect of the enhanced staging accuracy will be an increased overall treatment burden.

The role of baseline PET/CT for modern early stage HL radiotherapy planning

The advances of modern radiotherapy for HL have led to dramatic reductions in the volume of normal tissue being irradiated and similar reductions in the risk of serious late effects of radiotherapy(21;22). But such modern therapy also demands a higher accuracy of the imaging procedures used for treatment planning. Since PET/CT is more accurate for staging of HL, it is by implication also more precise in defining the initially involved regions or nodes which are intended to be irradiated in patients with early stage disease. Relatively limited clinical data are available on the role of PET/CT in target definition for the planning of radiotherapy for HL. However, in the setting of modern conformal radiotherapy techniques such as involved-field radiotherapy (IFRT) and involved-node radiotherapy (INRT), the definition of the involved nodes and thus the radiotherapy volumes is significantly different with PET/CT vs. CT alone, both in classical HL and NLP HL(20;23;24).

Early treatment monitoring with FDG-PET

Clinical stage and prognostic factors are used to determine the initial treatment strategy. However, the tumor response to induction treatment is strongly prognostic. A reliable and early prediction of response to therapy may identify good-risk patients who will be cured with conventional therapy or even less intensive and less toxic regimens, and poor-risk patients for whom an early switch to alternative, more aggressive treatment strategies could improve the chance of remission and cure.

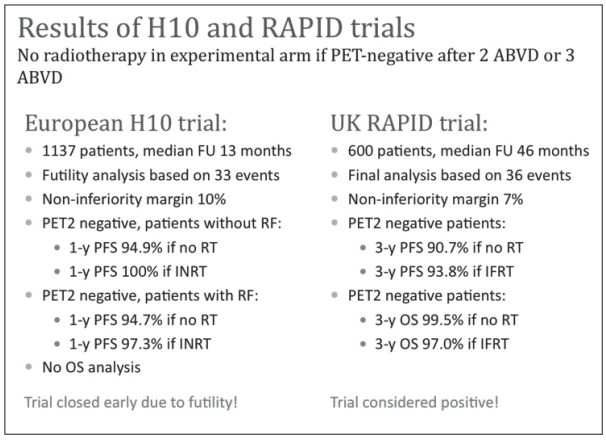
This concept called risk-adapted therapy is widely recognized as one potential way to achieve higher cure rates without increasing, and perhaps even decreasing, the risk of treatment-related morbidity and mortality(25).

Conventional methods for treatment response monitoring are based on morphological criteria, and a reduction in tumor size on computerized tomography (CT) is the most important determinant(26). However, size reduction is not necessarily an accurate predictor of outcome. In HL, the malignant cells make up only a small fraction of the tumor volume, which is dominated by reactive infiltrating cells not directly affected by anti-neoplastic therapy(27). But even more importantly, tumor shrinkage takes time and depends on a number of factors in the host. So the rate of structural regression cannot form the basis for therapy response assessment until rather late during treatment, at which point a treatment modification might be less useful.

As opposed to the morphological changes of the lymphoma occurring later during therapy, functional imaging with FDG-PET enables early evaluation of the metabolic changes that take place very early during the treatment induction. Several studies of FDG-PET after 1-3 cycles of chemotherapy (28-32) have shown that these early metabolic changes are highly predictive of final treatment response and progression-free survival (PFS). Most evidence is available for FDG-PET after two cycles of chemotherapy. However, there are data to suggest that the prognostic accuracy is very high already after only one cycle of chemotherapy, and that the negative predictive value (NPV) may be higher(33).

A retrospective analysis of 88 patients scanned after 2 or 3 cycles of ABVD-like chemotherapy (ABVD = adriamycin, bleomycin, vinblastine and dacarbazine) for HL showed a 5-year PFS of 39% in the PET-positive group compared with 92% in the PET-negative group(28). These results were later confirmed in several prospective studies(29-31), showing excellent outcomes for early PET-negative patients (app. 95% long-term PFS) and rather poor outcomes for early PET-positive patients. In patients with advanced disease, the high prognostic value of early FDG-PET overshadows the role of the IPS(29;32). The prognostic value of PET/CT in advanced HL was recently validated by Gallamini et al., who showed 3-year failure-free survival of 28% and 95% for early PET-positive and early PET-negative patients, respectively *(Gallamini et al. Manuscript submitted for publication)*. In this international validation study, the interobserver agreement was very high between six independent PET/CT reviewers, using the Deauville criteria for interim PET which have become widely recognized(34). Apart from giving reproducible results, the Deauville criteria are very simple in use, thus their use in most of the recently opened PET response adapted trials will hopefully enhance comparability between clinical trials and also enable a better translation of clinical trial results into clinical practice outside of trials.

Table 6. Results of the H10 and RAPID trials of early stage Hodgkin lymphoma



The positive predictive value of early FDG-PET seems to be lower in patients treated with the more dose-intensive BEACOPPesc regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) than in patients treated with ABVD(35). Also, the positive predictive value is lower in patients with early stage HL, probably due to both the inherent better prognosis for this patient group and due to the subsequent radiotherapy which may in many early stage patients overcome an insufficent chemotherapy response(29;30).

PET-response adapted HL therapy - early and advanced stage

There is still no evidence that HL patients benefit from having treatment adapted according to the results of early PET/CT. More than 90% of early stage HL patients are cured with standard therapy. But the patients still have a dramatically reduced life expectancy due to treatment-related illness including second cancers and cardiopulmonary disease. In fact, early-stage HL patients more often die from late effects of therapy than from the disease itself(36). This suggests that a substantial number of early-stage HL patients are subject to some amount of over-treatment, and it is the background for using early PET/CT to identify good-risk early stage patients eligible for less intensive treatment. A number

of trials investigate such PET-response adapted therapy in early-stage HL (table 5). The UK National Cancer Research Institute (NCRI) Lymphoma Group RAPID trial for early stage patients as well as the German Hodgkin Study Group (GHSG) HD16 protocol investigate the non-inferiority of reducing treatment intensity by omitting radiotherapy to interim PET-negative early stage patients. The experimental arms of EORTC/GELA/IIL[1] H10 protocol also omitted radiotherapy to PET-negative patients while escalating to BEACOPPesc followed by radiotherapy in PET-positive patients. In other words, this trial tests the non-inferiority of a less toxic treatment to good-risk patients, while at the same time attempting treatment intensification for patients regarded as having a high risk of failure based on a positive interim PET/CT. The German HD16 trial is still recruiting patients, but results from the RAPID trial and the H10 trial were presented at the 2013 annual meeting of the American Society of Hematology(37;38). The results are summarized in table 6. The results from the RAPID trial were based on a mature analysis with a median follow-up of 46 months, while the H10 results were based on an interim analysis after a median follow-up of 13 months. Apart from this, the results were remarkably similar. Early PET-negative patients who according to randomization did or did not receive radiotherapy showed differences in PFS rates which were well within the predefined margins of non-inferiority. Nevertheless, the conclusions from the two studies were completely the opposite of one another. The RAPID trial is considered a positive trial, since mature results show what is considered non-inferiority of the experimental arm. The experimental arms for early PET-negative patients in the H10 trial, on the contrary, were closed after a futility analysis of the presented interim data rendered it unlikely that non-inferiority of the chemotherapy-only treatment could be demonstrated in a mature analysis, when compared with the combined-modality standard arms. This analysis used the assumption the hazard ratio for recurrences in each arm is unchanged during the entire observation period. This is an assumption which is hardly correct, since the vast majority of recurrences in HL occur within the first two years, and since it is likely that patients not receiving radiotherapy may relapse earlier than those relapsing after combined-modality treatment. All in all, the jury is still out on whether PET/CT can select early stage HL patients who may be safely treated without radiotherapy, and the German HD16 trial results are highly anticipated.

Around 70% of advanced stage HL patients are cured with 6(-8) cycles of ABVD with or without consolidation radiotherapy, which is first-line therapy in most centers. BEACOPPesc cures 85-90% of patients if given upfront, but serious concerns regarding acute toxicity and second myeloid neoplasias are the reason why many centers in Europe and North America are very reluctant to use this regimen as standard therapy(39). A number of trials investigating PET-response adapted therapy for advanced stage HL patients are ongoing (Table 5). A number of non-randomized trials use early treatment intensification with BEACOPPesc (Italian GITIL trial and the UK-Nordic RATHL trial)[2] or even ASCT (Italian FIL trial) in patients who are still PET-positive after two cycles of ABVD. The randomized German GHSG HD18 trial tests abbreviation of BEACOPPesc therapy based on PET results after two therapy cycles. The French AHL 2011 trial is also a BEACOPPesc-based randomized trial with treatment modifications based of PET after both two and four cycles. The recently opened EORTC/PLRG H11 trial compares BEACOPPesc (standard arm) against an experimental arm where PET/CT after one cycle of ABVD determines whether patients continue with ABVD or BEACOPPesc. As with the trials in early stage disease, none of the PET-response adapted trial in advanced HL have reached mature results yet.

Post-chemotherapy PET/CT for selection of advanced-stage patients for consolidation radiotherapy

In advanced disease, radiotherapy is used less frequently and usually only to residual disease. In this situation PET/CT may help in discriminating between a residual mass with viable lymphoma cells and a residual mass consisting only of fibrotic tissue. However, since PET/CT cannot detect microscopic disease, it has not been entirely clear whether a PET-negative residual mass requires radiotherapy or not. The mature results of the German HD15 trial shed light on this for patients treated with BEACOPP regimens. In this study, consolidation radiotherapy was given only to patients with a PET-positive residual mass of more than 2.5 cm. The remaining majority patients who did not receive radiotherapy had a relapse-free survival of 94% after one year, indicating that radiotherapy can be safely omitted in advanced stage HL patients who are PET-negative after the end of BEACOPPesc. The situation is a little less clear for ABVD treated patients. However, a retrospective analysis from the British Columbia Cancer Agency was presented at the Annual Meeting of the American Society of Clinical Oncology in 2011. This retrospective study reported a 5-year experience where patients with

1 EORTC: European Organisation for the Research and Treatment of Cancer, GELA: Groupe des Etudes des Lymphomes de l'Adulte, FIL: Fondazione Italiana Linfomi.

2 GITIL: Gruppo Italiano Therapie Innovative nei Linfomi, RATHL: Response-adapted Therapy in Hodgkin Lymphoma.

residual masses > 2cm after chemotherapy underwent PET/CT (n=163). Only patients with a positive post-treatment PET/CT received radiotherapy. Of the patients with a negative PET/CT (n=130, 80%), the 3-year PFS was 89% with a median follow-up of 34 months, as opposed to the PET-positive patients who had a 3-year PFS of 55% despite receiving radiotherapy(40). These results support the omission of radiotherapy to advanced stage HL patients who receive a PET-negative remission after six cycles of chemotherapy.

PET/CT for final response evaluation

An extensive number of studies have shown that FDG-PET performed post-treatment is highly predictive of PFS and OS in HL patients with and without residual masses on CT(41;42). Based on these findings the International Harmonization Project developed recommendations for response criteria for aggressive malignant lymphomas, incorporating PET/CT into the definitions of end-of-treatment response in FDG-avid lymphomas, including HL(43). Subsequent retrospective analyses confirm the superiority of the new response criteria in HL compared with the previous criteria which were based on morphological imaging alone(44). The new recommendations for response criteria are not as yet supported by substantial amounts of clinical data. Long-term follow-up of lymphoma patients evaluated by these criteria should be widely reported and is awaited with great interest. It should be kept in mind that a negative PET/CT does not rule out the presence of microscopic disease, just as a positive PET/CT does not establish treatment failure without verification by biopsy.

PET/CT before high-dose salvage therapy in relapsed HL

Duration of remission prior to relapse, and the response to induction therapy are important prognostic factors that predict a good outcome after high-dose chemotherapy with autologous stem cell support (HD+ASCT). A number of studies have shown that PET/CT performed after induction therapy and before HD+ASCT can predict which HL patients will achieve long-term remission after the salvage regimen(45-47). These studies all report a poor long-term PFS (after 2-5 years) in patients who are PET-positive after induction chemotherapy (31-41%), compared to a PFS of 73-82% in the patients who reach a PET-negative remission before HD+ASCT. However, these studies also report a higher false positive rate than with PET/CT performed early during first-line therapy. The role of PET/CT in this setting is still unclear, but the available evidence calls for clinical trials in order to improve the outcomes for patients who are still PET-positive after induction salvage chemotherapy. Encouraging results were published recently be Moscowitz *et al.*, who showed that a PET-guided approach may indeed help these patients. In this study, patients who were still PET-positive after the standard induction regimen (ICE) were not taken to HD+ASCT but instead given a non-cross-resistant regimen consisting of four biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) before HD+ASCT. Those patients who converted to PET-negative after GVD and before HD+ASCT had similar outcomes as those who were PET-negative after ICE and went on with the initially planned HD+ASCT(48).

PET/CT before and after allogeneic stem cell transplantation for relapsed HL

Little is known about the value of PET/CT in patients who relapse after, or who are ineligible for HD+ASCT. There are data to suggest that the remission status determined by PET/CT before allogeneic stem cell transplantation with reduced-intensity conditioning is highly predictive of outcome(49). Two studies indicate that after allogeneic stem cell transplantation, PET/CT may have a role in guiding the use of donor lymphocyte infusions(50;51).

Conclusions

Hodgkin lymphoma is treated according to clinical staging stage and prognostic scoring systems. The staging system has been practically unchanged for decades and despite developments in therapy, the prognostic importance of the clinical stage is intact. The risk factors for early stage disease and the IPS for advanced stage disease are based on well-established clinical prognostic factors which also seem to maintain their importance in more recent series. However, none of these prognostic factors have proven useful for more refined therapeutic tailoring. Increasing insight into the molecular biology of the disease has given us more knowledge about biologic markers with important prognostic properties. Some of those markers may in future show predictive properties and hopefully also lead us toward relevant therapeutic targets allowing for more individualized treatment.

In the continued absence of more risk-adapted HL therapy, response-adapted HL therapy may be a useful way to tailor therapy, with modification of treatment according to the results of early PET/

CT. PET/CT has become the most important imaging modality in the management of HL. Its use is based on much evidence and it clearly enhances the quality and accuracy of staging, response assessment, and treatment evaluation. While PET/CT seems to exceed any other existing tools in terms of diagnostic and prognostic properties, its clinical value to the patients depends on the way clinicians use it. There is a general agreement that it is desirable to have access to the most accurate determination of disease extent at the time of diagnosis, and also to have access to the most prognostic assessment of final treatment response. For those reasons, PET/CT has been accepted as standard of care at staging and final response assessment of HL, and consequently incorporated into the current guidelines.

The situation is still less clear during therapy. It seems clear that interim PET/CT allows for a better and earlier prediction of final treatment response and long-term outcome that CT. While PET/CT is an excellent tool for HL treatment monitoring, we are only beginning to understand how to best use this tool. In order to keep improving this understanding, we should continue to offer our patients treatment within clinical trials investigating risk- and response-adapted HL therapy. In clinical use outside the context of clinical trials, it is important to avoid inappropriate use of PET/CT, and particularly to avoid using PET/CT results to guide therapeutic decisions if not supported by evidence from clinical trials.

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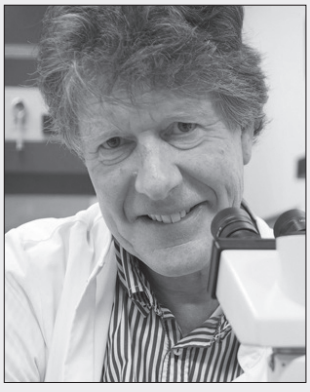

CURRICULUM VITAE

Professor Anton Hagenbeek

Professor Anton Hagenbeek received his M.D. degree from the Erasmus University in Rotterdam. He was trained in experimental hematology in the Radiobiological Institute T.N.O. in Rijswijk where he obtained his Ph.D. in 1977 and was, after training in internal medicine / hematology in Rotterdam, a fellow in hematology at U.C.L.A.

He worked as a staff member of the Dr Daniel den Hoed Cancer Center in Rotterdam, Department of Hematology from 1982 until 1997, and was in charge of the autologous and allogeneic stem cell transplantation program there between 1987 and 1994. In 1993 he was appointed Professor of Clinical and Experimental Hemato-Oncology, at the Erasmus University, Rotterdam. His main research interests were in developmental therapeutics for leukemia, focussing on translational research from preclinical animal models and in vitro studies to clinical application. From studies on minimal residual disease and experimental bone marrow transplantation (GVHD-GVL) in the early 1980s, he then moved into immuno-gene therapy of hematological malignancies. To date, his clinical research activities are mainly in the field of (intergroup) studies in non-Hodgkin's lymphomas and Hodgkin lymphomas. He has established two (international) consortia dealing with (1) developing new biological prognostic indices in lymphoma and (2) running first-in-man phase I/II studies with new agents in the lymphomas and chronic lymphocytic leukaemia (CLL). He has (co-)authored 335 papers in peer-reviewed journals. In 1997, he was appointed Professor of Hematology at the University Medical Center Utrecht, The Netherlands. Since 2006 he holds a joined appointment as Professor of Hematology in the Department of Hematology, Academic Medical Center, University of Amsterdam, the Netherlands.

Early Stage Hodgkin Lymphoma: Open Questions And Controversies

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Combined modality treatment remains the therapy of choice for patients with both favorable and unfavorable early stage Hodgkin lymphoma. Based on clinical prognostic factors, as established by various Lymphoma Cooperative Groups less and more intense treatment regimens were explored in prospective, randomized phase III clinical trials. In particular, large studies with a long follow-up done by EORTC-GELA and the German Hodgkin Study Group will be presented. In these studies further reduction in the number of cycles of chemotherapy and a decrease in radiation doses appeared to be feasible, maintaining the highest possible cure rate and at the same time reducing early- and late side effects.

Introduction

In the history of cancer treatment, Hodgkin lymphoma (HL) appeared to be the first malignancy that could be cured. The development of treatment strategies through the past 50 years can be subdivided in 4 major areas, i.e. first of all employment of radiotherapy with massive doses and large radiation fields focussing on response and subsequent cure with toxic side effects as a posteriority; secondly, exploring combined modality treatment with lower doses of radiation and smaller radiation fields in combination with chemotherapy to maintain the high cure rate and reduce the acute- and late side effects; thirdly, further reduction of radiation doses and a further decrease of radiation field size (from "involved field" to "involved node" radiotherapy) in combination with less and less toxic chemotherapy to further reduce acute and late toxicity; finally, during the past years, it is explored through PET-guided randomized phase III clinical trials whether in specific subgroups of patients the number of cycles of chemotherapy can be further reduced and radiotherapy can be abandoned aiming at the highest possible cure rate, further reduction in side effects and maintenance of optimal quality of life.

In this Chapter prognostic factors and treatment results in HL patients presenting with stage I or II supradiaphragmatic disease will be presented. As only 7% of limited stage HL patients present with infradiaphragmatic disease, this subgroup will not be discussed.

Prognostic factors

Through the long term follow-up of large cohorts of patients participating in phase I prospective clinical trials, various Lymphoma Cooperative Groups established prognostic factors for HL patients presenting with limited disease. One should realize that these factors were mainly derived from clinical

Table 1. Definition of favorable and unfavorable early stage Hodgkin lymphoma

	EORTC	GHSG	NCIC/ECOG
Risk factors	(a) large mediastinal mass	(a) large mediastinal mass	(a) histology other than LP/NS
	(b) age ≥ 50 yrs	(b) extranodal disease	(b) age ≥ 40 yrs
	(c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms	(c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms	(c) ESR ≥ 50
	(d) ≥ 4 nodal areas	(d) ≥ 3 nodal areas	(d) ≥ 4 nodal areas
Favorable	CS I-II (supradiahragmatic) without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavorable	CS I-II (supradiahragmatic) with ≥ 1 risk factors	CS I or CS IIA with ≥ 1 risk factors CS IIB with (c) or (d) but without (a) and (b)	CS I-II with ≥ 1 risk factors

EORTC European Organization for Research and Treatment of Cancer; *GHSG* German Hodgkin Study Group; *NCIC* National Cancer Institute of Canada; *ECOG* Eastern Cooperative Oncology Group; *ESR* Erythrocyte sedimentation rate; *LP* Lymphocyte predominance; *NS* Nodular sclerosis; *CS* Clinical stage

trials in which standard field radiotherapy was applied and FDG PET scanning was not an integral part of the staging procedure.

Risk factors defining favorable and unfavorable early stage HL are presented in Table 1.

Apart from these prognostic factors assessed after diagnosis of HL, the treatment modality as well as the quality of response (i.e. partial remission/complete remission) as assessed during and/or after completion of treatment are crucial in determining the final outcome. During the past years several Lymphoma Cooperative Groups have embarked on PET-guided studies with the aim to further tailor therapy to prevent under- and overtreatment. First results of these trials, which may lead to further reduction of the number of cycles of chemotherapy and/or delete additional radiotherapy, are presented by Dr. Martin Hutchings in this session in his lecture entitled "Prognostic factors and the role of PET in Hodgkin lymphoma".

Treatment of early stage favorable Hodgkin lymphoma

Two large randomized trials are discussed, i.e. the H9 study from the EORTC/GELA Groups and the HD10 study from the German Hodgkin Study Group (GHSG). Designs and results are presented in Table 2.

EORTC European Organization for Research and Treatment of Cancer; *GHSG* German Hodgkin Study Group; *GELA* Groupe d'Etude des Lymphomes de l'Adulte; *IF-RT* involved-field radiotherapy; *RT* radiotherapy; *RFS* relapse free survival; *FFTF* freedom from treatment failure; *OS* overall survival

Table 2. Early stage (CS I/II) favorable Hodgkin lymphoma: The 2 large prospective randomized phase III trials

Trial (reference)	Years	Study arms	Number of patients	Outcome (RFS/FFTF)	Overall survival
EORTC/GELA H9 Favorable (1)	1998-2004	A. 6xEBVP + IF-RT 36 Gy B. 6xEBVP + IF-RT 20 Gy C. 6xEBVP (no RT) median follow-up 66 months	783	A. RFS 89% (5-yrs) B. RFS 84% (5-yrs) C. RFS 70% (5-yrs) no RT arm closed because of excess failure rate ($p < 0.001$)	A. OS 98% (5-yrs) B. OS 100% (5-yrs) C. OS 97% (5-yrs)
GHSG HD10 (2)	1998-2003	A. 2xABVD + IF-RT 30 Gy B. 2xABVD + IF-RT 20 GY C. 4xABVD + IF-RT 30 Gy D. 4xABVD + IF-RT 20 Gy median follow-up 91 months	1370	No differences in FFTF between patients given 2 or 4 cycles of ABVD or 20 or 30 Gy IF-RT (FFTF 86-90% at 8 yrs)	No overall survival differences between patients given 2 or 4 cycles of ABVD or 20 or 30 Gy IF-RT (OS 94-95% at 8 yrs)

Table 3. The HD-13-GHSG study in early stage favorable Hodgkin lymphoma
(ABVD vs AVD vs ABV vs AV)

	N	CR%	PD%	FFTF*	OS*
ABVD	198	97.5	1.0	93.5	98.4
vs					
ABV	191	95.8	3.1	84.5	95.9
ABVD	167	97.0	1.2	92.3	98.1
vs					
AV	156	91.0	5.8	75.3	98.7

* at 4 years

CR complete remission; PD progressive disease; FFTF freedom from treatment failure; OS overall survival

A total of 1710 patients were enrolled between 1/03 and 9/09.
Final analysis ABVD vs AVD: 2013.

The EORTC/GELA study (1) showed that there was no difference when involved field radiotherapy (IF-RT) of 36 Gy or 20 Gy was given subsequent to 6 courses of EBVP given every 3 weeks (Epiadriamycine; Bleomycine, Vinblastine, Prednisone). However, deleting radiotherapy led to a significant decrease in relapse free survival (RFS). Thus, this arm without radiotherapy was closed prematurely. Because of efficacious salvage regimens overall survival (OS) stayed at the same high level as compared to the EBVP cohorts that received IF-RT.

The GHSG-HD10 trial (2) indicated that only 2 cycles of ABVD (Adriamycine, Bleomycine, Vinblastine, Dacarbazine) followed by 20 Gy IF-RT was not inferior to the cohorts that either received more courses of ABVD and/or a higher dose of IF-RT. Thus, in patients without risk factors 2 courses of ABVD followed by 20 Gy IF-RT has become standard treatment, according to the GHSG.

In addition to the studies above, the GHSG undertook a most interesting study to explore whether certain components could be deleted from the ABVD regimen. In this HD13 study in early stage favorable HL, patients were randomized between 2 cycles of ABVD, AVD, ABV or AV, followed in all arms by 30 Gy IF-RT (3). The AV and ABV arms were closed prematurely due to more events, defined as progressive disease, relapse or death, during a continuous safety analysis (Table 3).

It is clear that reduction of the ABVD regimen to ABV or AV results in a decreased complete remission rate and an increase of patients with progressive disease or relapse. As a consequence, the percentage Freedom From Treatment Failure (FFTF) at 4 years is quite different between ABVD and ABV (9%) and between ABVD and AV (17%), both in favor of the ABVD standard arm. No differences in overall survival (OS) were noted so far, indicating successful salvage treatment in the second line. The HD13 study shows that Dacarbazine apparently is an essential component of the ABVD regimen. The final analysis of this study (ABVD versus AVD), which will be performed in 2013, will reveal whether Bleomycine can be deleted in the ABVD regimen.

Recently, a new international randomized phase III clinical trial was initiated (LYSA et al.) prospectively comparing ABVD with AVD in which regimen Bleomycine is replaced by Brentuximab Vedotin (Adcetris), the most effective antibody-drug conjugate consisting of anti-CD30, linked to monomethyl auristatin-E (MMA-E).

Treatment of early stage unfavorable Hodgkin lymphoma

Three large prospective randomized clinical trials will be presented, i.e. the EORTC/GELA H9-Unfavorable trial and the HD11 and HD14 studies from the GHSG. A summary of results is presented in Table 4.

Both the EORTC/GELA H9-Unfavorable trial and the HD11 study did not show an increase in progression free survival (PFS) comparing 4 cycles of BEACOPP-baseline with 4 cycles of standard ABVD (1,4). In the HD11 study 4x ABVD followed by 20 Gy IF-RT was inferior to the same regimen followed by 30 Gy IF-RT as far as PFS is concerned (81% vs 85%, respectively). The 4x ABVD + IF-RT 30 Gy was found to be non-inferior to the BEACOPP regimens and was recommended as the treatment of choice because of the greater toxicity of BEACOPP. Overall survival (OS) was not different between all arms in each of the two studies.

From the HD14 final analysis it appeared that intensified chemotherapy with 2 cycles of BEACOPP-escalated followed by 2 cycles of ABVD (2+2 regimen) followed by 30 Gy IF-RT significantly improved tumor control in patients with early stage unfavorable HL (5). There was significantly more severe hematologic toxicity with 2+2 (WHO grades 3 to 4: 87.1%) as compare with 4 cycles of ABVD (50.7%). In addition, a recent analysis revealed no significant differences in female fertility after 4 cycles of ABVD or the 2+2 regimen (6). Finally, there were no differences in treatment-related mortality or secondary malignancies between the two arms of the study. So far, OS is identical in both groups. It remains to be seen whether at long term the gain in the PFS achieved with BEACOPP-escalated outbalances a possible increased toxicity, in particular

Table 4. Phase III randomized clinical trials in unfavorable CS I/II Hodgkin lymphoma on ABVD vs. alternative chemotherapy regimens

Trial (ref).	Treatment	No. of patients	PFS included	OS (years)	Remarks (years)
EORTC/GELA H9-U (1)	ABVD x6 + IF-RT 30-36 Gy	276	91% (4)	95% (4)	No final analysis
mFU: 66 mths	ABVD x4 + IF-RT 30-36 Gy	277	87% (4)	94% (4)	EFS instead of PFS
	BEACOPP-baseline (b) x4 + IF-RT 30-36 Gy	255	90% (4)	93% (4)	n.s.
GHSG HD11 (4)	ABVD x4 + IF-RT 30 Gy	356	85% (5)	94% (5)	Final analysis
mFU: 82 mths	ABVD x4 + IF-RT 20 Gy	347	81% (5)	94% (5)	n.s.
	BEACOPP-b x4 + IF-RT 30 Gy	341	87% (5)	95% (5)	
	BEACOPP-b x4 + IF-RT 20 Gy	351	87% (5)	95% (5)	
GHSG HD14 (5)	ABVD x4 + IF-RT 30 Gy	818	88% (5)	97% (5)	$p<0.01$ (PFS)
mFU: 43 mths	BEACOPP-esc. x2 + ABVD x2 + IF-RT 30 Gy	805	95% (5)	97% (5)	n.s. (OS)

mFU median follow-up; *PFS* progression free survival; *EFS* event free survival; *OS* overall survival
BEACOPP: Bleomycine, Etoposide, Adriamycine, Cyclophosphamide, Oncovin, Procarbazine, Prednisone given every 3 weeks

the occurrence of secondary malignancies.

The GHSG has now adopted the 2+2 regimen as the new standard of care for early stage unfavorable HL. ABVDx4 followed by 30 Gy IF-RT remains an alternative for those clinicians outside the GHSG who want to wait for long term follow-up of patients treated with BEACOPP-escalated. However, one should keep in mind that the majority of patients relapsing after ABVD will undergo high dose treatment followed by autologous stem cell transplantation, which in itself may also lead to an increase in secondary malignancies. How these 2 different approaches balance out in the near future remains to be established.

The GHSG currently explores 2 modified BEACOPP regimens in patients with advanced stages HL (6x escalated ECAPP-B) versus 6x escalated ECADD-B) from which Vincristine and Bleomycine have been removed, the alkylating agent Procarbazine is replaced by Dacarbazine and doses of Etoposide and Adriamycine are reduced. Instead, Brentuximab Vedotin (Adcetris) has been substituted.

Finally, a recently published systematic review on combined modality treatment in patients with early stage HL confirmed that this strategy improves tumor control as well as overall survival (7).

Radiotherapy in early stage favorable and unfavorable Hodgkin lymphoma

As was shown in the above, it appeared to be possible to reduce the radiation dose, without jeopardizing progression free- and overall survival. The extent of the radiation field size underwent serial changes during the last decades, from extended field radiotherapy, employing subtotal nodal irradiation (STNI) via involved field radiotherapy, finally – since 2001 – to involved node radiotherapy with margins from 1.5 to 5 cm. From the data available, it appears that there are no statistically significantly differences between the 3 groups, both for progression free survival and overall survival. In addition, there were no marginal recurrences in the involved node radiotherapy patient group (8). It remains to be established whether the reduction in radiation dose and field size will finally lead to a decrease in the incidence of late side effects, in particular radiation-induced malignancies.

Conclusions

From the above it appears that for early stage favorable HL the generally accepted approach is 2 cycles of ABVD followed by 20 Gy IF-RT. For unfavorable early stage HL the GHSG has adopted 2 cycles of BEACOPP-escalated + 2 cycles of ABVD followed by 30 Gy IF-RT as standard of care, while others outside the GHSG – awaiting the possible long term side effects of BEACOPP-escalated – stick for the time being to 4 cycles of ABVD followed by 30 Gy IF-RT.

In the past, various trials have been reported comparing chemotherapy alone with chemotherapy followed by (extended- or involved field) radiotherapy. These were generally relatively small studies, from which no firm conclusions can be drawn. The only reliable set of data available comes from the EORTC-GELA H9-Favorable study, in which deletion of IF-RT after 6x EBVP yielded an inferior relapse free survival.

FDG-PET guided studies will shed more light on those subgroups of patients that may fare well with (less) chemotherapy only. The first controversial results on this clinical research topic are presented by Dr. Martin Hutchings elsewhere in the proceedings of this congress.

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CURRICULUM VITAE

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Treatment of advanced and relapsed Hodgkin lymphoma

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Introduction

Hodgkin lymphoma (HL) is a lymphoid malignancy that was regarded incurable 50 years ago particularly when diagnosed in advanced stages. The introduction of polychemo- and radiotherapy has substantially improved the prognosis with 70 – 80% of all patients cured long-term. The chance for cure depends on the prognostic profile as well as the treatment given. Hodgkin patients in remission are at high risk for developing late effects that include secondary neoplasia, heart, lung and other severe organ dysfunctions [1]. In addition, many patients become infertile depending on the amount and choice of chemotherapy given and the size and dose of the radiation fields. Also fatigue and other social problems can be observed in Hodgkin survivors.

Since the first description by Thomas Hodgkin [2], the origin of this disease has remained enigmatic for nearly 150 years. It was speculated that this disease could have an infectious or autoimmune origin. This changed with the establishment of Hodgkin lymphoma cell lines and the prove of their clonal nature. In addition, the CD30 antigen was identified which is strongly expressed on Hodgkin- and Sternberg-Reed cells [3]. After initial successful reports on radiotherapy for localized Hodgkin lymphoma, the introduction of multi-agent chemotherapy such as MOPP and later ABVD fundamentally changed the treatment of this malignancy. The reported long-term disease control were around 60% in the original reports [4]. For many years, more effective regimen than ABVD have thus been investigated.

The introduction of BEACOPP escalated by the German Hodgkin Study Group (GHSG) finally demonstrated, that this regimen is superior in both, tumor control and overall survival when compared to COPP/ABVD or a reduced dose BEACOPP variant. With longer follow up, these differences have become more obvious with an advantage of 18% in tumor control and 11% in survival for BEACOPP escalated [5]. Since then, our group has worked on further improving on the safety of this regimen. In our more recent HD15 trial, more than 2200 patients were randomized between the old standard (8xBEACOPP escalated), and two experimental arms (6xBEACOPP escalated or 8xBEACOPP-14 in baseline doses). This trial included more than 400 centers from five European countries demonstrating that 6xBEACOPP escalated is more effective than the previous standard and BEACOPP-14 [6]. In addition, this regimen is also associated with less toxicity including a treatment related mortality of 0,8% and a rate of secondary leukemia/MDS of 0,3%. Subsequently, 6 cycles of BEACOPP escalated were adapted as new standard of care in the GHSG follow up HD18 trial. In addition, PET performed after chemotherapy in HD15 allowed to identify those patients who were in need for additional radiotherapy. Only those patients having at least 2.5 cm residual tumor after chemotherapy that was PET-positive received radiotherapy. This helped to reduce the number of patients receiving additional radiotherapy to 11% as compared to 70% in the prior HD9 study.

There has been an ongoing discussion as to the standard of care and best treatment of choice for advanced-stage Hodgkin lymphoma. Overall, three prospectively randomized trials directly compared ABVD with BEACOPP escalated in different variants (4 escalated+4 baseline or 4 escalated +2 baseline). These trials enrolled between 197 and 549 patients and were only powered to show differences in terms of 5-year progression free survival. These endpoints were indeed met for all three trials ranging from 12 to 15% difference in PFS at 5 years (p=0,0003 - 0,038). The overall survival difference at 5 years ranged from 4 to 8% and was not

significant. However, none of these trials were powered to detect differences in overall survival since the number of patients recruited was not sufficient. Taken together, these trials have confirmed the superior efficacy of BEACOPP escalated over ABVD although there were different views [7].

Positron emission tomography might guide us in the optimal treatment for Hodgkin lymphoma patients. This tool has been shown to reliably indicate metabolic activity in patients with Hodgkin lymphoma. To this end, a number of prospectively randomized trials currently evaluate the use of PET to better guide intensity of treatment in this group of patients.

In patients with relapsed Hodgkin lymphoma, two randomized trials demonstrated that high dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) gives significantly better tumor control and are thus the standard of care in this group of patients [8,9]. The more recent European HDR2 intergroup study aimed at further improving the outcome for relapsed patients. However, a more aggressive variant with high dose single agent treatment added to initial re-induction phase failed to improve outcome in this trial [10]. Thus, two cycles of chemotherapy followed by HDCT (BEAM) is usually being recommended for relapsed HL. There are no major differences between induction regimen including DHAP, ICE, or IGEV.

There clearly is a need to develop new reagents for patients with Hodgkin lymphoma relapsing after HDCT. In this group of patients, particularly those who relapse early have a dismal prognosis [11]. The more recently described anti-CD30 antibody drug conjugate Brentuximab Vedotin has given very impressive result rates even in the initial phase I trial [12]. Subsequently, two pivotal studies in patients with relapsed and refractory Hodgkin lymphoma [13,14] and systemic Anaplastic Large Cell Lymphoma (sALCL) were performed. Both trials found impressive responses with 75% CR and PR in Hodgkin lymphoma patients and 86% in sALCL patients (CR rate 33 and 58%, respectively). Brentuximab Vedotin is also well tolerated with moderate neutropenia and peripheral neuropathy. The drug was subsequently registered by the US FDA in 2011 and the European EMA in 2012. Apart from the role in treating relapsed and refractory CD30-positive patients, Brentuximab Vedotin might also have a role as maintenance after HDCT. In the frontline setting, a new ABVD variant, AVD-A, is currently being compared to ABVD in advanced stage HL patients. In addition, a new BEACOPP variant is also being developed in a GHSG phase II randomized trial. Apart from Brentuximab Vedotin, there are a number of interesting new drugs that have shown clinical activity in patients with relapsed or refractory Hodgkin lymphoma. This includes Lenalidomid, Everolimus, and others such as JAK-II inhibitors, anti-CD20 monoclonal antibodies, FMS inhibitors, JAK-II inhibitors as well as BTK inhibitors.

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9. Schmitz N et al: Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomized trial. Lancet 2002;359:2065-71.
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13. Younes A et al: Results of a pivotal phase II study of Brentuximab Vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012;20(18):2183-2189.
14. Pro B et al: Brentuximab Vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012;18(20):2190-2196.

ICLLM 2013

Pediatric Acute Lymphoblastic Leukemia

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ACADEMIC DEGREES:

M.D.	1980	University of Torino, Italy (cum laude) (Medicine)
Specialty	1983	University of Pavia, Italy (cum laude) (Clinical and Laboratory Hematology)
Ph.D.	1988	University of Milano, Italy (Experimental Hematology)

PROFESSIONAL APPOINTMENTS:

1981-83	Department of Internal Medicine, University of Torino, Torino, Italy (Clinical Training in Hematology)
	Royal Free Hospital School of Medicine, University of London, England
1983-85	Research Scientist, Department of Immunology
1986-90	Lecturer, Department of Immunology
	St. Jude Children's Research Hospital, Memphis, Tennessee
1990-93	Assistant Member, Department of Hematology/Oncology,
1993-1999	Associate Member, Department of Hematology/Oncology
1999-2006	Member, Departments of Hematology/Oncology and Pathology
2006-2011	Member, Departments of Oncology and Pathology
2007-2011	Vice Chair for Laboratory Research, Department of Oncology
	University of Tennessee Health Science Center, Memphis, Tennessee
1991-93	Assistant Professor, Department of Pediatrics,
1993-2000	Associate Professor, Department of Pediatrics
2000-2011	Professor, Department of Pediatrics
	National University of Singapore
2011-present	Professor, Department of Paediatrics

OTHER PROFESSIONAL ACTIVITIES

St. Jude Children's Research Hospital:

1996-1998	Member, Postdoctoral Review Committee
1998-1999	Member, Clinical Protocol Scientific Review and Monitoring Committee
1999-2002	Member and Vice-Chair, Faculty Appointments and Promotions Committee
1996-2005	Chair, Tumor Cell Utilization Committee
2001-2008	Member, Flow Cytometry Core Facility Oversight Committee
2002-2004	Member, International Outreach Program Advisory Committee
2002-2005	Member, Education Program Committee
2002-2006	Member, Clinical Protocol Scientific Review and Monitoring Committee
2003-2011	Member, Molecular Clinical Trials Core Oversight Committee
2006-2008	Vice-Chair, Clinical Protocol Scientific Review and Monitoring Committee
2006-2007	Member, Faculty Appointments and Promotions Committee
2006-2011	Chair, Tissue Resource Committee
2009-2010	Chair, Clinical Protocol Scientific Review and Monitoring Committee
2010-2011	Member, Institutional Review Board
2010-2011	Member, Faculty Appointments and Promotions Committee

Other:

1989-91	Member, Expert panel for immunodiagnosis of leukemia and lymphoma, International Committee for Standardization in Hematology
1995	Member, European Working Group on Leukemia Immunophenotyping
2002-2011	Member, Children's Oncology Group
2010	Member, Scientific Committee of Guido Paolucci International Award

MEDICAL LICENSURE State of Tennessee License # 41872

PATENT United States Patent 7,435,596: Modified cell line and method for expansion of NK cells

JOURNALS

Editorial Boards

1992-2011	LEUKEMIA
1995-1999	BLOOD
1997-2007	HAEMATOLOGICA
2007-present	AMERICAN JOURNAL OF HEMATOLOGY
2007-present	CLINICAL CYTOMETRY
2008-present	IMMUNOTHERAPY INSIGHTS
2012-present	KOREAN JOURNAL OF HEMATOLOGY

Reviewer

Acta Hematol., Am J Hematol, Am J Pathol, Blood, Bone Marrow Transplant, Br J Cancer, Br J Haematol, Cancer, Cancer Cell, Cancer Res, Cancer Chemother Pharmacol, Cancer Detect Prevent, Clin Cancer Res, Clin Exp Immunol, Critical Rev Clin Lab Sciences, Critical Rev Oncol Hematol Cytometry, Eur J Haematol, Eur J Immunol, Exp Hemat, Haematologica, Hematology, Human Gene Ther, Immunology, Immunol Lett, Int J Cancer, JAMA, J Clin Invest, J Clin Oncol, J Immunol, J Immunol Meth, J Leuk Biol, J Ped Hematol Oncol, Lab Invest, Lancet, Lancet Oncology, Leukemia, Leuk Res, Mol Cell Biol, Mol Medicine Today, N Engl J Med, Oncogene, Ped Blood Cancer, Ped Int, Science Transl Med

GRANT REVIEW

National Institutes of Health Study Sections

1999-2000	Special Emphasis Panel on Shared Instrumentation Program
2001-2003	Member, Cancer Molecular Pathobiology Study Section
2004-2008	Member, Cancer Biomarkers Study Section
2003	RFA "Molecular Interactions between Tumor Cells and Bone"
2003	SPORE in Leukemia –Lymphoma
2006-2011	Special Emphasis Panel - NIH Loan Repayment Program

National Medical Research Council, Singapore

2012-	Local Review Panel Member, Cooperative Basic Research Grants

Ad Hoc Reviewer
National Institutes of Health
Leukaemia Research Fund of Great Britain
Medical Research Council of Great Britain
Cancer Research UK
Israel Science Foundation
Dutch Cancer Society
Italian Association for Cancer Research
Canadian Institutes of Health Research
French National Cancer Institute
United Arab Emirates University
Children's Research Foundation, Memphis, TN
Swiss National Science Foundation
European Hematology Association
Biomedical Research Council of Singapore
Health Research Council of New Zealand
Auckland DHB Charitable Trust, New Zealand
Sultan Qaboos University, Oman
French National Research Agency
Italian Ministry of University and Research
Solving Kids' Cancer Foundation

HONORS AND AWARDS

1998	Elected Member, American Society for Clinical Investigation
2000	First Rizzo Memorial Award from the Leukemia Research Foundation
2000	Distinguished Visitor, Anti-Cancer Foundation of South Australia
2002	Dozor Visiting Scholar, Ben Gurion University of the Negev, Israel
2007	Distinguished Faculty Medical License, State of Tennessee
2008	Elected Member, Association of American Physicians
2009	American Asssociation for Cancer Research, Team Science Award
2010	STaR Investigator Award, National Medical Research Council, Singapore

PROFESSIONAL SOCIETY MEMBERSHIPS

American Society of Hematology
Clinical Cytometry Society
International Society for Laboratory Hematology
Singaporean Society for Immunology

LANGUAGES

English plus Italian and Spanish (native languages)

RESEARCH INTERESTS

Novel approaches to the classification, monitoring and treatment of leukemia and lymphoma. Leukemia microenvironment. Cell therapy of cancer

PUBLICATIONS (Total printed or in press = 305):

Original Peer-Reviewed Articles

1. Caligaris-Cappio F, Vigliani R, Novarino A, Camussi G, **Campana D**, Gavosto F. Idiopathic myelofibrosis: a possible role for immune-complexes in the pathogenesis of bone marrow fibrosis. Br J Haematol 49:17-22, 1981.
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55. Silvennoinen O, Nishigaki H, Kitanaka A, Kumagai M, Ito C, Malavasi F, Lin Q, Conley ME, **Campana D**. CD38 signal transduction in human B-cell precursors: rapid induction of tyrosine phosphorylation, activation of *syk* tyrosine kinase, and phosphorylation of phospholipase C-γ and phosphatydilinositol 3-kinase. J Immunol 156:100-107, 1996.
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Bowman L, Grossman M, Rill D, Brown M, Zhong W-Y, Alexander B, Leimig T, Coustan-Smith E, **Campana D**, Jenkins J, Woods D, Brenner M. Interleukin-2 gene-modified allogeneic tumor cells for treatment of relapsed neuroblastoma. Hum Gene Ther, 9:1303-1311, 1998.

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43. Pui C-H, Relling MV, Sandlund JT, **Campana D**, Evans WE. Pharmacodynamics in childhood acute lymphoblastic leukemia. Acute Leukemias VIII – Prognostic Factors and Treatment Strategies, Buchner T, Hiddemann W, Ritter J, Wormann B, eds., Hematology and Blood Transfusion, Springer-Verlag (Berlin, Heidelberg), 364-369, 2001.
44. Pui C-H, Yeoh AE-J, Relling MV, **Campana D**, Downing JR, Evans WE. Molecular and cytogenetic risk groups in acute lymphoblastic leukemia. Educational Book, 6th Meeting of the European Haematology Association, 46-48, 2001
45. Sandlund JT, Coustan-Smith E, **Campana D**. Detection of submicroscopic bone marrow and peripheral blood involvement in T-cell lymphoblastic lymphoma. Educational Book, ASCO 2003.
46. Pui CH, Relling MV, Sandlund JT, Downing JR, **Campana D**, Evans WE: Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. Ann Hematol 83 (suppl 1): S124-126, 2004.
47. **Campana D**, Coustan-Smith E, Howard SC, Lorenzana R, Ribeiro RC. Classification and monitoring of childhood leukemia in developing countries. Educational Book, ASCO 2006.
48. Pui CH, Relling MV, Sandlund JT, Downing JR, **Campana D**, Evans WE. Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia: study design and preliminary results. Ann Hematol 85 (suppl 1): 88-91, 2006.
49. Ribeiro RC, Razzouk BI, Pounds S, Crews KR, Hijiya N, Pui CH, **Campana D**, Rubnitz JE. Clinical trials for childhood acute myeloid leukemia at St. Jude Children's Research Hospital, 1980 through 2005. Ann Hematol 85 (suppl 1): 96-98, 2006.
50. **Campana D**, Flotho C, Coustan-Smith E, Pui CH, Downing JR. Molecular predictors of outcome in acute lymphoblastic leukemia. Ann Hematol 87 (suppl 1): 40-42, 2008.
51. **Campana D**. Molecular determinants of treatment response in acute lymphoblastic leukemia. Hematology 2008 (ASH Education Program Book), 366-373, 2008.
52. Shook D, Coustan-Smith E, Ribeiro RC, Rubnitz JE, **Campana D**. Minimal residual disease quantitation in acute myeloid leukemia. Clin Lymphoma Myeloma, 9 Suppl 3:S281-285, 2009.

53. **Campana D**. Minimal residual disease in acute lymphoblastic leukemia. Hematology 2010 (ASH Education Program Book), 7-12, 2010.
54. Pounds S, Cao X, Cheng C, Yang J, **Campana D**, Evans W, Pui CH, Relling M. Integrated analysis of pharmacokinetic, clinical, and SNP microarray data using projection onto the most interesting statistical evidence with adaptive permutation testing. Int. J. Data Mining and Bioinformatics, 5: 143-157, 2011
55. Pui CH, **Campana D**, Sandlund JT, Bhojwani D, Evans WE, Relling MV, Jeha S. Treatment of childhood acute lymphoblastic leukemia without cranial irradiation. Ann Hematol, 90 (Suppl 1): S61–S63, 2011.

GRANT SUPPORT

Active

National Medical Research Council, Singapore; STaR Investigator Award; Cell Therapy of Cancer. 07/01/11-06/30/16, Dario Campana M.D. Ph.D., Principal Investigator

National Medical Research Council, Singapore; IRG Award; Detection of minimal residual disease in acute myeloid leukemia; 07/01/11-06/30/14, Dario Campana M.D. Ph.D., Principal Investigator

Completed

ASSISI Foundation – Component L; Development of expanded, genetically modified natural killer cells, 11/01/2010-10/31/2011, Dario Campana M.D. Ph.D., Principal Investigator

Fondation de Gouverneurs de l'espoir – NK cell therapy of Ewing family of tumors. 01/01/2008-12/31/2010, Dario Campana M.D. Ph.D., Principal Investigator

Columbia - Genzyme (subcontract); Clofarabine in combination with cytarabine and Total body irradiation followed by allogeneic stem cell transplantation. 01/01/2009-12/31/2010, Dario Campana M.D. Ph.D., Principal Investigator

1 RO1 CA120772; Molecular and Pharmacologic Correlates of Acute Myeloid Leukemia in Down Syndrome. 07/01/07-06/30/12; Jeffrey Taub M.D., Principal Investigator

1 RO1 CA113482; Cell Therapy of Refractory Leukemia. 03/01/06-02/28/11; Dario Campana M.D. Ph.D., Principal Investigator

1 RO1 CA115422; Clinical Significance of Residual Myeloid Leukemia. 06/01/06-05/31/11; Dario Campana M.D. Ph.D., Principal Investigator

2 R01 CA 60419-10; Detection and Therapy of Residual Leukemia in Children; 09/01/93-07/31/08; Dario Campana, M.D. Ph.D., Principal Investigator

2 RO1 CA 58297-12; B Cell Progenitors and Bone Marrow Microenvironment; 02/01/93-06/30/05, 20% effort; Dario Campana, M.D. Ph.D., Principal Investigator

2 RO1 CA 52259-13; Immunoglobulin Gene Rearrangement/Expression in Leukemia 07/01/1991-01/31/2006; Dario Campana, M.D. Ph.D., Principal Investigator

Rizzo Award – Leukemia Research Foundation; Detection of Minimal Residual Disease; 07/01/2000-06/30/2002; Dario Campana, M.D. Ph.D., Principal Investigator

5 UO1 RFA CA 58211; Treatment of Neuroblastoma with IL2 Transduced Tumor; Malcolm K. Brenner, M.D., Ph.D., Principal Investigator

1 RO1 CA 68237; Growth of Human Leukemic Lymphoblasts in Vitro; Kuruganti G. Murti, Ph.D., Principal Investigator

FDR-00010330-031; Study of Interleukin-4 in Childhood Leukemia; Wayne Furman, MD, Principal Investigator

TRAINEES

Students, fellows and post-docs

Ghada Mikhail - BSc student, 1988
Simon Ho - BSc student, 1990
Atsushi Manabe, MD - Postdoctoral research associate, 1991-1993
Ifti Hanif, MD – Hematology-Oncology Fellow, 1994
Masaaki Kumagai, MD - Postdoctoral research associate, 1993-1995
Akira Kitanaka, MD PhD - Postdoctoral research associate, 1995-1999
Cristina Tecchio, MD - Postdoctoral research associate, 1995-1996
Hikari Nishigaki, MD PhD - Postdoctoral research associate, 1995-1997
Chikako Ito, MD - Postdoctoral research associate, 1995-1999
Joaquin Sanchez, MD - Postdoctoral research associate, 1997
Cobie Groenendijk - Medical student, 1997
Anne Marie Schilder - Medical student, 1997
Toshio Suzuki, MD PhD - Postdoctoral research associate, 1997-2000
Frank Boddendijk - Medical student, 1997-1998
Elisabetta Todisco, MD - Postdoctoral research associate, 1998-2000
Zoltan Nemeth, MD - Postdoctoral research associate, 1998-2000
Jiann-Shiuh Chen, MD - Postdoctoral research associate, 1998-1999
Kleebsabai Srivannaboon, MD – Hematology-oncology fellow, 1998-2000
Hulya Cakmak – Medical student, 1999
Keegan Smith – Medical student, 1999
Keichiro Mihara, MD - Postdoctoral research associate, 1999-2003
Monica Cypriano, MD – Hematology-Oncology fellow, 2000-2001
Martin Andreansky – Hematology-Oncology Fellow, 2001-2003
Chihaya Imai, MD – Postdoctoral research associate, 2001-2005
Shotaro Iwamoto, MD – Postdoctoral research associate, 2003-2007
Hiroyuki Fujisaki, MD – Postdoctoral research associate, 2004-2009
Harumi Kakuda, MD – Postdoctoral research associate, 2004-2007
Virna Marin – PhD student, 2005
Deok Cho, MD – Postdoctoral research associate, 2007-2009
Noriko Shimasaki, MD – Postdoctoral research associate, 2007-present
Daniel Molanus – Medical student, 2007–2008
David Shook, MD – Hematology-Oncology Fellow, 2008-2011
Marika Masselli – PhD student, 2009
Chang Yu-Hsiang, MD PhD – Postdoctoral research associate, 2009-2012
Ko Kudo, MD – Postdoctoral research associate, 2009-present
Masaru Imamura MD– Postdoctoral research associate, 2011-present
Takahiro Kamiya MD – Postdoctoral research associate, 2011-present
Seow See Voon PhD – Postdoctoral research associate, 2011-present
Sally Chai MS – Research associate, 2011-present
Png Yi Tian – Honors project student, 2012-present
Ameera Binte Ahmad Jailani – BSc student, 2012-present
Paolo Lorenzini – Research associate, 2012-present
Arthur Yong Jun Jie – Undergraduate Science Research Programme Student, 2012-present
Chan Jing Ru – Honors project student, 2013-present

Visitors learning methods developed in our laboratory

Rosemary Otubo (Brazil) - Visiting laboratory technologist, 1993
Maurizio Arico, MD (Italy) - Visiting scientist, 1994
Emin Kansu, MD (Turkey) - Visiting scientist, 1994
Matilde Tsuchiya (Brazil) - Visiting laboratory technologist, 1994
Mary Drake (Ireland) - Visiting laboratory technologist, 1996
Rita Consolini, MD (Italy) - Visiting scientist, 1996-1997
Andre Baruchel, MD (France) - Visiting scientist, 1997
Manabu Sotomatsu, MD (Japan) – Visiting scientist, 1998
Giuseppe Gaipa, PhD (Italy) – Visiting scientist, 1998
Mona Ghasham (Lebanon) – Visiting laboratory technologist, 1999
Jeremy Hancock, PhD (England) - Visiting scientist, 1999, 2000
Kirk Reinhardt, MD (Germany) – Visiting scientist, 2000
Ashok Kumar (India) – Visiting laboratory technologist, 2000
Julie Irving, PhD (England)- Visiting scientist, 2000
Leping Zhang, MD (China)– Visiting scientist, 2000
Shotaro Iwamoto, MD (Japan) - Visiting Scientist, 2001
Clarks Cheung (Hong Kong)- Visiting laboratory technologist, 2001
Ms. Yang (Taiwan) - Visiting laboratory technologist, 2001
Chong Xu (China) - Visiting laboratory technologist, 2001
Ching Ching Seah (Singapore) - Visiting laboratory technologist, 2001
Eti Rosenthal (Israel)– Visiting Scientist, 2001
Gunter Kerst, MD (Germany) – Visiting Scientist, 2001
Jan Trka, MD (Czech Republic) - Visiting Scientist, 2001
Neda Marinov (Chile) – Visiting laboratory technologist, 2002 and 2004
Rebeca Montalva (Chile) – Visiting laboratory technologist, 2002
Chandrika Nair, MD (India) – Visiting Scientist, 2002
Patrizia Mancuso, PhD (Italy) – Visiting Scientist, 2002
Berta Valverde, MD (Costa Rica) – Visiting Scientist, 2002
Omar Perbellini, MD (Italy) – Visiting Scientist, 2002
Carlo Vincenzi (Italy) – Visiting Laboratory Technologist, 2002
Esperanza Tuset, MD (Spain) – Visiting Scientist, 2003
Sean Rooney (Ireland) – Visiting Laboratory Technologist, 2003
Patricia Disperati, MD (Brazil) – Visiting Scientist, 2003
Jhon Pando (Peru) – Visiting Laboratory Technologist, 2003
Barbara Buldini, MD (Italy) – Visiting Scientist, 2004
Li Zhi-Gang (China) – Visiting Laboratory Technologist, 2004
Lydene McArthur (New Zealand) – Visiting Laboratory Technologist, 2005
Veruska Alves, MD (Brazil) – Visiting Laboratory Technologist, 2005
Rodelio Lim, MD (Philippines) – Visiting Scientist, 2005
Hernan Webster, MD (Ecuador) – Visiting Scientist, 2005
Roger Devis, MD (Venezuela) – Visiting Scientist, 2005
Jorge Rossi, MS (Argentina) – Visiting Scientist, 2005
Grigory Tsaur, MD (Russia) – Visiting Scientist, 2005
Sebastian Boettcher, MD (Germany) – Visiting Scientist, 2005
Igor Olejnic, MD (Poland) – Visiting Scientist, 2005
Sharon Yeo Hui Joo (Singapore) – Visiting Laboratory Technologist, 2006
Tan Poh Lin MD (Singapore) – Visiting Scientist, 2006
Ebrahim Sayah (Canada) – Visiting Scientist, 2006
Paola Cabrera (Ecuador) – Visiting Laboratory Technologist, 2006
Migle Janeliuniene MD (Lithuania) – Visiting Scientist, 2006
Dima Oweiss (Jordan) – Visiting Laboratory Technologist, 2006
Xiomara Arevalo (Guatemala) – Visiting Laboratory Technologist, 2006
Carlos Bueno (Ecuador) – Visiting Laboratory Technologist, 2006
Ruidong Zang (China) – Visiting Scientist, 2007
Elias Perez Becerra MD (Mexico) – Visiting Scientist, 2007
Rose Otubo (Brazil) – Visiting Laboratory Technologist, 2007

Patricia Perez Vera PhD (Mexico) – Visiting Scientist, 2007
Khaleed Shaaban MD (Egypt) – Visiting Scientist, 2007
Shamilla Ghosh MD (India) – Visiting Scientist, 2008
Zsuzsa Hevessy PhD (Hungary) – Visiting Scientist, 2008
Blanca Vega (Peru) – Visiting Laboratory Technologist, 2008
Suzy Figueredo MD (Paraguay) – Visiting Scientist, 2008
Ila Bansal MD (UAMS, Little Rock, AR) – Visiting Scientist, 2008
Nachla Al-Sharkawi MD (Egypt) – Visiting Scientist, 2008
Anisya Shuryeva (Russia) – Visiting Laboratory Technologist, 2008
Elena Boyakova (Russia) – Visiting Laboratory Technologist, 2008
Kai Witte (Germany) – Visiting Laboratory Technologist, 2008
Badrinath Yajamanam (India) – Visiting Laboratory Technologist, 2008
M. Juarez Velazquez (Mexico) – Visiting Scientist, 2009
Shuei-Ming Wang (Taiwan) – Visiting Laboratory Technologist, 2009
Siew Peng Chen (Singapore) – Visiting Laboratory Technologist, 2009
Yekaterina Zueva MD (Russia) – Visiting Scientist, 2009
Alejandro Arevalo MD (Philippines) – Visiting Scientist, 2009
Fatmeh Abbas (Lebanon) – Visiting Laboratory Technologist, 2009
Rami Mahfouz, MD (Lebanon) – Visiting Scientist, 2009
Elisabete Delbuono (Brazil) – Visiting Laboratory Technologist, 2009
Manu Goyal (India) – Visiting Laboratory Technologist, 2009
Nereida Mendez (Mexico) – Visiting Laboratory Technologist, 2010
Tathagat Chatterjee (India) – Visiting Scientist, 2010
Isabelle Louis (Canada) – Visiting Scientist, 2010
Shotaro Iwamoto (Japan) – Visiting Scientist, 2011
Kao Hsiao-Wen (Taiwan) – Visiting Scientist, 2011
Huang Ying-Jung (Taiwan) – Visiting Scientist, 2011
Behzad Poopak (Iran) – Visiting Scientist, 2012
Eva Su Ying Hui (Taiwan) – Visiting Laboratory Technologist, 2012
Shiann-Tarng Jou (Taiwan) – Visiting Scientist, 2012
Khalikur Rahman (India) – Visiting Scientist, 2012
Chan-Jeoung Park (South Korea) – Visiting Scientist, 2012
Normal Lucena (Brazil) – Visiting Scientist, 2013

CLINICAL PROTOCOLS

Principal Investigator

NKCARCD19 - Pilot study of redirected haploidentical natural killer cell infusions for B-lineage acute lymphoblastic leukemia (with Dr. TAN Poh Lin et al.)

Initiating Principal Investigator

NKCD19 – Pilot study of genetically modified haploidentical natural killer cell infusion for B-lineage acute lymphoblastic leukemia (Current Principal Investigator: Dr. D. Shook)

NKEXP – Pilot study of expanded, activated haploidentical natural killer cell infusion for non-B-lineage hematologic malignancies (Current Principal Investigator: Dr. D. Shook)

Co-Investigator

Total Therapy Study XIIIB for Newly Diagnosed Patients with Acute Lymphoblastic Leukemia (with Dr. C-H Pui et al.)
Total Therapy Study XIV for Newly Diagnosed Patients with Acute Lymphoblastic Leukemia (with Dr. C-H Pui et al.)
Total Therapy Study XV for Newly Diagnosed Patients with Acute Lymphoblastic Leukemia (with Dr. C-H Pui et al.)
Total Therapy Study XVI for Newly Diagnosed Patients with Acute Lymphoblastic Leukemia (with Dr. S. Jeha et al.)
ALLR17 Treatment of patients with relapsed acute lymphoblastic leukemia (with Dr. S. Jeha et al.)
AML97 Study for Newly Diagnosed Patients with Acute Myeloid Leukemia (with Dr. R.C. Ribeiro et al.)
AML2002 Treatment of patients with newly diagnosed acute myeloid leukemia or myelodysplasia (with Dr. J.E. Rubnitz et al.)
AML2008 Treatment of patients with newly diagnosed acute myeloid leukemia or myelodysplasia (with Dr. J.E. Rubnitz et al.)
Phase I Study of Cytokine-Gene modified Autologous Neuroblastoma Cells for Treatment of Relapse/Refractory Neuroblastoma (with Dr. M.K. Brenner et al.)
Cord Blood Stem Cell Transplantation in Patients with Agammaglobulinemia (with Dr. M.E. Conley et al.)
Haploidentical stem cell transplantation utilizing megadoses of purified CD34+ hematopoietic cells for patients with hematologic malignancies (with Dr. G. Hale et al.)
HAPREF Haploidenticat transplantaion in patients with leukemia (with Dr. G. Hale et al.)
NKAML NK cell therapy in patients with AML (With Drs. Rubnitz, Leung et al.)
NB05 Therapy for children with advanced stage high risk neuroblastoma (with Dr. Furman et al.)
RELLA-2005 RECIFE ALL Pilot study (with Drs Pedrosa, Rivera, Ribeiro et al.)

INVITED SEMINARS, LECTURES, ETC.

February 29, 1984 Department of Haematology, St.Thomas Hospital, London, England
Monoclonal antibodies in clinical and experimental haematology

June 3, 1984 Department of Immunology, University of Birmingham, Birmingham, England
B cell heterogeneity in human bone marrow

April 4, 1984 Department of Haematology, University of Verona, Verona, Italy
Monoclonal antibodies in autologous bone marrow transplantation

September 12, 1985 3rd Annual Meeting of the European Society for Haemapheresis, Bournemouth, England
Elimination of leukaemic cells with monoclonal antibodies and complement in autologous bone marrow transplantation

March 12, 1986 2nd National Congress of the Italian Society for Hemapheresis, Torino, Italy
Purging with monoclonal antibodies in bone marrow transplantation

June 16, 1986 Scuola Superiore di Oncologia e Scienze Biomediche, S.Margherita Ligure, Italy
Recent results in the application of monoclonal antibodies for the diagnosis of leukemia

July 3, 1986 Annual Meeting of the British Autograft Group, Birmingham, England
Results and practicalities of purging the bone marrow with cocktails of monoclonal antibodies

October 13, 1986 Department of Haematology, University of Liverpool, Liverpool, England
Immunophenotyping for leukaemia diagnosis and autologous bone marrow transplantation

December 17, 1986 Department of Haematology, St. Thomas Hospital, London, England
Characterization of leukaemic cells for purging in autologous bone marrow transplantation

January 15, 1987 Department of Immunology, Institute of Child Health, London, England
Immunological characterization and proliferative capacity of acute lymphoblastic leukaemia cells and their normal counterpart

March 19, 1987 Amersham International, Amersham, England
Therapeutic use of monoclonal antibodies

April 22, 1987 Workshop "Thymus microenvironment and T lymphocyte differentiation", Department of Immunology, Royal Postgraduate Medical School, London, England
Proliferating capacity of thymocyte populations

April 30, 1987 Symposium "New approaches in oncology", Gleneagles, Scotland
Immunological purging in lymphoproliferative disorders

June 19, 1987 Symposium "Clinical applications of antileucocyte monoclonal antibodies", SANOFI, ClinMidy, Montpellier, France
Monoclonal antibodies for purging in bone marrow transplantation: a review

June 21, 1987 18th International Leucocyte Culture Conference, Symposium "Differentiation of T and B lymphocytes", La Grande Motte, France
Antigen expression and proliferative activity during B and T cell development

September 7, 1987 Symposium "Purging bone marrow for transplantation", European School of Oncology, Milano, Italy
Selection of antibodies

October 7, 1987 9th Meeting of the Turkish Society of Immunology, Bursa, Turkey
Cell cycle analysis of leukaemic blasts and their normal counterparts
Antigenic phenotypes of lymphoproliferative diseases

November 13, 1987 British Society for Immunology and Haematology Joint Autumn Meeting, London, England
Chair, "Cell heterogeneity" session

December 8, 1987 MSc Course in Immunology, King's College, London, England
Lymphocyte markers and malignancy

December 9, 1987 IMLS Fellowship Haematology Course, Paddington College, London, England
Lymphocytes

January 25, 1988 Diagnostic Haemopathology Course. Postgraduate Medical School, Hammersmith Hospital, London, England
Phenotypic changes and proliferative activity during lymphoid development

January 27, 1988 Special Haematology Course, Harrow College, Harrow, England
The lymphocytes and immunological aspects of leukaemia

March 10, 1988 International Committee for Standardization in Haematology. Workshop on Immunophenotyping of Leukaemia and Lymphoma, Amsterdam, The Netherlands
Labelling cells with immunofluorescence

April 9, 1988 Joint Meeting of the British and French Societies for Immunology. Workshop "Thymus and the differentiation of T lymphocytes", Paris, France
The expression of T cell receptor proteins during ontogeny

May 19, 1988 Symposium on Morphology of Blood Cells, Royal Manchester Infirmary, Manchester, England
Applications of immunofluorescence and immunocytochemistry in leukaemia diagnosis

June 22, 1988 Modern Trends in Human Leukemia VIII, Wilsede, Germany
Ontogeny of T cell receptor proteins in man

August 18, 1988 Meeting on Paediatric Bone Marrow Transplantation, Salford University, Manchester, England
Autologous bone marrow transplantation in acute lymphoblastic leukaemia

October 7, 1988 University of Alicante Summer Course, Benidorm, Spain
The immunology of bone marrow transplantation

October 25, 1988 British Council Course "Recent advances in bone marrow transplantation", University College Hospital, London, England
Detection of minimal residual leukaemia

November 15, 1988 Symposium "Leukaemia '88", Northern General Hospital, Sheffield, England
The application of immunofluorescence for leukaemia diagnosis

November 29, 1988 UCLA Symposium "Acute lymphoblastic leukemia", Tapatio Springs, TX
Critical analysis of detecting minimal residual leukemia

January 27, 1989 British Lymphoma Pathology Group Meeting. Charing Cross Hospital, London, England
The pathology of thymic lymphocyte differentiation

January 30, 1989 Diagnostic Haemopathology Course. Postgraduate Medical School, Hammersmith Hospital, London, England
Immunodiagnosis of leukaemia and detection of minimal residual disease

February 24, 1989 4th International Conference on Human Leucocyte Differentiation Antigens, Vienna, Austria
Co-Chair, "B Cell Ontogeny" session

March 7, 1989 MSc Course in Immunology, King's College, London, England
Lymphocyte markers and malignancy

March 21, 1989 International Symposium on the Clinical Application of Flow Cytometry, London, England
Flow cytometry in the diagnosis and management of leukaemias

April 3, 1989 2nd Workshop "The Thymus. Histophysiology and Dynamics in the Immune System", Kerkrade, The Netherlands
Ontogeny of T cell receptor proteins in man

April 5, 1989 British Society for Haematology and Netherland Society for Haematology Combined Scientific Meeting, Educational Session, Canterbury, England
The reliability of immunophenotyping in the diagnosis of leukaemia

May 30, 1989 International Symposium, "New Aspects in Childhood Leukemia". Weimar, Germany
Co-Chair, "Biology of Leukaemia" session

June 5, 1989 3rd European Cytometry User's Meeting, Ghent, Belgium
Strategies for leukaemia phenotyping and minimal disease detection

June 27, 1989 Department of Haematology, University Hospital, Groningen, The Netherlands *Leukaemia phenotyping and detection of residual disease*

June 28, 1989 Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands
T cell receptor ontogeny in man

July 4, 1989 Department of Haematology, King's Hospital, London, England
Immunophenotyping of leukaemia and detection of minimal residual disease

July 31, 1989 7th International Congress of Immunology, Berlin, Germany. Symposium S6: Development of T cells
Ontogeny of the human T cell receptors

September 5, 1989 10th Congress of the International Society of Haematology (European and African Division), Jerusalem, Israel
Chair, Educational session, "Cell markers"
Lecture: Immunophenotyping of ALL

October 4, 1989 Department of Molecular Biology, University of Ulm, West Germany
The detection of residual leukaemia with immunological methods

November 9, 1989 MSc Course in Immunology, King's College, London, England
Lymphocyte markers and malignancy

November 28, 1989 Department of Immunology, Guy's Hospital, London, England
The development of human T cell receptors

December 5, 1989 Department of Immunology, Royal Postgraduate Medical School, London, England
Ontogeny of T cell receptor proteins in man

January 10, 1990 "The Antibody Club", Middlesex Hospital, London, England
Development of T cell receptor gamma/delta bearing cells

January 22, 1990 Department of Immunology, University College and Middlesex School of Medicine, London, England
Ontogeny of T cell receptor proteins in man

April 23, 1990 Tenovus Research Laboratory, University of Southampton, Southampton, England
The detection of minimal residual disease with immunologic methods

August 22, 1990 15th International Cancer Congress, Hamburg, Germany
Strategies for detecting residual leukemia with immunological methods

September 20, 1990 2nd Marmara Medical Days, Instanbul, Turkey
Critical analysis of detecting residual leukemia. Improving the outcome of bone marrow transplantation using immunological methods

September 22, 1990 5th Mediterranean Blood Club, Antalya, Turkey
Similarities and discrepancies between normal and malignant lymphohematopoietic development. Novel approaches for detecting and eliminating residual leukemia

May 8, 1991 Postgraduate School of Hematology, Verona, Italy
The detection of residual disease in acute leukemia

June 28, 1991 International Workshop "Recent advances in tumor cell biology of acute leukemias - Impact on clinical diagnosis and therapy", Berlin, Germany
Co-Chair, "Hematopoietic Differentiation" session
Invited lecture "*Discrete maturation stages of T-ALL identified by T-cell differentiation antigens and TCR protein expression*"

November 16, 1991 7th Congress of the Italian Association for Immunopharmacology, Stresa, Italy *Monoclonal antibodies for the identification and elimination of residual disease*

December 12, 1992 International Symposium on Recent Advances in Pathology, Riyadh, Saudi Arabia *The applications of flow cytometry in immuno-hematology*

September 16, 1993 8th Annual Meeting, Clinical Applications of Cytometry, Charleston, South Carolina
Leukemia immunophenotyping for predicting and assessing the treatment response in childhood acute leukemia

October 1, 1993 6th Annual Meeting of the American Society of Pediatric Hematology-Oncology, Chicago, Illinois
Monitoring minimal residual disease

October 30, 1993 35th Meeting of the Spanish Society of Hematology, Pamplona, Spain
Detection of minimal residual disease in acute lymphoblastic leukemia

April 18, 1994 25th Congress of the International Society of Hematology, Cancun, Mexico
Immunologic markers to detect minimal residual leukemia

April 26, 1994 International Symposium on Immunology and Leukemia, Nancy, France
Chair "Immunophenotyping of leukemia" session
Lecture: Detection of residual disease with immunologic methods: technical developments and clinical significance

April 29, 1994 Schering-Plough Research Center, Dardilly, France
In vitro growth of normal and leukemic human B cell progenitors

May 13, 1994 Nordic Hematology Society, Uppsala, Sweden
Minimal residual disease - technical and clinical aspects

August 30, 1994 British Council Symposium on "Biology of normal and leukemic differentiation", Ankara, Turkey
Inducers and suppressors of normal and leukemic B cell growth

March 31, 1995 8th Meeting of the German Cancer Society, Division of Experimental Cancer Research, Heidelberg, Germany
Growth requirements of normal and leukemic B cell precursors

June 14, 1995 European School of Flow Cytometry, Urbino, Italy
Detection of minimal residual disease by flow cytometry

October 15, 1995 8th Congress of the International Society of Haematology, Asian Pacific Division, Brisbane, Australia; Education Session "Haemopoiesis"
Cell biology of acute leukemia

October 16, 1995 8th Congress of the International Society of Haematology, Asian Pacific Division, Brisbane, Australia; Symposium "Cellular Interactions"
B cell development and bone marrow microenvironment

October 19, 1995 Institute of Clinical Pathology and Medical Research, Dept of Haematology, Westmead Hospital, Sydney, Australia
Microenvironmental factors that regulate B lymphopoiesis

October 20, 1995 Children's Leukaemia and Cancer Research Center, University of South Wales, Sydney, Australia
Detection of minimal residual disease in acute leukemia

February 1, 1996 2nd CD38 Workshop, Hopital Pitie-Salpetriere, Paris, France
CD38 signalling in immature B cells

April 12, 1996 Finnish Immunology Society Annual Meeting, Helsinki, Finland
Regulation of normal and leukemic B lymphopoiesis

May 8, 1996 School of Biological Sciences, University of Urbino, Italy
Detection of minimal residual disease in childhood leukemia

August 27, 1996 Tokyo Children's Cancer Study Group, Tokyo, Japan
In vitro growth of human immature lymphoid cells: biologic and clinical significance

August 28, 1996 International Congress on Human Cell and Cell Culture, Tokyo, Japan
Human B cell progenitors and bone marrow microenvironment

August 30, 1996 Kyoto Prefectural University of Medicine, Kyoto, Japan
Growth requirements of normal and leukemic immature B cells

November 21, 1996 University of Minnesota Cancer Center, Minneapolis, Minnesota
In vitro growth of human immature lymphoid cells: biologic and clinical significance

March 20, 1997 University of Campinas, Campinas (Sao Paulo), Brazil
Detection of minimal residual disease in acute leukemia

March 22, 1997 1st International Symposium of Pediatric Oncology, Hospital do Servidor Publico Estadual, Sao Paulo, Brazil
Detection of minimal residual disease in acute leukemia

April 4, 1997 Applications of Flow Cytometry in Blood and Marrow Stem Cell Transplantation -ISHAGE, Stone Mountain, GA
Detection of minimal residual disease in childhood acute lymphoblastic leukemia

June 5, 1997 5th Meeting of the Iberic Society of Flow Cytometry, Lisbon, Portugal
Detection of minimal residual disease in acute leukemia with immunologic methods

October 24, 1997 3rd International CD38 Workshop, Hopital Pitie-Salpetriere, Paris, France
Chair "CD38-related molecules' session
Lecture: CD38-mediated signaling in immature B cells

October 31, 1997 International Symposium on Minimal Residual Disease, Salamanca, Spain
Immunologic detection of residual disease in childhood acute lymphoblastic leukemia

February 28, 1998 International Society for Analytical Cytology, XIX Symposium, Colorado Springs, CO
Tutorial: Detection of minimal residual disease

June 26, 1998 Guatemala City, Guatemala
Diagnosis of acute leukemia and detection of minimal residual disease

July 11, 1998 FASEB Summer Research Conference "Recent Advances in CD38 and Related Family of Proteins", Saxton River, VT
Chair "CD38 Transmembrane Signaling in Human B cells" session

March 9, 1999 American Society of Clinical Pathologists Teleconference
Detection of Minimal Residual Disease

May 6, 1999 M.D. Anderson Cancer Center, Houston, TX
Modern approaches to define remission in acute lymphoblastic leukemia

May 30, 1999 26th National Meeting of the Italian Society of Pediatric Hematology-Oncology, Brescia, Italy
Keynote lecture: Biologic and clinical aspects of acute lymphoblastic leukemia

June 10, 1999 European Society of Hematology, Barcelona, Spain
Symposium on Minimal residual disease; Lecture: *Definition of immunologic and molecular remission in acute lymphoblastic leukemia*
Co-chair of symposium on Acute myeloid leukemia biology

October 5, 1999 Annual Meeting of the German/Austrian Society of Hematology and Oncology, Jena, Germany
Detection of minimal residual disease in acute lymphoblastic leukemia by immunologic and molecular techniques

October 6, 1999 Max Delbruck Center for Molecular Medicine, Berlin, Germany
Regulation of apoptosis in acute lymphoblastic leukemia

October 24, 1999 9th Expert Meeting for Pediatric Oncology and Hematology, Reisensburg, Germany
Detection of minimal residual disease in acute leukemia

March 1, 2000 Leukaemia Research Fund Forum for Translational Research, London, England
The application of flow cytometry to define remission in acute leukemia

March 25, 2000 10th Asia Congress of Pediatrics, Taipei, Taiwan
Modern definition of remission in childhood leukemia

June 17, 2000 6th Annual Meeting of the ISHAGE, San Diego, CA
Definition of remission in childhood leukemia

July 17, 2000 Royal Adelaide Hospital/Institute of Medical and Veterinary Science, Adelaide, Australia
Regulation of cell growth in acute lymphoblastic leukemia

July 18, 2000 Adelaide Women's and Children Hospital/Child Health Research Institute, Adelaide, Australia
Detection of minimal residual disease in childhood leukemia

July 20, 2000 Flinders Cancer Centre, Adelaide, Australia
Detection of minimal residual disease in childhood leukemia

July 21, 2000 Blood Club Breakfast Meeting, Adelaide, Australia
Detection of minimal residual disease in childhood leukemia

July 21, 2000 Flinders Cancer Centre, Adelaide, Australia
Regulation of cell growth in acute lymphoblastic leukemia

July 25, 2000 Annual Meeting of the Haematology Society of Australia and New Zealand, Perth, Australia
Detection of residual disease in childhood acute lymphoblastic leukemia

July 27, 2000 Annual Meeting of the Haematology Society of Australia and New Zealand, Perth, Australia
Detection of residual leukemia by flow cytometry

August 18, 2000 Trudeau Institute, Lake Placid, NY
Factors influencing survival and growth of human immature B cells

August 23, 2000 Hospital Calvo Mackenna, Santiago, Chile
Monitoring of residual leukemia

September 17, 2000 New York University, New York, Course on Leukemia and Lymphoma Classification
Detection of minimal residual disease

October 19, 2000 International Symposium of Childhood Leukemia, Shanghai, China
Detection of minimal residual disease

December 18, 2000 Children's Research Institute, Children's National Medical Center, Washington, DC
Factors influencing the growth of acute lymphoblastic leukemia cells

March 16, 2001 International Symposium on Minimal Residual Disease, Marseille, France
Flow cytometric definition of remission in childhood acute lymphoblastic leukemia

April 27, 2001 Sociedad Latinoamericana de Oncologia Pediatrica, Puerto Velero, Chile
Detection of minimal residual disease

February 14, 2002 Asociacion de Hemato-Oncologos Pediatricos de Centro-America, San Jose, Costa Rica
Classification and monitoring of acute leukemia

August 23, 2002 Peruvian Society of Medical Oncology, Lima, Peru
Classification of leukemia and detection of minimal residual disease

September, 2002 NIH-sponsored Meeting on Microenvironment, Washington, DC
Bone marrow microenvironment and hematopoiesis

October 14, 2002 International Symposium on Minimal Residual Disease, Tel Aviv, Israel
Detection of minimal residual disease by flow cytometry

October 16, 2002 Soroka University Medical Center, Beer Sheva, Israel
Detection of minimal residual disease in acute leukemia

October 17, 2002 Faculty of Health Sciences, Beer Sheva, Israel
Biology of acute lymphoblastic leukemia

November 2, 2002 Meharry-Vanderbilt Cancer Alliance, Nashville, TN
Clinical and biologic advances in childhood acute lymphoblastic leukemia

November 9, 2002 Minimal residual disease monitoring in the clinical treatment of acute leukemia, Tokyo, Japan
Modern definition of remission in childhood acute leukemia

November 11, 2002 Graduate School of Medicine, Kyoto University, Kyoto, Japan
Classification and monitoring of childhood leukemia

November 13, 2002 Hirosaki University, Hirosaki, Japan
Classification and monitoring of childhood leukemia

November 14, 2002 Mie University, Tsu, Japan
Modern definition of remission in childhood acute leukemia

February 22, 2003 International Panel Discussion on Leukemia Immunophenotyping, Padova, Italy

March 16, 2003 Annual Meting of the Hematology Society of Taiwan, Kaohsiung, Taiwan
Detection of minimal residual disease in acute leukemia

April 1, 2003 National Congress of the Italian Association of Clinical and Experimental Cytometry, Firenze, Italy
Keynote lecture: modern applications of flow cytometry to the study of leukemia

April 4, 2003 Fondazione Tettamanti, University of Milano, Monza, Italy
Acute leukemia and bone marrow microenvironment

May 25, 2003 Annual Meeting of the Nordic Society for Pediatric Hematology and Oncology, Umea, Sweden
Detection of minimal residual disease in acute myeloid leukemia

June 20, 2003 13th Symposium of Leukemia and Lymphoma Diagnostics, Max Delbruck Center, Berlin, Germany
Detection of minimal residual disease in acute leukemia

June 25, 2003 UK NEQAS for Leucocyte Immunophenotyping, Sheffield, England
Flow cytometry to define remission in acute leukemia

October 24, 2003 Workshop of the Society for Hemopathology and European Association for Hematopathology, Memphis, TN
Definition of remission in acute leukemia

November 5, 2003 Tumor Microenvironment Think Tank, National Cancer Institute, Rockville, MD
Invited participant

November 14, 2003 Hellenic Haematology Association, Alexandroupolis, Thrace, Greece
Minimal residual disease in acute lymphoblastic leukemia, and "Meet the Expert" Session on Classification and prognosis of leukemia

December 7, 2003 American Society of Hematology Annual Meeting, San Diego, CA
Moderator "Tumor Immunotherapy" session

February 23, 2004 Arkansas Cancer Research Center, Little Rock, AR
Microenvironmental factors that regulate leukemia cell growth

July 2, 2004 International Symposium on Minimal Residual Disease, Kiel, Germany
Detection of minimal residual disease in acute myeloid leukemia

August 27, 2004 Asociacion de Hemato-Oncologia Clinica, Annual Congress, Guatemala City, Guatemala
Classification and monitoring of acute leukemia

September 17, 2004 SIOP, International Society of Pediatric Oncology Annual Meeting, Oslo, Norway
Clinical significance of minimal residual disease in acute myeloid leukemia

October 18, 2004 Clinical Cytometry Society Meeting, Long Beach, CA
Minimal residual disease strategies to improve leukemia treatment

November 3, 2004 Children's Oncology Group Semi-Annual Meeting, Non Hodgkin's lymphoma Subcommittee, Atlanta, GA
Minimal residual disease studies in lymphoblastic lymphoma

January 14, 2005 BFM Minimal Residual Disease Meeting, Berlin, Germany
Invited participant

March 31, 2005 Children's Oncology Group Semi-Annual Meeting, Non Hodgkin's Lymphoma Subcommittee, Los Angeles, CA
Minimal residual disease studies in lymphoblastic lymphoma

April 13, 2005 West Virginia School of Medicine, Morgantown, WV
Microenvironmental factors that regulate leukemia cell growth

June 23, 2005 Congress of the Venezuelan Society of Hematology, Caracas, Venezuela
Detection of minimal residual disease in acute leukemia

July 1, 2005 Arkansas Cancer Research Center, Little Rock, AR
Natural killer cell therapy

August 22, 2005 MISPHO Workshop, Bogota, Colombia
Risk classification in acute lymphoblastic leukemia

November 2, 2005 Meeting of the River Plate Cytometry Society, Cordoba, Argentina
Detection of minimal residual disease in acute leukemia

December 11, 2005 American Society of Hematology Annual Meeting, Atlanta, GA
Moderator "Cytogenetics and Molecular Markers in Diagnosis and Prognosis I" session

January 13, 2006 Instituto del Cancer SOLCA, Cuenca, Ecuador
Classification and monitoring of acute leukemia

May 18, 2006 Second International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin's Lymphoma, New York, NY
Detection of minimal residual disease in lymphoid malignancies

May 23, 2006 II Simposio Nacional de Oncohematologia, Maracaibo, Venezuela
Minimal residual disease in acute leukemia

June 2, 2006 American Society of Clinical Oncology Annual Meeting, Education Session "Curing Pediatric Cancer in the Developing World", Atlanta, GA
Classification and monitoring in childhood acute lymphoblastic leukemia in developing countries

June 28, 2006 Royal Microscopical Society Meeting, Microscience 2006, London, England
Detection of minimal residual disease in acute leukemia

July 14, 2006 Clinical Cytometry Society Consensus Conference, NIH, Bethesda, MD
Invited participant

September 25, 2006 MISPHO Workshop, Monza, Italy
Classification and monitoring in childhood acute lymphoblastic leukemia in developing countries

October 17, 2006 Department of Oncology, University of Modena, Italy
Translational research in oncology: the childhood leukemia model

November 13, 2006 6th Flow Cytometry Workshop, National Cancer Institute, Cairo, Egypt
Classification, monitoring and treatment of leukemia and lymphoma

November 27, 2006 Meharry Medical College, Nashville, TN
Improving treatment outcome in childhood leukemia through translational research

February 16, 2007 The Japan Society for Hematopoietic Cell Transplantation, Fukuoka, Japan
Detection and eradication of residual leukemia

February 28, 2007 Leukemia Grand Rounds, MD Anderson Cancer Center, Houston, TX
Monitoring and eradication of minimal residual leukemia

March 3, 2007 Children's Oncology Group Cytogenetics Workshop, St Louis, MO
Minimal residual disease in the treatment of acute lymphoblastic leukemia

March 9, 2007 First Annual St Jude-Asian Forum of Pediatric Oncology, Singapore
Detection and elimination of residual leukemia

March 12, 2007 Workshop "Flow cytometry for diagnosis and minimal residual disease detection" National University of Singapore, Singapore
Co-organizer

April 5, 2007 Division of Hemopathology, Hospital for Sick Children, Toronto, Canada
Detection and eradication of residual leukemia

May 11, 2007 International Society for Laboratory Hematology, Miami, FL
Pediatric leukemia and minimal residual disease detection

June 10, 2007 ECOG Meeting, Washington, DC

Clinical significance of minimal residual disease in acute leukemia

September 7, 2007 7th Euroconference on Clinical Cell Analysis, European Society for Clinical Cell Analysis, Rotterdam, The Netherlands
Minimal residual disease in acute leukaemia: clinical correlates

September 8, 2007 Second Pediatric Regional Congress, Amman, Jordan
Classification and monitoring of leukemia and lymphoma

October 2, 2007 Division of Bone Marrow Transplantation, Morgan Stanley Children's Hospital, Columbia University, New York, NY
Monitoring and eradication of minimal residual disease

October 24, 2007 VIII Congreso de la Sociedad Argentina de Hematología, Salta, Argentina
Detection and eradication of minimal residual disease in acute leukemia

November 1, 2007 Hot topics in paediatric & adolescent leukaemia and other blood diseases, Dublin, Ireland
Status of minimal residual disease testing in hematological malignancies

November 15, 2007 Commissioned Training Programme of The Hong Kong Hospital Authority, Hong Kong
Classification and monitoring of leukemia and lymphoma
Development of cell therapies for cancer

February 19, 2008 Acute Leukemias XII, Munich, Germany
Molecular predictors of outcome in childhood acute lymphoblastic leukemia

March 5, 2008 St Jude-Asian Forum of Pediatric Oncology 2008, Singapore
Clinical significance of minimal residual disease in acute myeloid leukemia

March 15, 2008 Guidelines in Clinical Cytometry Meeting, Tata Memorial Hospital, India
Recent advances in childhood hematologic malignancies

April 10, 2008 Department of Pathology, University of Arkansas Medical Center, Little Rock, AR
Detection of minimal residual disease

April 23, 2008 Hematological Diseases of Childhood: Genotypic and Phenotypic Correlations, Ospedale Meyer, Florence, Italy
Determinants of treatment response in acute leukemia

May 12, 2008 2nd International Workshop on Mesenchymal Stem Cells for Regenerative Medicine and Immune regulation, Tours, France
Mesenchymal cells and acute leukemia

May 28, 2008 11th Annual Meeting of the American Society of Gene Therapy, Boston, MA
Microenvironmental mechanisms of drug resistance in acute leukemia

September 8, 2008 Immunotherapy for Childhood Cancer: Progress and Challenges, NIH, Bethesda, MD
NK cell therapy of leukemia

September 20, 2008 2nd International Symposium on Minimal Residual Disease in Hematological Malignancies, Kiel, Germany
Determinants of treatment response

September 27, 2008 Leukemia 2008 conference, Houston, TX
Can we quantitate minimal residual disease?

November 15, 2008 National Pediatric Oncology Congress, Japan
Natural killer cell therapy of hematologic malignancies and solid tumors

December 3, 2008 Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX
Detection and elimination of drug resistant disease

December 5/6, 2008 American Society of Hematology, Educational Session "Acute Lymphoblastic Leukemia", San Francisco, CA
Molecular determinants of treatment response in acute lymphoblastic leukemia

December 10, 2008 American Society of Clinical Pathology Teleconference
Minimal residual disease testing in acute leukemia

February 23, 2009 Children's Hospital of Philadelphia, Philadelphia, PA
Identification and eradication of drug-resistant leukemia

March 5, 2009 St Jude-Asian Forum of Pediatric Oncology 2009, Singapore
Translational research in leukemia and lymphoma

March 18, 2009 Grand rounds, Department of Pathology and Laboratory Medicine, Northwestern University, Chicago IL
Clinical significance of minimal disease in leukemia and lymphoma

March 19, 2009 Tumor Cell Biology Seminars, RH Lurie Cancer Center, Northwestern University, Chicago IL
Identification and elimination of drug-resistant leukemia

April 19, 2009 III International Symposium on Flow Cytometry, Sao Paulo, Brazil
Detection of minimal residual disease

April 30, 2009 Grand Rounds, Division of Pediatric Bone Marrow Transplant, Memorial Sloan Kettering Cancer Center, New York, NY
Identification and elimination of drug-resistant leukemia

May 6, 2009 Annual meeting of the Italian Society of Clinical Cytometry, Catania, Italy
Detection of minimal residual disease in acute lymphoblastic leukemia

May 8, 2009 Annual Meeting of the International Berlin-Frankfurt-Munster Group, Bergamo, Italy
Invited participant

October 5, 2009 Department of Pathology, University of California San Diego, San Diego CA
Identification and elimination of drug-resistant leukemia

November 5, 2009 20th Annual Meeting of the Hellenic Society of Haematology, Crete, Greece
Clinical importance of minimal residual disease detection in acute lymphoblastic leukemia

February 15, 2010 VIII World Day against Childhood Cancer, Rome, Italy
Pediatric oncology in the United States

February 26, 2010 BMT Tandem Meetings, Symposium "Therapy for Acute Myelogenous Leukemia: What Therapy and When", Orlando, FL
Impact of minimal residual disease measurement in AML

March 3, 2010 St Jude-Asian Forum of Pediatric Oncology 2010, Singapore
Minimal residual disease in leukemia

April 10, 2010 Immunotherapy Symposium, 23rd Annual Meeting of the American Society of Pediatric Hematology/Oncology, Montreal, Canada
Natural killer cell therapy of cancer

June 15 2010 Safety Symposium - Gene-Modified T Cells: Challenges in Clinical Trial Design, National Institutes of Health, Bethesda, MD
Gene modified natural killer cells

June 27, 2010 King Abdulaziz Medical City, Riyadh, Saudi Arabia
Workshop organizer: *Leukemia immunophenotyping and detection of minimal residual disease*
Lecture: *Identification and elimination of drug-resistant cancer cells*

September 28, 2010 36th Annual Meeting, American Society for Histocompatibility and Immunogenetics, Hollywood, FL
Expansion and genetic modification of natural killer cells for cancer therapy

October 12, 2010 2nd International Conference on Immunotherapy in Pediatric Oncology, Houston, TX
Engineering natural killer cells

December 6, 2010 American Society of Hematology, Educational Session "Acute Lymphoblastic Leukemia", Orlando, FL
Minimal residual disease in acute lymphoblastic leukemia

February 5, 2011 10th Annual International conference on Malignancies in Childhood, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
Workshop co-organizer: *Flow cytometry in acute leukemia*
Lecture: *Detection and eradication of minimal residual disease in acute leukemia*

March 14, 2011 Chang Gung Memorial Hospital(CGMH) Linkou, Taiwan
Clinical significance of minimal residual disease in acute lymphoblastic leukemia

March 15, 2011 Mackay Memorial Hospital, Taipei, Taiwan
Identification and elimination of drug-resistant cancer cells

March 22, 2011 St Jude-Asian Forum of Pediatric Oncology 2011, Singapore
Minimal residual disease in leukemia

April 16, 2011 Symposium "The Best of St Jude International Outreach Program", King Fahad Specialist Hospital, Dammam, Saudi Arabia
Minimal residual disease in leukemia

May 6, 2011 International Society of Laboratory Hematology Annual Meeting, New Orleans, LA
The changing definition of remission in acute leukemia

May 17, 2011 Becton Dickinson, San Jose, CA
The changing definition of remission in acute leukemia

June 16, 2011 Cook Children's Medical Center, Fort Worth, Texas
Grand Rounds:
Expansion and Modification of Natural Killer cells for Cancer Therapy
The changing definition of remission in acute leukemia

September 13, 2011 European Society for Clinical Cell Analysis, 7th European Course on Clinical Cytometry, Dublin, Ireland
Minimal residual disease studies by flow cytometry in acute myeloid leukemia

September 15, 2011 Children's Oncology Group Fall Meeting, Hematology-Oncology Educational Session, Atlanta, GA
The significance of minimal residual disease in risk-group classification

September 23, 2011 Duke – National University of Singapore
Speaker - Medical School Course "Molecules and Cells"

October 11, 2011 2nd Symposium on Flow Cytometry, Recife, Brazil
Clinical significance of minimal residual leukemia in acute leukemia

October 18, 2011 International Clinical Cytometry Society Annual Meeting, Portland, OR
Novel markers for minimal residual disease detection in acute lymphoblastic leukemia

November 10, 2011 Duke – National University of Singapore, Singapore
CSCB Seminar *"Identification and elimination of drug-resistant acute leukemia"*

December 7, 2011 1st Singapore NK Cell Workshop, Centre for Life Sciences, Singapore
NK Cell Therapy of Cancer

December 11, 2011 American Society of Hematology 53rd Annual Meeting, San Diego, CA
Moderator, *"Acute Lymphoblastic Leukemia - Therapy, excluding Transplantation: Biological Strategies"* session

December 16, 2011 National University of Singapore Health System, Singapore
Grand Rounds: "*Targeting drug-resistant disease in hematologic malignancies*"

March 3, 2012 St Jude-Asian Forum of Pediatric Oncology 2012, Singapore
Advances in monitoring minimal residual leukemia

March 22, 2012 International Workshop on Cell and Tissue Therapy; Converging Science & Regulations, Singapore
Animal models in cell and tissue based therapies: proof of concept

April 17, 2012 Symposium "Biology of Leukemia and the Bone Marrow Niche: a Long and Winding Road towards Translational Research", Padova, Italy
Pathogenesis, prognosis and treatment of T-lineage acute lymphoblastic leukemia

April 19, 2012 International Conference "Leukemia 2012", Milan, Italy
Minimal residual disease

June 7, 2012 International Singapore Symposium of Immunology "Innate and Adaptive Mechanisms of Immunity", Singapore
Natural killer cell therapy of cancer

June 29, 2012 National Taiwan University Hospital, Taipei, Taiwan
Recent advances in minimal residual disease detection in acute leukemia

June 30, 2012 2012 Tai Cheng International Symposium on Fighting Against Acute Myeloid Leukemia, National Taiwan University Hospital, Taipei, Taiwan
Recent advances in NK-cell therapy of acute leukemia

August 29, 2012	Asan Medical Center, Seoul, South Korea *NK cell therapy of cancer*
August 31, 2012	Annual summer meeting of the Korean Society of Blood and Marrow Transplantation, Busan, South Korea *Significance of minimal residual disease in patients with acute leukemia undergoing hematopoietic stem cell transplant*
October 27, 2012	3rd International Congress of Pathology and Laboratory Medicine, Lima, Peru Teleconference: *Advances in monitoring minimal residual disease*
November 11, 2012	Joint European Hematology Association-Indian Society of Hematology and Blood Transfusion Symposium, Puri, India *Minimal residual disease diagnostics in acute lymphoblastic leukemia treatment protocols*
November 16, 2012	3rd Meeting of the Asian Cellular Therapy Organization, Chiangmai, Thailand *Minimal residual disease in leukemia* *Adoptive natural killer cell therapy*
February 2, 2013	Congress of the Korean Society of Blood and Marrow Transplantation, Seoul, South Korea *NK cell therapy of cancer*
March 8, 2013	St Jude-Asian Forum of Pediatric Oncology 2013, Singapore *Advances in monitoring minimal residual leukemia*
March 14, 2013	Conference of application of flow cytometry in diagnosing myeloid malignancies, Münchner Leukämielabor, Munich, Germany *Invited participant*
March 21, 2013	Gene & Immunotherapy Conference, Ho Chi Min City, Vietnam *Cellular immunotherapy of cancer*
April 7, 2013	Singapore Society of Haematology, Leukaemia Symposium 2013, Singapore *Minimal residual disease monitoring in acute leukemia*
April 24, 2013	International Society for Cell Therapy Annual Meeting, Auckland, New Zealand *Activation and genetic modification of natural killer cells for cancer therapy*
May 14, 2013	14th Ponte di Legno Meeting, Glücksburg, Germany *Invited participant*
May 24, 2013	4th International Congress on Leukemia Lymphoma Myeloma, Istanbul, Turkey *Minimal residual disease in acute leukemia*
July 27, 2013	Symposium on Pediatric Hematology/Oncology and Immunodeficiency, Chang Gung Children's Hospital 20th Anniversary, Taoyuan, Taiwan *Advances in cellular therapy for childhood malignancies*
August 31, 2013	2013 Chang Gung Memorial Hospital International Cancer Conference-Translational Research in Blood Cancer, Taoyuan, Taiwan *Minimal residual disease analysis in guiding therapy and reducing risk of leukemia relapse*
October 10, 2013	Italian Society of Cytometry, Lucca, Italy *Keynote lecture*

Significance of Minimal Residual Disease in Acute Lymphoblastic Leukemia

Dario Campana

Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

Studies of minimal residual disease (MRD), i.e., leukemic cells undetectable by standard methods, improve the determination of initial treatment response and the clinical management of patients with acute leukemia. The most reliable methods to study MRD in acute leukemia are flow cytometric detection of aberrant immunophenotypes and polymerase chain reaction amplification of rearranged immunoglobulin and T-cell receptor genes and chromosomal breakpoints. These methods can detect 1 leukemic cell among 10,000 or more normal bone marrow or peripheral blood cells. The results obtained with the two methods in childhood acute lymphoblastic leukemia (ALL) are highly concordant and application of the two methods in tandem allows the monitoring of all patients. Newer methods relying on deep sequencing of antigen receptor genes promise to improve the sensitivity of molecular analysis of MRD in ALL. With this approach, it is also possible to monitor clonal evolution during treatment. Prospective studies of MRD in patients with newly diagnosed ALL have shown that presence of MRD in bone marrow is strongly and independently associated with a higher risk of relapse. There is strong evidence that MRD levels before hematopoietic stem cell transplantation in patients with ALL are closely related to the risk of relapse post-transplant. Methodological advances in MRD detection, insights on its clinical significance, and possible treatment strategies targeting MRD will be discussed.

CURRICULUM VITAE

Charles G. Mullighan
Qualifications: M.B.,B.S. (Hons)(Adel) M.Sc.(Lond) M.D.(Adel) FRACP FRCPA FFSc(RCPA)
Date of birth: 16th February 1970. Adelaide, South Australia. US Permanent Resident.
Address: (W): Pathology, MS #342, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN, 38105, W: 901-595-3387, F: 901-595-5947, Email: charles.mullighan@stjude.org, www.stjude.org/mullighan
(H): 1718 Overton Park Ave, Memphis, TN, 38112, T: 901-216-5104

PROFESSIONAL QUALIFICATIONS
Fellow of the Royal Australasian College of Physicians (2003)
Fellow of the Royal College of Pathologists of Australasia (Haematology, 2004)

ACADEMIC
Bachelor of Medicine and Bachelor of Surgery (with Honours)
University of Adelaide 1987 - 1992. Graduated 1993
Dux of fifth year; Honours; Dean's List; Pediatric Surgery, Psychiatry Prizes
Master of Science (Hons)(Medical Immunology)
University of London. Graduated with Distinction, July 1997
Thesis Title: "Lymphotropic Herpesviruses and Common Variable Immunodeficiency"
Doctor of Medicine (equivalent to US Ph.D.)
University of Adelaide, 1994-1997. Graduated April 1998.
Thesis: "Immunogenetics of Common Variable Immunodeficiency"; attained top A grading by both examiners.

EMPLOYMENT
Internship and residency 1993-1994: Royal Adelaide Hospital.
University of Adelaide George Murray Scholar, 1994-1997: Held in Departments of Immunology and Transplantation Immunology, Oxford Radcliffe Hospitals and University of Oxford, UK.
Immunology Registrar 1994-1997: Churchill and John Radcliffe Hospitals, Oxford Radcliffe Hospitals NHS Trust, Oxford, UK
Physician trainee 1998-2000 Royal Adelaide Hospital.
Chief Medical Resident, Royal Adelaide Hospital 2001.
Royal Australian College of Physicians (SA) Advanced Training representative 2001-2002
Haematology and Haematopathology advanced trainee 2001-3: Department of Haematology, Institute of Medical and Veterinary Science and Royal Adelaide Hospital, Adelaide.
Physician Scientist Postdoctoral Fellow, St Jude Children's Research Hospital 2004 – 2008.
Assistant Member, Pathology, St Jude Children's Research Hospital. 2008 - 2011.
Associate Member, Pathology, St Jude Children's Research Hospital. 2011-present
Co-leader, Hematologic Malignancies Program, St Jude Children's Research Hospital. 2011-present

AWARDS
1992 Deans List, Honors, University of Adelaide Medical School
2001 Chief Medical Resident, Royal Adelaide Hospital, South Australia
2001 Royal Australasian College of Physicians (SA Branch) Professor John Chalmers Prize
2001 Haematology Society of Australia and New Zealand Albert Baikie Memorial Award
2001-2002 Advanced Training Representative, Royal Australian College of Physicians, South Australia
2002 Royal Australasian College of Physicians Pfizer Advanced Trainee Prize
2002 Royal College of Pathologists of Australasia D.S. Nelson Prize
2003 Royal College of Pathologists of Australasia Kanematsu Award
2007 American Society of Hematology Merit Award
2007 American Society of Hematology Scholar Award
2007 American Association of Cancer Research / Aflac Career Development Award
2008 American Society of Hematology Joanne Levy, MD, Memorial Award for Outstanding Achievement
2009 Society for Pediatric Pathology Lotte Strauss Prize
2009 American Association for Cancer Research Team Science Award (with the St Jude Children's Research Hospital Hematologic Malignancies Program)
2009 Pew Scholar in the Biomedical Sciences
2009 Section Editor, *Leukemia*
2010 Editor, *Blood*
2010 Editor, *Journal of Adolescent and Young Adult Oncology*
2010 Founding Fellow, Faculty of Science, Royal College of Pathologists of Australasia
2011 Associate Editor, *Frontiers in Pediatric Oncology*
2012 American Society of Clinical Investigation
2012 Editorial Board, Clinical and Translational Immunology
2012 Faculty of 1000
2012 Meyenburg Cancer Research Award

RESEARCH SUPPORT
Ongoing Research Support
NCI 1R01CA161202-01 (co-PIs BRINDLE AND MULLIGHAN) 07/01/12-06/30/2017
Functional analysis of leukemic CREBBP mutations $389,986 pa
1. To determine the role of CREBBP mutations identified in ALL in lymphoid development and leukemogenesis.
2. To develop preclinical models of CREBBP-mutated ALL to test the activity of histone deacetylase inhibitors.
3. To identify mutations in relapsed ALL

ST. BALDRICK'S FOUNDATION CONSORTIUM GRANT (PIs Hunger, Loh, Mullighan) 2011-2014
Recurrence testing of new genomic lesions in childhood ALL $600,000
Aim 1: To determine the incidence and prognostic significance of newly discovered recurrent somatic mutations in childhood ALL.
Aim 2: To investigate potential associations between specific recurrent somatic mutations in childhood ALL and sentinel chromosome translocations (e.g. t(9;22), t(1;19), MLL translocations, rearrangement or mutation of CRLF2) and new subgroups of BCP-ALL identified by unsupervised clustering of gene expression profiles.

ST. BALDRICK'S FOUNDATION SCHOLAR AWARD (PI MULLIGHAN) 2011-2015
Characterizing the spectrum of genetic alterations in high-risk ALL $550,000
(1) To identify the spectrum and frequency of novel chromosomal rearrangements in high-risk, "BCR-ABL-like" (Ph-like) ALL, and to develop experimental models testing the efficacy of tyrosine kinase inhibitors.
(2) To identify genetic alterations in hypodiploid ALL, and examine the potential for novel therapies targeting Ras/Raf/MEK/ERK signaling in ALL.
(3) To identify DNA sequence alterations in relapsed ALL.

STAND UP TO CANCER INNOVATIVE RESEARCH GRANT (PI MULLIGHAN) 06/01/2011-05/31/2014
Identification and targeting of novel rearrangements in high-risk ALL $750,000
1. To use genomic profiling to identify novel targets of rearrangement in high-risk ALL
2. To develop experimental models of B-progenitor ALL

AACR GETRUDE B. ELION CANCER RESEARCH AWARD (PI MULLIGHAN) 07/01/2011-06/30/2012
Exome sequencing of hypodiploid acute lymphoblastic leukemia $50,000
1. To perform exome capture and next generation sequencing of tumor and matched normal DNA in a panel of hypodiploid ALL cases.
2. To determine the spectrum and frequency of novel targets of mutation identified by exome sequencing. .
3. To analyse associations between genetic alterations and clinical features in hypodiploid ALL.

ARRA RC4CA156329 (PI MULLIGHAN) 9/30/2010-8/31/2013
Identifying the spectrum of genetic alterations in high-risk leukemia. $696,484 pa
1. To perform detailed genomic analysis of BCR-ABL1 positive (Ph+) leukemia, and to correlate genomic variants with disease outcome and progression.
2. To identify genetic alterations in hypodiploid ALL, and to correlate genetic alterations in RAS pathway activity in vitro.
3. To identify genetic alterations in high risk B-progenitor ALL lacking cytogenetic abnormalities.

ARRA 5 RC1CA145707-02 (PI MULLIGHAN) 09/01/2009-08/31/2010
Genomic analysis of adolescent and young adult acute lymphoblastic leukemia.
$392,147 pa
1. To perform high resolution genome-wide profiling of genetic alterations in 400 cases of AYA ALL
2. To perform integrated cross platform analysis of genomic data to identify dysregulated and mutated genes, and to compare these data with childhood and older adult ALL
3. To correlate genomic profiling data with clinical features and therapeutic outcome data in order to determine the prognostic significance of genomic alterations
4. To interrogate genomic profiling data to identify novel targets and pathways for therapeutic intervention

ARRA 3 U10CA98543-07S6 (PI REAMAN) 09/01/2009-08/31/2010
Expansion to Oncology Group Chair's Grant $147,342
1. To determine gene expression profiles of 175 diagnostic and 25 relapsed leukemia specimens using Affymetrix U133 Plus 2.0 Arrays and Human Exon 1.0 Arrays.
2. To determine DNA Copy number alterations and loss-of-heterozygosity using Affymetrix SNP 6.0 microarrays.
3. To characterize epigenomic profiles we will use HELP assay..

ARRA RC2CA148529 (PI LOH, MULLIGHAN, HUNGER) 09/30/2009-09/29/2011
Targeted Therapies in Childhood Acute Lymphoblastic Leukemia. $152,008
1. To validate COG P9906 copy number alteration and mutation data in the first 500 consecutively enrolled high risk B-precursor ALL patients on AALL0232.
2. To determine the incidence and prognostic significance of the identified COG P9906 BCR/ABL kinase-like signature in standard risk B-precursor ALL patients.
3. To implement real-time testing using the most robust identifier of poor risk genetic features in patients consecutively enrolled in COG ALL trials.

PEW SCHOLARS PROGRAM (MULLIGHAN) 2009-2012
Genomic analysis and experimental modeling of high risk acute leukemia. $60,000 pa
1. Identify genetic alterations in high risk and relapsed acute lymphoblastic leukemia.
2. Experimental modeling of genetic alterations in leukemia.

NIGMS U01GM092666-01 (PI RELLING) 07/15/2010-06/30-2015
PAAR 4 KIDS – Research Projects $1,230,922
1. To improve the outcome of childhood ALL by tailoring therapy based on genomic variations.
2. To define genomic determinants of antileukemic effects and their relationship to tumor-specific acquired genomic variation , and genomic determinants of adverse effects and pharmacokinetics of antileukemic agents.
3. To begin to integrate pharmacogenetics into clinical settings.
4. To collaborate with other investigators to leverage pharmacogenomic knowledge from pediatric ALL to other disciplines.

Pending Research Support
SPORE IN ACUTE LYMPHOBLASTIC LEUKEMIA (PIs Hunger and Carroll)2012-2016
Project 2 (PIs MULLIGHAN and HUNGER) Identification and therapeutic targeting of new genetic alterations in BCR-ABL1-like hig-risk B-progenitor acute lymphoblastic leukemia
1. What is the spectrum and frequency of novel chromosomal rearrangements in high-risk, *BCR-ABL1*–like B-ALL?
2. Are the genetic alterations resulting in activated cytokine receptor and kinase signaling amenable to treatment with targeted therapeutic agents?

PEER REVIEW
Journal review (journals repeatedly reviewed for are underlined)
Biochemical Genetics, Blood, BMC Gastroenterology, BMC Genomics, Bone Marrow Transplantation, British Journal of Haematology, Cancer Epidemiology Biomarkers and Prevention, Cancer Cell, Cancer Research, Carcinogenesis, Clinical Cancer Research, Clinical Chemistry, European Journal of Cancer, European Journal of Haematology, Genes Chromosomes and Cancer, Genes and Immunity, Genome Biology, Genome Research, Gut, Haematologica, Human Immunology, Human Mutation, Internal Medicine Journal, Journal of Clinical Immunology, Journal Of Clinical Investigation, Journal of Clinical Oncology, Journal of Experimental Medicine, Journal of Infectious Diseases, Lancet, Lancet Oncology, Leukemia, Leukemia and Lymphoma, Leukemia Research, Molecular Cancer Research, Nature, Nature Genetics, Nature Medicine, New England Journal of Medicine, Oncogene, Proceedings of the National Academy of Sciences USA, Scandinavian Journal of Rheumatology, Science, Thrombosis and Haemostasis, Tissue Antigens.

Abstract Review:
American Society of Hematology Annual Scientific Meeting 2008, 2009, 2010 (coordinating reviewer 2009); European Haematology Association Congresses 2009, 2010, 2011

Grant reviewer: (recurring reviews are underlined)
Alex's Lemonade Stand, American Association for Cancer Research, American Society for Hematology Scholar Awards, Associazione Italiana per la Ricerca sul Cancro, Children with Leukemia, US Department of Defence, Dutch Cancer Society, Genome Canada, Genome Quebec, Italian Ministry of Health, Kay Kendall Leukemia Foundation, Leukemia Research (UK), Merieux Research Grants, NIAID (Ad hoc); NH&MRC (Australia); Cochrane Reviews, Qatar National Research Foundation, St. Baldrick's Foundation

Editorial board:
Blood, BMC Medical Genetics, Clinical and Translational Immunology, Current Stem Cell Research & Therapy, European Journal of Clinical Investigation, Frontiers in Pediatric Oncology; Journal of Adolescent and Young Adult Oncology; Leukemia (section editor); PLoS Genetics (Guest Editor)

MEMBERSHIPS OF PROFESSIONAL GROUPS AND SOCIETIES
American Association for Cancer Research
American Society for Bone Marrow Transplantation
American Society for Clinical Investigation
American Society of Clinical Oncology
American Society of Hematology
2010-present: Founding Member of ASH Working Committee on Scientific Affairs.
American Society of Human Genetics
American Society of Pediatric Hematology and Oncology
Australian and New Zealand Society for Blood Transfusion
Australasian Society for Thrombosis and Haemostasis
Children's Oncology Group
Haematology Society of Australia and New Zealand
International Society for Stem Cell Research
Royal Australasian College of Physicians
Royal College of Pathologists of Australasia
NIH/NCI ALL Working Group

PEER REVIEWED PUBLICATIONS (in reverse chronological order)
117 indexed in Pubmed; h-factor 39; 18 papers with >100 citations; 5728 citations total.

1. Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton J, Tang B, Orisme W, Punchihewa C, Qaddoumi I, Boop FA, Lu C, Kandoth C, Ding L, Parker M, Lee R, Huether R, Chen X, Hedlund E, Nagahawatte P, Rusch M, Boggs K, Cheng J, Becksfort J, Ma J, Song G, Li Y, Wei L, Wang J, Shurtleff S, Easton J,Zhao D, Fulton RS, Fulton LA, Dooling DJ, Vadodaria B, Mulder HL, Tang C, Ochoa K, **Mullighan CG**, Gajjar A, Kriwacki R, Sheer D, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Baker SJ, Ellison DW. Novel genetic alterations in pediatric low-grade gliomas: therapeutic targets for challenging disease subtypes. Nat Genet 2013; in press.
2. Inaba H, Greaves M, **Mullighan CG**. Acute Lymphoblastic Leukemia. Lancet, in press. [review]
3. Cleveland SM, Smith S, Tripathi R, Mathias EM, Goodings C, Elliott N, Peng D, El-Rifai W, Yi D, Chen X, Li L, **Mullighan C**, Downing JR, Love P, Davé UP. Lmo2 induces hematopoietic stem cell like features in T-cell progenitor cells Prior to leukemia. Stem Cells. 2013 Feb 4. doi: 10.1002/stem.1345. [Epub ahead of print]
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5. Kreso A, O'Brien CA, van Galen P, Gan O, Notta F, Brown AM, Ng K, Ma J, Wienholds E, Dunant C, Pollett A, Gallinger S, McPherson J, **Mullighan CG**, Shibata D, Dick JE. Variable Clonal Repopulation Dynamics Influence Chemotherapy Response in Colorectal Cancer. Science. 2013;339:543-8. See comment: Marusyk A, Polyak K. Cancer cell phenotypes, in fifty shades of grey. Science 2013;339:528-9. doi: 10.1126/science.1234415.
6. **Mullighan CG**. The Molecular Genetic Makeup of Acute Lymphoblastic Leukemia.

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7. Parker M, Chen X, Bahrami A, Dalton J, Rusch M, Wu G, Easton J, Cheung NK, Dyer M, Mardis ER, Wilson RK, Mullighan C, Gilbertson R, Baker SJ, Zambetti G, Ellison DW, Downing JR, Zhang J. Assessing telomeric DNA content in pediatric cancers using whole-genome sequencing data. Genome Biol. 2012;13:R113.
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77. **Mullighan CG,** Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, White D, Hughes TP, Le Beau MM, Pui C.-H., Relling MV, Shurtleff, SA, Downing JR. *BCR-ABL1* lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453:110-4.
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81. **Mullighan CG**, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, Girtman K, Mathew S, Ma J, Pounds SB, Su X, Pui C-H, Relling MV, Evans WE, Shurtleff SA, Downing JR Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007;446:758-64.
82. Worthley DL, **Mullighan CG**, Dean MM, Gordon DL, Phillips P, Heatley SL, Young GP, Bardy PG. Mannose-binding lectin deficiency does not increase the prevalence of Helicobacter pylori seropositivity. Eur J Gastroenterol and Hepatol 2007;19:147-152 (co-first author)
83. Mullighan **CG,** Bardy, PG. New directions in the genomics of allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2007;13:127-144 [review]
84. Downing JR, **Mullighan CG.** Tumor Specific Genetic Lesions and Their Influence on Therapy in Pediatric Acute Lymphoblastic Leukemia. Hematology Am Soc Hematol Educ Program. 2006;118-22 [review]
85. Worthley DL, Bardy PG, Gordon DL, **Mullighan CG** Mannose-Binding Lectin and Maladies of the Bowel and Liver**.** World J Gastroenterol. 2006; 12:6420-8 [review]
86. **Mullighan CG**, Bogdanos D-P, Vergani D, Bardy PG. Cytochrome P450 1A2 is a target antigen in hepatitic graft-versus-host disease. Bone Marrow Transplant. 2006;38:703-5
87. **Mullighan CG,** Petersdorf E. Genomic polymorphism and allogeneic hematopoietic transplantation outcome. Biol Blood Marrow Transplant. 2006;12(1 Suppl 1):19-27 [review]
88. **Mullighan CG**, Flotho C, Downing JR. Genomic assessment of pediatric acute leukemia. Cancer J. 2005; 11:268-82 [review]
89. Worthley DL, Bardy PG, Angus P, Harley H, **Mullighan CG**. Mannose-binding lectin polymorphisms and liver transplantation. Gastroenterology 2005;129:1805-6.
90. Worthley DL, Bardy PG, **Mullighan CG**. Biology and Clinical Relevance of Mannose binding lectin. Drug Design Reviews – Online. 2005; 2: 457–465 [review]
91. Annells MF, Hart PH, **Mullighan CG**, Heatley SL, Robinson JS, McDonald HM. Polymorphisms in immunoregulatory genes and the risk of histologic chorioamnionitis in Caucasoid women: a case control study. BMC Pregnancy Childbirth. 2005;21:4
92. Worthley DL, Bardy PG, **Mullighan CG**. Mannose-binding lectin: biology and clinical implication. Internal Medicine Journal, 2005; 35: 548-555 [review]
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96. **Mullighan CG** and Bardy PG. Advances in the Genomics of Allogeneic Haemopoietic Stem Cell Transplantation. Drug Development Research 2004;62:273-292 [review]
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98. **Mullighan CG**, Heatley S, Lester S, Rischmueller M, Gordon T, Bardy P. Fas gene promoter polymorphisms in primary Sjogren's syndrome. Ann Rheum Dis 2004;63:98-101.
99. Helbig KJ, Heatley SL, Harris RJ, **Mullighan CG**, Bardy PG, Marmion BP. Variation in immune response genes and chronic Q fever. Concepts: preliminary test with post-Q fever fatigue syndrome. Genes Immun 2003;4:82-5.
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101. **Mullighan CG**, Heatley S, Doherty K, Szabo F, Grigg A, Hughes TP, Schwarer A, Szer J, Tait BD, To LB, Bardy PG. Mannose-binding lectin gene polymorphisms are associated with major infection following allogeneic hemopoietic stem cell transplantation. Blood 2002;99:3524-9.
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111. Sewell WA. Marshall SE. **Mullighan CG**. Bird AG. A hypogammaglobulinaemic man with respiratory failure. Postgrad Med J. 74:503-4, 1998.
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116. Sewell WA, **Mullighan CG**, Christie J, Chapel HM. Hepatitis C after intravenous immunoglobulin. Annals of Allergy, Asthma, & Immunology. 79:466-7, 1997.
117. Mullighan CG, Read SJ, Bird AG, Kurtz JB, Chapel HM, Welsh KI. Human cytomegalovirus infection is not increased in common variable immunodeficiency. J Clin Immunol. 16:272-7, 1996.
118. Whyte AM, **Mullighan CG**, Heysen JP, Langlois SL. Evaluation by Magnetic Resonance Imaging (MRI) of the Prevalence and Aetiology of Benign Paranasal Sinus Disease. Journal of the Otolaryngological Society of Australia 1991; 6:380.

Book chapters
1. **Mullighan CG.** Molecular Genetics of Acute lymphoblastic leukemia. In Childhood Leukemias, 3rd Edn, Ed Ching-Hon Pui, Cambridge University Press, 2012.
2. **Mullighan CG,** Hunger SP, Meshinchi S. Molecular Genetics in Children, Adolescents and Young Adults with acute lymphoblastic leukemia and acute myeloid leukemia. Cairo M and Perkins S Eds, World Scientific Publishing 2010, in press
3. **Mullighan CG**. Pancytopenia in a child. A teaching case of acute leukemia. Clinical Problems in General Medicine and Surgery, 3rd Edition. Eds Devitt PG, Barker JN, Mitchell J and Hamilton-Craig C. Churchill Livingstone, 2011.
4. **Mullighan CG**. Back pain in a 50 year old woman. A teaching case of myeloma. Clinical Problems in General Medicine and Surgery, 2nd Edition. Eds Devitt PG, Barker JN, Mitchell J and Hamilton-Craig C. Churchill Livingstone, August 2003.

PRESENTATIONS AT SCIENTIFIC MEETINGS (LAST THREE YEARS)
1. American Association of Cancer Research Annual Meeting 2012
2. Van der Weyden L, Rust A, Perez-Mancera P, Tuveson D, Jonkers J, **Mullighan C,** Winton D, Adams D. Large scale screens for cancer genes in the mouse. Oral presentation, Major Symposium: *In vivo* systems Biology: Modeling Regulatory Networks in the mouse
3. Andersson A, Ma J, Wang J, Chen X, Rusch M, Wu G, Easton J, Parker M, Raimondi S, Holmfeldt L, Becksfort J, Gupta P, Gedman A, Nakitandwe J, Payne-Turner D, Song G, Sutton R, Venn N, Chetcuti A, Rush A, Catchpole D, Heldrup J, Fioretos T, Lu C, Ding L, Pui C-H, Shurtleff S, Gruber T, Mullighan C, Mardis E, Wilson R, Zhang J, Downing J. Whole genome sequence analysis of MLL rearranged infant acute lymphoblastic leukemias reveals remarkably few somatic mutations: A Report From the St Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project. Oral Presentation, Minisymposium, Genomics of Pediatric Cancer.
4. Holmfeldt L, Diaz-Flores E, Zhang J, Payne-Turner D, Andersson A, Chen S-C, Becksfort J, Ma J, Wei L, Easton J, Pei D, Cheng C, Pui C-H, Devidas M, Carroll AJ, Heerema NH, Gastier-Foster JM, Raimondi SC, Mardis EM, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. Integrated genomic analysis of hypodiploid acute lymphoblastic leukemia. Oral Presentation, Minisymposium, Genomics of Pediatric Cancer.
5. Parker MD, Wu G, Chen X, Rusch M, Bahrami A, Ding L, Mardis E, Mullighan C, Gilbertson R, Dyer MA, Wilson RK, Downing J, Zhang J. Comprehensive analysis of 160 whole-genome sequences reveals striking telomere alteration patterns in 9 pediatric cancers. Oral Presentation, Minisymposium, Genomics of Pediatric Cancer.
6. Chen X, Wang J, Roberts K, Pounds S, Dyer M, **Mullighan C**, Downing J, Zhang J. CONSERTING: an accurate method for detecting focal and gross somatic copy number alterations in cancer genome by next generation sequencing. Poster session, Pediatric Oncology

American Society of Hematology 53rd Annual Meeting December 2011
1. Andersson AK, Ma J, Wang J, Chen X, Rusch M, Wu G, Easton J, Parker M, Raimondi SC, Holmfeldt L, Gedman AL, Song G, Becksfort J, Gupta P, Ulyanov A, Payne-Turner D, Sutton R, Venn NV, Chetcuti A, Rush A, Catchpoole D, Heldrup J, Fioretos T, Hong X, Lu C, Ding L, Pui C-H, Shurtleff SA, Gruber TA, **Mullighan CG**, Mardis ER, Wilson RK, Zhang J, Downing JR. Whole Genome Sequence Analysis of 22 MLL Rearranged Infant Acute Lymphoblastic Leukemias Reveals Remarkably Few Somatic Mutations: A Report From the St Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project. ASH Annual Meeting Abstracts 2011;118:69. (oral)
2. Buitenkamp T, Izraeli S, Zimmermann M, Forestier E, Heerema NA, van den Heuvel MM, Pieters R, de Haas V, Silverman LB, Schmiegelow K, Liang D-C, Horibe K, Arico M, Cazzaniga G, Basso G, Rabin KR, Schrappe M, Cario G, Mann G, Mondelaers V, Lammens T, Cave H, Stark B, Moorman AV, Vora AJ, Hunger S, Pui C-H, **Mullighan CG**, Manabe A, Escherich G, Kowalczyk J, Whitlock JA, Zwaan CM. Acute Lymphoblastic Leukemia in Children with Down Syndrome: A Report From the Ponte Di Legno Study Group. ASH Annual Meeting Abstracts 2011;118:3579. (poster)
3. Loh ML, Harvey RC, **Mullighan CG**, Linda SB, Devidas M, Borowitz MJ, Carroll AJ, Chen I-M, Gastier-Foster JM, Heerema NA, Kang H, Raetz EA, Roberts KG, Zhang J, Winick N, Wood BL, Larsen EC, Carroll WL, Willman CL, Hunger SP. A BCR-ABL1-Like Gene Expression Profile Confers a Poor Prognosis In Patients with High-Risk Acute Lymphoblastic Leukemia (HR-ALL): A Report From Children's Oncology Group (COG) AALL0232. ASH Annual Meeting Abstracts 2011;118:743. (oral)
4. Mangum DS, Shams S, Downie JM, von Schwedler U, Rodic V, Engel M, Barnette P, Frazer JK, Trede N, Pei D, Cheng C, Pui C-H, Hunger SP, Yang JJ, Miles RR, **Mullighan CG**, Schiffman JD. Focal 22q11.22 Loss Combined with IKZF1 Alterations Predict Very Poor Outcome in Childhood Acute Lymphoblastic Leukemia. ASH Annual Meeting Abstracts 2011;118:741. (oral)
5. Maude SL, Tasian SK, Vincent T, Hall JW, Collins-Underwood R, **Mullighan CG**, Hunger SP, Willman CL, Loh ML, Grupp SA, Teachey DT. Targeting mTOR and JAK2 in Xenograft Models of CRLF2-Overexpressing Acute Lymphoblastic Leukemia (ALL). ASH Annual Meeting Abstracts 2011;118:249. (oral)
6. Roberts KG, Morin RD, Zhang J, Hirst M, Harvey RC, Kasap C, Chen X, Edmonson M, Chen I-M, Shah N, Devidas M, Reaman GH, Smith MA, Pui C-H, Downing JR, Gerhard DS, Willman CL, Loh ML, Hunger SP, Marra MA, **Mullighan CG**. Novel Chromosomal Rearrangements and Sequence Mutations in High-Risk Ph-Like Acute Lymphoblastic Leukemia. ASH Annual Meeting Abstracts 2011;118:67. (oral; winner of oustanding abstract achievement award)
7. Smith SB, Tripathi R, Cleveland S, Mathias E, Yi A, **Mullighan CG**, Downing JR, Copeland NG, Jenkins NA, Dave UP. Cooperating Oncogenes and Their Targets in LMO2-Induced T-Cell Leukemia. ASH Annual Meeting Abstracts 2011;118:2458. (poster)
8. Treanor LM, Zhou S, Lu T, **Mullighan CG**, Sorrentino BP. Lmo2 Overexpression and Arf Loss Induce Myeloid Differentiation in Primitive Thymocytes. ASH Annual Meeting Abstracts 2011;118:47. (oral)
9. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, Easton J, Chen X, Wang J, Rusch M, Lu C, Chen S-C, Collins-Underwood R, Ma J, Roberts KG, Pounds S, Wei L, Ulyanov A, Becksfort J, Gupta P, Huether R, Kriwacki R, McGoldrick D, Zhao D, Alford D, Espy S, Bobba KC, Song G, Pei D, Cheng C, Roberts S, Barbato M, Campana D, Coustan-Smith E, Evans WE, Shurtleff SA, Kleppe M, Cools J, Shimano K, Hermiston ML, Doulatov S, Eppert K, Laurenti E, Notta F, Dick JE, Basso G, Hunger SP, Loh ML, Devidas M, Wood BL, Winter SS, Dunsmore K, Fulton RS, Fulton LA, Hong X, Harris CC, Dooling DJ, Ochoa K, Johnson KJ, Obenauer JC, Pui C-H, Raimondi SC, Naeve CW, Ley TJ, Mardis ER, Wilson RK, Downing JR, **Mullighan CG**. Discovery of Novel Recurrent Mutations in Childhood Early T-Cell Precursor Acute Lymphoblastic Leukemia by Whole Genome Sequencing - a Report From the St Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project. ASH Annual Meeting Abstracts 2011;118:68. (oral).

American Society of Human Genetics Annual Meeting 2011
1. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, Easton J, Chen X, Wang J, Rusch M, Lu C, Chen S-C, Collins-Underwood R, Ma J, Roberts KG, Pounds S, Wei L, Ulyanov A, Becksfort J, Gupta P, Huether R, Kriwacki R, McGoldrick D, Zhao D, Alford D, Espy S, Bobba KC, Song G, Pei D, Cheng C, Roberts S, Barbato M, Campana D, Coustan-Smith E, Evans WE, Shurtleff SA, Kleppe M, Cools J, Shimano K, Hermiston ML, Doulatov S, Eppert K, Laurenti E, Notta F, Dick JE, Basso G, Hunger SP, Loh ML, Devidas M, Wood BL, Winter SS, Dunsmore K, Fulton RS, Fulton LA, Hong X, Harris CC, Dooling DJ, Ochoa K, Johnson KJ, Obenauer JC, Pui C-H, Raimondi SC, Naeve CW, Ley TJ, Mardis ER, Wilson RK, Downing JR, **Mullighan CG**. Discovery of Novel Recurrent Mutations in Childhood Early T-Cell Precursor Acute Lymphoblastic Leukemia by Whole Genome Sequencing - a Report From the St Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project. (oral).

American Society of Hematology 52nd Annual Meeting December 2010
1. **Mullighan CG**, Zhang J, Kasper LH, Lerach S, Payne-Turner D, Phillips LA, Collins-Underwood JR, Heatley SL, Ma J, Buetow K, Pui C-H, Brindle PK, Downing JR. CREBBP Mutations In Relapsed Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2010;116:413. Oral presentation
2. Collins-Underwood JR, Boulos N, Payne-Turner D, Chen S-C, Williams R, **Mullighan CG**. The Role of Dominant-Negative IKAROS Mutations In the Pathogenesis and Treatment Responsiveness of BCR-ABL1 positive Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2010;116:540. Oral presentation
3. Holmfeldt L, Zhang J, Ma J, Devidas M, Carroll AJ, Heerema NA, Gastier-Foster JM, Raimondi SC, Loh ML, Hunger S, **Mullighan CG**. Genome-Wide Analysis of Genetic Alterations In Hypodiploid Acute Lymphoblastic Leukemia Identifies a High Frequency of Mutations Targeting the IKAROS Gene Family and Ras Signaling. Blood (ASH Annual Meeting Abstracts). 2010;116:411. Oral Presentation, Selected as "Best of ASH"
4. Figueroa ME, Chen S-C, Andersson AK, Liu W, Cheng C, Phillips LA, Li Y, Downing JR, Melnick AM, **Mullighan CG**. Integrated Genetic and Epigenetic Analysis of Childhood Acute Lymphoblastic Leukemia Reveals a Synergistic Role for Structural and Epigenetic Lesions In Determining Disease Phenotype. Blood (ASH Annual Meeting Abstracts). 2010;116:537. Oral Presentation
5. Notta F, **Mullighan CG**, Wang J, Poeppl AG, Doulatov S, Phillips LA, Ma J, Minden MD, Downing JR, Dick JE. Evolution of Human BCR-ABL1 lymphoblastic Leukaemia-Initiating Cells. Blood (ASH Annual Meeting Abstracts). 2010;116:1023. Poster Presentation
6. Pasqualucci L, Dominguez-Sola D, Chiarenza A, Fabbri G, Grunn A, Trifonov V, Kasper LH, Lerach S, Jing M, Rossi D, **Mullighan CG**, Gaidano G, Rabadan R, Brindle PK, Dalla-Favera R. Genome-Wide Analysis Reveals Frequent Inactivating Mutations of Acetyltransferase Genes In B-Cell Lymphoma. Blood (ASH Annual Meeting Abstracts). 2010;116:474. Oral

Presentation

7. Tasian SK, Doral MY, Wood BL, Borowitz MJ, Collins-Underwood JR, Harvey RC, Sakamoto KM, Willman CL, Hunger SP, **Mullighan CG**, Loh ML. Thymic Stromal Lymphopoietin Stimulation of Pediatric Acute Lymphoblastic Leukemias with CRLF2 Alterations Induces JAK/STAT and PI3K Phosphosignaling. Blood (ASH Annual Meeting Abstracts). 2010;116:410. Oral Presentation
8. Zhang J, **Mullighan CG**, Harvey R, Carroll WL, Chen I-ML, Devidas M, Larsen E, Edmonson M, Buetow K, Gerhard DS, Loh ML, Reaman GH, Relling MV, Smith MA, Downing JR, Willman CL, Hunger S. Lack of Somatic Sequence Mutations In Protein Tyrosine Kinase Genes Other Than the JAK Kinase Family In High Risk B-Precursor Childhood Acute Lymphoblastic Leukemia (ALL): A Report From the Children's Oncology Group (COG) High-Risk (HR) ALL TARGET Project. Blood (ASH Annual Meeting Abstracts). 2010;116:2752. Poster Presentation
9. Teachey DT, Vincent T, Willman CL, Loh ML, **Mullighan CG**, Hunger S, Grupp SA. Targeting mTOR Signaling Is An Effective Treatment Strategy for IKAROS and JAK Kinase Mutated Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2010;116:3251. Poster Presentation
10. Downie J, Barnette P, Rodic V, Frazer JK, Trede N, Devidas M, **Mullighan CG**, Hunger S, Miles RR, Schiffman JD. T-Cell Receptor Gene Deletions Are Associated with High Risk Features and Worse Outcome In Childhood Precursor B-Cell Acute Lymphoblastic Leukemia (ALL). Blood (ASH Annual Meeting Abstracts). 2010;116:275. Poster Presentation

American Society of Hematology 51st Annual Meeting December 2009

1. Collins-Underwood R, Miller CB, Downing JR, **Mullighan CG**. Ikzf1 Haploinsufficiency Contributes to the Pathogenesis of BCR-ABL1 Positive Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2009;114:678. Oral Presentation.
2. **Mullighan CG**, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Cheng J, Mikhail FM, Meyer J, Williams RT, Carroll AJ, Heerema NA, Basso G, Pession A, Pui C-H, Raimondi SC, Hunger SP, Downing JR, Carroll WL, Rabin KR. Rearrangement of CRLF2 in B-Progenitor and Down Syndrome Associated Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2009;114:182. Oral Presentation.
3. **Mullighan CG**, Morin R, Zhang J, Hirst M, Zhao Y, Yan C, Finney R, Edmonson M, Su X, Buetow KE, Carroll WL, Chen I-M, Devidas M, Gerhard D, Harvey RC, Hu Y, Loh ML, Reaman G, Relling MV, Smith MA, Downing JR, Hunger SP, Willman CL, Marra M. Next Generation Transcriptomic Resequencing Identifies Novel Genetic Alterations in High-Risk (HR) Childhood Acute Lymphoblastic Leukemia (ALL): A Report From the Children's Oncology Group (COG) HR ALL TARGET Project. Blood (ASH Annual Meeting Abstracts). 2009;114:704. Oral Presentation
4. **Mullighan CG**, Zhang J, Phillips LA, Pui C-H, Downing JR. Identification of Novel Recurring Mutations in Relapsed Acute Lymphoblastic Leukemia. Blood (ASH Annual Meeting Abstracts). 2009;114:703. Oral Presentation
5. Hauer J, **Mullighan CG**, Morillon E, Wang GP, Bruneau J, Brousse N, Borkhardt A, Bushmann FD, Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M. Leukemia Prone B-Precursor Population in a p19ARF-/-RAG1-/- Mouse Model. Blood (ASH Annual Meeting Abstracts). 2009;114:3971. Poster Presentation
6. Rabin KR, Wang J, Meyer J, Loudin MG, Bhojwani D, Morrison D, Devidas M, Heerema NA, Carroll AJ, Pession A, Basso G, **Mullighan CG**, Hunger SP, Carroll WL. Gene Expression Profiling in Down Syndrome Acute Lymphoblastic Leukemia Identifies Distinct Profiles Associated with CRLF2 Expression Status. Blood (ASH Annual Meeting Abstracts). 2009;114:2389. Poster Presentation
7. Zhang J, **Mullighan CG**, Harvey RC, Buetow KE, Carroll WL, Chen I-M, Devidas M, Edmonson M, Gerhard D, Hu Y, Loh ML, Phillips LA, Reaman GH, Relling MV, Smith M, Downing JR, Willman CL, Hunger SP. Mutations in the RAS Signaling, B-Cell Development, TP53/RB1, and JAK Signaling Pathways Are Common in High Risk B-Precursor Childhood Acute Lymphoblastic Leukemia (ALL): A Report From the Children's Oncology Group (COG) High-Risk (HR) ALL TARGET Project. Blood (ASH Annual Meeting Abstracts). 2009;114:85. Oral Presentation

MEETING ORGANIZATION

New Directions in Leukaemia Research, Sunshine Coast, Australia, 2008, 2010, 2012, 2014

INVITED LECTURES (2009-2013)

2013

1. Society for Hematopathology / European Association for Haematopathology, 2013 Workshop: Progress in Acute Myeloid Leukemia, Myelodysplastic Sundromes and Acute Lymphoblastic Leukemia: Classification and Molecular Pathogenesis. Invited Faculty Speaker, October 24-26, 2013, MD Anderson, Houston, Texas
2. FASEB Meeting for Hematological Malignancies, Saxton's River, Vermont, Invited Speaker August 2013
3. 4th International Congress on Leukemia, Lymphoma and Myeloma, Istanbul, Turkey, May 22-25, 2013. Invited Speaker.
4. American Society of Pediatric Hematology Oncology Presidential Symposium - 2013: The Future Of Pediatric Oncology April 25, 2013
5. Gordon Conference on Cancer Genetics and Epigenetics, April 2013
6. Innovations in Hematology, Caesarea, Israel April 2013
7. Societe Francaise d/Hematologie March 27-29 2013, Invited Speaker
8. Acute Leukemias XIV: Biology and Treatment Strategies, Munich, Germany, Feb 24-27 2013. Invited speaker in symposium "ALL: Biology and Treatment Strategies – Whole Genome Sequencing: Results and Perspectives in Pediatric ALL"
9. Department of Cancer Biology at the University of Massachusetts Medical School in Worcester, Seminar Series, Invited Speaker, February 2013

2012

1. American Society of Hematology Annual Scientific Meeting, December 2012. Speaker in Educational Session "New Insights into the genetic pathogenesis of ALL and New Treatment Strategies – The Molecular Genetic Makeup of ALL".
2. Chemotherapy Foundation Symposium, New York, November 2012. Invited Speaker.
3. Aflac and Blood Disorders Center, Emory University, Atlanta, Georgia. Visiting Professor, October, 2012
4. Northwestern Cancer Center Grand Rounds, September 2012
5. ComBio Meeting, Adelaide, September 2012. Invited Speaker.
6. XII Congresso Nazionale della Società Italiana di Ematologia Sperimentale, Rome, October 2012, Invited Speaker
7. 14th International Conference, CML – Biology and Therapy, Baltimore, 20-23 Sep 2012. Special Guest Speaker.
8. European Haematology Association 17th Congress, Rotterdam, June 2012. Educational Session, Acute Lymphoblastic Leukemia
9. 42nd Biennial American Cytogenetics Conference. Plenary Speaker. "Insights into the biology of acute leukemia from genomic profiling and next-generation sequencing". April 2012.
10. American Association for Cancer Research, 2012 Annual Meeting. Chicago, April 2012. Speaker in St Jude 50th Anniversary Symposium.
11. New Directions in Leukemia Research, Sunshine Coast, Queensland, March 2012. Invited International Speaker.
12. Human Genome Meeting, Sydney, March 2012. Plenary Speaker. "Recent advances in the genetics of acute leukemia: from genomics to the clinic".

2011

1. 53rd meeting of the Japanese Society of Pediatric Hematology and Oncology. November 2011. Plenary Speaker. "High-risk acute lymphoblastic leukemia – insights into pathogenesis and therapy from genomic profiling"
2. Haematology Association of Australasia Annual Meeting. October 2011. Plenary Speaker
3. National Cancer Institute Center for Cancer Research Grand Rounds September 2011.
4. Walter and Eliza Hall Institute for Medical Research. Translational Research Forum, Plenary Speaker, July 2010
5. Ontario Institute for Cancer Research, Cancer Stem Cell Program Cancer Stem Cell Seminar Series, Toronto May 2011
6. University of Minnesota Laboratory Medicine & Pathology Grand Rounds May 2011.
7. American Association of Cancer Research. Pediatric Cancer Forum April 2011. "Sequencing the genome of pediatric acute lymphoblastic leukemia."
8. Acute Leukemia Forum 2011: "Advances and Controversies in the Biology and Therapy of Acute Leukemia and Myelodysplasia", San Francisco, CA, Friday, March 25, 2011.
9. Keystone Conferences Stem Cells and Cancer, March 2011
10. American Society of Bone Marrow Transplantation. Plenary Scientific Session
11. Harvard University Pathology Grand Rounds, February 2011
12. MD Anderson Cancer Center. Pathology Grand Rounds. January 2011
13. University of Chicago Committee on Cancer Biology Seminar, January 2011
14. University of California San Francisco Helen Diller Family Comprehensive Cancer Center Friday Seminar Series, January 2011

2010

1. New York Pediatric Hematology-Oncology-BMT forum. December 2010. Keynote address. "New insights into the genomic basis of acute lymphoblastic leukemia"
2. Association for Molecular Pathology Annual Meeting, November 2010. Haematopathology Plenary Session. "Genetic alterations in lymphoid development"
3. Aegean Conference, Gene regulation in lymphocyte development, Crete, October 2010
4. SIOP State of the art symposium, acute lymphoblastic leukemia. October 2010
5. Advances in Haematology, Hammersmith Hospital, London, September 2010. Galton Prize Lecture
6. Memorial Sloan Kettering Cancer Center Grand Rounds, July 2010
7. American Society of Clinical Oncology Annual Meeting, June 2010. Educational Session, Acute Lymphoblastic Leukemia
8. American Society of Pediatric Hematology and Oncology, Montreal, April 2010. Symposium Chair: Improving outcomes for high-risk ALL: Translating New Discoveries into Clinical Care
9. St Jude – VIVA Forum, March 2010. Genetics of ALL
10. New Directions in Leukaemia Research, Australia, March 2010. Invited speaker (2 lectures): Genomic analysis of acute lymphoblastic leukemia; Genetics of Relapsed ALL
11. Leucémies Aiguës - Des gènes aux traitements, Paris January 2010. Genomic Profiling of Acute Lymphoblastic Leukemia

2009

1. American Society of Haematology 51st Annual Meeting, December 2009. Scientific Committee on Lymphoid Neoplasia: Genomic Profiling of Acute Lymphoblastic Leukemia: Insights into Pathogenesis, Prognosis, and Therapeutic Targets
2. Society of Pediatric Pathology. Lotte-Strauss Prize Lecture, November 2009
3. National Cancer Research Institute (UK) Cancer Conference, October 2009. Educational Session, Acute Lymphoblastic Leukemia
4. European Society of Hematology Chronic Myeloid Leukemia Meeting, Bordeaux September 2009. *BCR-ABL1*-like high risk acute lymphoblastic leukemia
5. New Directions in Pediatric, Adolescent and Young Adult Lymphoma. July 2009. Genetics of Lymphoid Malignancies.
6. European Haematology Association 14th Congress, Berlin, June 2009. Educational Session, Acute Lymphoblastic Leukemia
7. NCI Adolescent and Young Adult Oncology Workshop, June 2009. Genomics of High Risk ALL
8. Korean Society of Hematology Annual Meeting Seoul May 2009. Plenary speaker
9. International Society of Laboratory Hematology, Las Vegas, May 2009. Plenary Lecture
10. American Association for Cancer Research 100th Annual Scientific Meeting, Denver, April 2009. Scientific Symposium on Pediatric Cancer.
11. Children's Oncology Group Cytogenetics Meeting St Louis, March 2009. Genomic analysis of ALL

The Molecular Genetics of Acute Lymphoblastic Leukemia

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Abstract

Genome-wide profiling has provided critical new insights into the genetic basis of acute lymphoblastic leukemia (ALL), and has provided new markers for diagnosis, risk stratification, and therapeutic intervention. These approaches have shown that ALL comprises multiple subtypes characterized by constellations of structural rearrangements, DNA copy number alterations and mutations. Genetic alterations targeting lymphoid development are a hallmark of ALL, alteration of the lymphoid transcription factor gene *IKZF1* (IKAROS) is associated with increased risk of treatment failure in B-ALL. Approximately 20% of childhood B-ALL case, and over 50% of ALL in adults harbor genetic alterations that activate kinase signaling that are potentially amenable to treatment with tyrosine kinase inhibitors, including rearrangements of *ABL1, CRLF2, JAK2, JAK2* and *PDGFRB.* Genome sequencing has also identified novel targets of mutation in T-lineage ALL, including hematopoietic regulators (*ETV6, RUNX1*), tyrosine kinases and epigenetic regulators. Ongoing studies are completing sequencing of the full spectrum of ALL in children and adults with ALL, and translating these new findings into faithrful experimental models and new treatment approaches to improve the outcome of therapy in ALL..

Introduction

Acute lymphoblastic leukemia (ALL) is the commonest childhood tumor,[1] and remains a leading cause of childhood mortality. The frequency of genetic alterations associated with favorable outcome in childhood ALL is lower in older patients with ALL, and alterations associated with poor outcome such as *BCR-ABL1* are more common. With the exception of tyrosine kinase inhibitors such as imatinib in the treatment of *BCR-ABL1* positive leukemia, current therapies do not target specific genetic alterations. Thus, genome-wide profiling approaches including microarray analysis and sequencing are now widely used to identify genetic alterations driving leukemogenesis, to predict treatment failure, and to identify novel targets for therapeutic intervention. This review and presentation will review recent insights obtained from genomic profiling of ALL, with an emphasis on high-risk B-progenitor ALL.

Approximately three-quarters of childhood ALL cases harbor a recurring gross chromosomal alteration detectable by cytogenetic analysis and molecular techniques (Figure 1). These include B-progenitor ALL with high hyperdiploidy (greater than 50 chromosomes), hypodiploidy with less than 44 chromosomes, and chromosomal rearrangements including t(12;21) *ETV6-RUNX1* (TEL-AML1); t(1;19) *TCF3-PBX1* (E2A-PBX1); t(9;22) *BCR-ABL1;* and rearrangement of *MLL* at 11q23. T-lineage ALL commonly harbors activating mutations of *NOTCH1* and rearrangements of transcription factors *TLX1 (HOX11), TLX3 (HOX11L2), LYL1, TAL1* and *MLL*.[2] These rearrangements are important initiating events but are insufficient to fully explain leukemogenesis. For example, several fusions such as *ETV6-RUNX1* are present years prior to the clinically manifest leukemia, and many do not alone result in the development of leukemia in experimental models. We now recognize that the

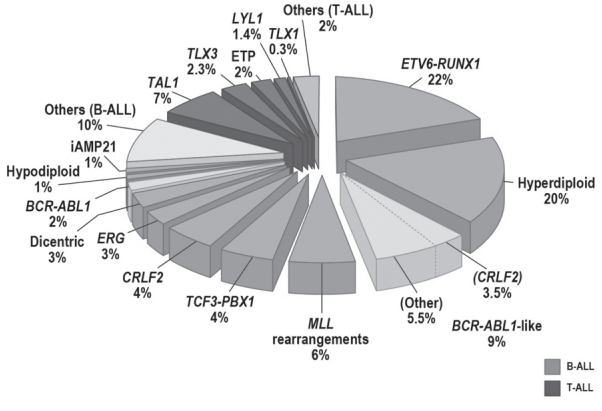

Figure 1. Frequency of cytogenetic subtypes of pediatric ALL.

Table 1. Recently identified mutations in B-progenitor ALL
The table lists recently identified recurring genetic alterations in B-progenitor ALL that have key roles in leukemogenesis, risk stratification, and/or therapeutic targeting.

Gene	Alteration	Frequency	Pathophysiologic and clinical consequences of alteration
PAX5	Deletions, translocations, sequence mutations	One third of B-progenitor ALL cases	Transcription factor required for B-lymphoid development. Mutations impair DNA binding and transcriptional activation. Cooperates in leukemogenesis, but no association with outcome
IKZF1	Focal deletions or sequence mutations	15% of all pediatric B-ALL cases, over 70% of BCR-ABL1 lymphoid leukemia, and one third of BCR-ABL1 negative ALL.	Transcription factor required for lymphoid development. Deletions and mutations result in loss of function or dominant negative isoforms. Cooperates in pathogenesis of BCR-ABL1 positive ALL. Associated with poor prognosis in BCR-ABL1 positive and negative B-ALL.
	Inherited variants		Associated with risk of ALL
JAK1/2	Pseudokinase and kinase domain mutations	18–35% DS-ALL and 10% High-risk BCR-ABL1-ALL. JAK1 mutations also identified in T-ALL	Result in JAK-STAT activation in model cell lines and primary leukemia cells, may be responsive to JAK inhibitors.
CRLF2	Rearrangement as IGH@-CRLF2 or P2RY8-CRLF2 resulting in overexpression. F232C mutations	5–16% pediatric and adult B-ALL, and >50% DS-ALL	Associated with mutant JAK in up to 50% of cases. Associated with IKZF1 alteration and poor outcome, particularly in non-DS-ALL
IL7R	Complex in-frame mutations in the transmembrane domain	Up to 7% of B- and T-ALL	Result in receptor dimerization and constitutive IL7R signaling and JAK-STAT activation; JAK inhibitors may also be useful.
CREBBP	Focal deletion and sequence mutations	19% of relapsed ALL; commonly acquired at relapse	Mutations result in impaired histone acetylation and transcriptional regulation. Associated with glucocorticoid resistance.
TP53	Deletions and sequence mutations	Up to12% B-ALL, commonly acquired at relapse	Loss of function or dominant negative. Associated with poor outcome
Kinase rearrangements and mutations	Rearrangements of ABL1, PDGFRB, EPOR, JAK2, deletions of SH2B3	Present in half of BCR-ABL1-like ALL cases	Result in kinase signaling activation that is attenuated with TKIs.

majority of ALL subtypes are characterized by distinct constellations of structural and submicroscopic genetic alterations and sequence mutations.

Submicroscopic genetic alterations in ALL

From 2007, multiple groups have reported studies profiling DNA copy number alterations in childhood ALL using array-based comparative genomic hybridization or single nucleotide polymorphism (SNP) microarrays (fewer studies have examined adult ALL). These studies have shown that ALL genomes are typically less complex than many solid tumors and malignancies, but harbor over 50 recurring regions of deletion or amplification, many of which involve a single gene or few genes[3] (Table 1). Many encode proteins that regulate lymphoid development (e.g., *PAX5, IZKF1, EBF1* and *LMO2*), cell cycle and tumor suppression (*CDKN2A/CDKN2B, PTEN, RB1*), and lymphoid signaling (*BTLA, CD200, TOX*). Additional targets include the glucocorticoid receptor *NR3C1,* and transcriptional regulators and co-activators (*TBL1XR1, ETV6* and *ERG*, Figure 2). Recent studies have implicated a number of genes regulating chromatin, including the histone acetyltransferase *CREBBP.* Importantly, several genes are involved by multiple types of genetic alteration, including copy number alterations, translocation and sequence mutation.

The patterns of genetic alterations are associated with ALL subtype. *MLL*-rearranged leukemias harbor very few additional genetic alterations.[4,5] In contrast, *ETV6-RUNX1* and *BCR-ABL1* ALL harbor an average of over 6 additional genetic lesions per case. Several of these alterations have now been known to cooperate in leukemogenesis. For example, deletion of *Pax5* and *Ikzf1* accelerates the onset of leukemia in retroviral bone marrow transplant and transgenic models of *BCR-ABL1* ALL.[6]

Deletions involving the ETS-family transcription factor *ERG* (ETS-related gene) are notable for being a hallmark of a novel subtype of B-ALL with a distinct gene expression profile and generally favorable outcome. The *ERG* deletions involve an internal subset of exons resulting in loss of the central inhibitory and pointed domains, and expression of an aberrant C-terminal ERG fragment that retains the ETS and transactivation domains, and functions as a competitive inhibitor of wild-type ERG.[7]

IKZF1 alterations in B-ALL

Alterations of the genes encoding transcriptional regulators of lymphoid development is a hallmark of B-ALL. Deletions, sequence mutations, or rearrangements of *PAX5, EBF1* and *IKZF1* are present in over two-thirds of cases.[4,8] *IKZF1* alterations, most commonly deletions are present in approximately

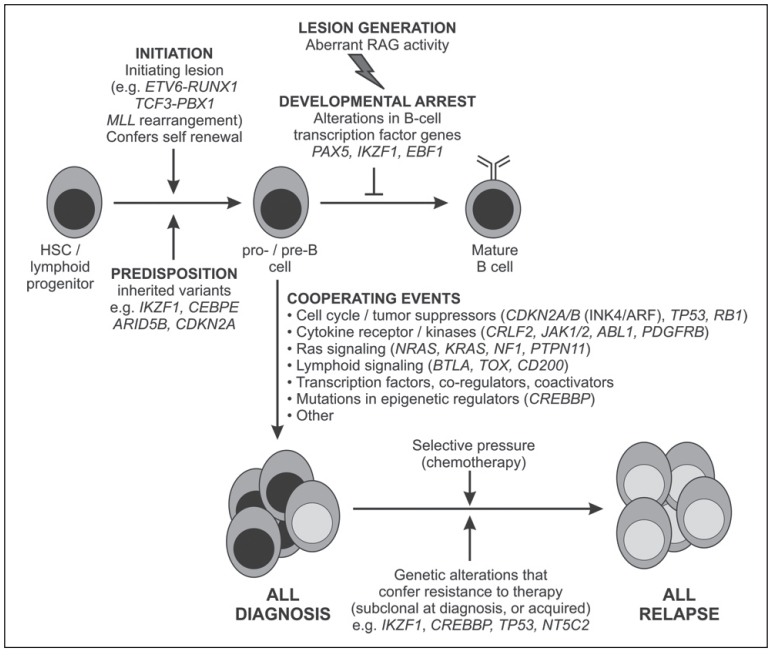

Figure 2. Schema for the role of genetic alterations in the pathogenesis of B-ALL. Many chromosomal rearrangements are acquired early in leukemogenesis, and drive transcriptional and epigenetic dysregulation and aberrant self-renewal. These lesions and/or secondary genetic alterations disrupt lymphoid development and result in an arrest in maturation. Additional genetic alterations target multiple cellular pathways, including cell cycle regulation and tumor suppression, chromatin modification. In a subset of cases (*BCR-ABL1* positive and *BCR-ABL1*-like ALL) genetic alterations drive aberrant cytokine receptor and kinase signaling. Together, these events result in proliferation and establishment of the leukemic clone. Diagnosis ALL samples are commonly clonally heterogeneous, and genetic alterations in minor clones may confer resistance to therapy and promote disease relapse. It should be noted a direct role of many of the genetic alterations shown in the pathogenesis of ALL has not yet been confirmed experimentally. A similar schema can be proposed for T-ALL, where lesions targeting lymphoid development, self renewal, and kinase signaling are also observed; and in which there are multiple targets of mutation of unknown role in leukemogenesis (e.g. *PHF6, WT1*). Reproduced from ref [46].

15% of childhood ALL cases, and are a hallmark of high risk ALL. *IKZF1* encodes IKAROS, the founding member of a family of zinc finger transcription factors that is required for the development of all lymphoid lineages.[9] The *IKZF1* alterations observed in ALL include deletions that result in loss of function, or internal deletions of coding exons 4-7 that remove the N-terminal DNA-binding zinc fingers, leading to expression of a dominant negative isoform, IK6. *IKZF1* alterations are present in over 70% of *BCR-ABL1* lymphoid leukemia, including *de novo* ALL and chronic myeloid leukemia (CML) at lymphoid blast crisis,[10] and are associated with poor outcome in BCR-ABL1 positive and negative ALL.[118,12] Moreover, a subset of *IKZF1*-mutated BCR-ABL1-negative ALL have a gene expression profile similar to *BCR-ABL1*-positive ALL, and harbor novel kinase-activating mutations and rearrangements. These cases are termed *BCR-ABL*-like ALL and are discussed below).

CRLF2 rearrangements and Janus kinase mutations in ALL

CRLF2 (cytokine receptor-like factor 2, also known as thymic stromal lymphopoietin) at the pseudoautosomal region 1 at Xp22.3/Yp11.3 is rearranged or mutated in 5-7% of childhood ALL (Figure 1), and over 50% of cases associated with Down syndrome (DS-ALL).[13,14] CRLF2 and interleukin-7 receptor alpha (IL7RA), form the heterodimeric receptor for TSLP. *CRLF2* is rearranged by translocation into the immunoglobulin heavy chain locus (*IGH@-CRLF2*), or a focal PAR1 deletion upstream of *CRLF2* that results in expression of *P2RY8-CRLF2*. Both rearrangements result in aberrant overexpression of CRLF2 on the cell surface of leukemic lymphoblasts that may be detected by immunophenotyping. Less commonly a p.Phe232Cys CRLF2 mutation results in receptor overexpression.[15]

CRLF2 alterations are associated with activating mutations in the Janus kinase genes *JAK1* and *JAK2.*[13-15]. The JAK/STAT pathway mediates signaling from cytokine, chemokine and growth factor receptors, via the JAK non-receptor tyrosine kinases and the STAT (signal transduction and transcription) family of transcription factors.[16] The JAK mutations are most commonly missense mutations at R683 in the pseudokinase domain of JAK2, in contrast to the JAK2 V617F mutations that are a hallmark of myeloproliferative diseases.[17] Up to 50% of *CRLF2*-rearranged cases harbor activating JAK1/2 mutations, and almost all cases of B-ALL with JAK1/2 mutations harbor concomitant rearrangements of *CRLF2*. Co-expression of CRLF2 and JAK1/2 mutations is transforming *in vitro* suggesting that these two lesions are central in lymphoid transformation.[18,19] The nature of alternative kinase signaling mutations in *CRLF2* rearranged cases that lack JAK mutations is presently unknown. In non-DS ALL, *CRLF2* alterations and JAK mutations are associated with *IKZF1* deletion/mutation, a gene expression profile similar to BCR-ABL1 positive ALL, and in some studies poor outcome.[20] The associations between CRLF2 and outcome have varied between studies and cohorts, but are most consistent in non-DS ALL.[21-23]. For example studies

performed by the Children's Oncology Group (COG) have shown that *CRLF2* and *IKZF1* alterations are associated with inferior outcome in multiple cohorts, and notably, that elevated *CRLF2* expression in the absence of rearrangement is also an adverse prognostic feature.[24]

Regardless of JAK mutation status, the leukemic cells harboring CRLF2 deregulation exhibit activation of JAK-STAT and PI3K/mTOR pathways, and are sensitive to JAK and mTOR inhibitors *in vitro* and *in vivo*. An early phase of the JAK inhibitor ruxolitinib in relapsed and refractory childhood tumors, including cases with CRLF2 rearrangement and/or JAK mutations, ADVL1011, has been initiated (clinicaltrials.gov identifier NCT01164163).

BCR-ABL1-like ALL

Up to 15% of childhood B-progenitor ALL cases have a gene expression profile similar to that of BCR-ABL1-positive ALL, and often alteration of *IKZF1*, which is also common in BCR-ABL1-ALL (Figure 1).[8,25] Ongoing studies suggest that *BCR-ABL1*-like ALL is also common in adolescent and young adult ALL (unpublished data). The prognosis of BCR-ABL1-like ALL is poor. In the COG AALL0232 study of high risk B-progenitor ALL, the event-free survival (EFS) for BCR-ABL1-like cases was 62.6±6.9% compared to 85.8±2.0% for non-BCR-ABL1-like cases (P<0.0001), and was associated with poor outcome after adjustment for age, sex, peripheral blood leukocyte count at presentation, and day 29 flow cytometric levels of minimal residual disease.[26] Up to half of *BCR-ABL1*-like cases harbor rearrangements of *CRLF2* and *JAK1/2* sequence mutations.[19,20]

Second generation sequencing, including transcriptome and whole genome sequencing has identified a range of novel rearrangements, copy number alterations, and sequence mutations activating kinase signaling in cases lacking *CRLF2* rearrangement. These include rearrangements of *PDGFRB, ABL1, JAK2*, and *EPOR*, as well as deletion/mutation of *SH2B3* (encoding the JAK2 negative regulator LNK) and the sequence mutations of *IL7R*.[27] Several of these alterations confer growth factor independence in murine Ba/F3 and Arf$^{-/-}$ cell lines that is attenuated with tyrosine kinase inhibitors (TKIs) such as the ABL1/PDGFRB inhibitors imatinib and dasatinib, and the JAK2 inhibitor ruxolitinib. Moreover, primary leukemic cells from patients with *BCR-ABL1*-like ALL exhibit activation of these signaling pathways on phosphoflow cytometry, and tumors engrafted into immunodeficient mice are sensitive to targeted TKI therapy.[28] Moreover, anecdotal evidence indicates that refractory EBF1-PDGFRB positive ALL is sensitive to imatinib therapy.[29] These findings strongly suggest that patients with BCR-ABL1-like ALL, many of whom are at high risk of relapse, may be successfully treated with TKIs. Ongoing work is sequencing many additional BCR-ABL1-like cases to identify the full repertoire of kinase activating lesions in childhood and adult ALL. In addition, as *BCR-ABL1*-like ALL is associated with a distinct gene expression signature (with overexpression of genes including *MUC4, PON2, IGJ* and *GPR110*)[27], patients may be identified at diagnosis by targeted gene expression profiling and or phosphoflow cytometry followed by sequencing approaches.

Intrachromosomal amplification of chromosome 21

Intrachromosomal amplification of chromosome 21 (iAMP21) occurs in up to 2% of B-progenitor ALL and in has been associated with older age poor outcome.[30] iAMP 21 is defined by gain of at least copies of the region of chromosome 21 containing RUNX1. The amplification is often large and complex, and accompanied by deletion of the subtelomeric regions of chromosome 21. The basis of generation of iAMP21 and the manner in which this contributes to leukemogenesis and poor outcome are currently unclear.

Hypodiploid ALL

Hypodiploidy with less than 45 chromosomes is associated with a high risk of treatment failure,[31] and has previously been subclassified into near haploid (NH, 24-31 chromosomes) and low hypodiploid (LH, 32-44 chromosomes) cases. We recently reported findings of genomic profiling (including exome, mRNA-seq and whole genome sequencing) of over 120 hypodiploid ALL cases.[32] This showed that NH ALL has a very high frequency of deletions and sequence mutations that activate Ras signaling, including recurring novel alterations of *NF1*, and that NH and LH ALL have a high frequency of inactivating alterations of IKAROS genes *IKZF2* (HELIOS) and *IKZF3* (AIOLOS) that are otherwise uncommon in ALL. With transcriptional profiling, these results indicate that NH and LH ALL are distinct diseases. Moreover, we demonstrated Ras and PI3K pathway activation by biochemical and flow cytometric analysis of primary leukemic cells, suggesting that therapeutic targeting of these pathways may represent an potential novel treatment outcome in this high risk leukemia.

Sequence mutations in ALL.

Candidate gene sequencing studies have identified multiple targets of mutation in ALL (e.g. *PAX5, BCL11B*, *FBXW7*, *IKZF1*, *LEF1*, *WT1*, *PTEN1* and

NF1). In general, these studies have shown that DNA copy number alterations are more common than sequence mutations in ALL, however until recently, detailed analysis of sequence mutations in large cohorts of ALL have been prohibitively costly.

To identify novel targets of mutation and examine patterns of mutational evolution from diagnosis to relapse, we sequenced 300 genes 24 B- and T-lineage ALL cases at diagnosis, relapse and remission.[33] The frequency of sequence mutation was low (0–5 per case), and as observed for DNA-copy number alterations, many deleterious mutations present at diagnosis were no longer evident at relapse, including mutations in the Ras signaling pathway (*NRAS, KRAS, PTPN11*, and *NF1*) and B cell development (e.g. *PAX5*, but not *IKZF1*, deletions/mutations of which were always preserved at relapse, or acquired as new lesions). Deletion or mutation of *CREBBP*, encoding the transcriptional coactivators and acetyltransferase CREB binding protein (also known as CBP) were present in almost 20% of relapsed ALL cases, and appear particularly enriched in relapsed hyperdiploid ALL, a subtype normally associated with favorable outcome.[34] The mutations identified are enriched in the histone acetyltransferase (HAT) domain and attenuated the normal HAT activity of murine Crebbp. Moreover, CREBBP mediates the transcriptional response to glucocorticoid therapy, and the mutations were shown to disrupt the normal transcriptional response to glucocorticoids. Thus, *CREBBP* mutations may represent an important mechanism underlying treatment failure in ALL, and may be targeted with agents that modulate the level of histone acetylation in leukemic cells, such as histone deacetylase inhibitors. Recent studies have also shown that mutations in *TP53* (p53), and the 5' nucleotidase gene *NT5C2* that otherwise infrequent in ALL, are also enriched at relapse, and associated with poor outcome.[35] Ongoing studies are peforming exome and whole genome sequencing of extended diagnosis and relapse cohorts to identify the full spectrum of genetic alterations underlying relapse in ALL.

Recent insights into the genetic basis of T-lineage ALL

Several studies have used second generation sequencing to identify genetic alterations in T-lineage ALL. T-ALL exhibits a peak in incidence in older male children, and to investigate this sex bias, the group of Adolfo Ferrando performed exon capture and sequencing of X chromosome genes.[36] This identified a high frequency of deleterious mutations in *PHF6*, which encodes PHD finger protein 6, a zinc finger containing putative transcriptional factor. The role of PHF6 alterations in T-cell leukemogenesis is at present unclear.

Subset of aggressive T-ALL cases termed "early T-cell precursor" ALL (ETP-ALL) exhibit an unusual immunophenotype with expression of cytoplasmic CD3, but lack of expression of CD1a and CD8, weak or absent expression of CD5 and aberrant expression of stem cell and myeloid markers, similar to the murine early T-cell precursor that retains developmental plasticity.[37] ETP-ALL comprises 10-15% of childhood and adult ALL and is associated with poor treatment response, induction failure and poor EFS. ETP ALL blasts lack alterations otherwise common in T-ALL, such as activating *NOTCH1* mutations and *CDKN2A/B* deletions but lack common chromosomal rearrangement.

Genome sequencing of 12 ETP-ALL cases, and recurrence testing of mutations in 54 ETP and 42 non-ETP T-ALL cases showed that three pathways are common mutations of three pathways in ETP ALL: hematopoietic development, Ras and/or cytokine receptor/JAK-STAT signaling, and histone modification.[38] Several other groups have also identified mutations in several of these genes/and pathways using non-WGS approaches.[39,40] Over half of ETP cases (compared with 17% of non-ETP T-ALL cases) harbored loss of function or dominant negative mutations in developmental genes, including *RUNX1, IKZF1, ETV6, GATA3*, and *EP300*. Several of these genes are also mutated in other hematopoietic malignancies (e.g., *RUNX1* in myeloid disorders and *ETV6* and *IKZF1* in B-progenitor ALL). Activating signaling mutations were identified in 67% of cases (compared with 19% of non-ETP T-ALL cases), including mutations in *NRAS, KRAS, JAK1, NF1*, and *PTPN11*, and novel mutations in *JAK3, SH2B3* (encoding LNK, a negative regulator of JAK2 signaling) and *IL7R*.[41] The IL7R mutations found in B- and T-ALL are located in the transmembrane domain, commonly introduce a cysteine that results in receptor dimerization, and result in constitutive JAK-STAT that is abrogated by pharmacologic JAK inhibitors, such as ruxolitinib.

ETP ALL cases harbor a high frequency of mutations in epigenetic regulators most commonly in genes encoding components of the polycomb repressor complex 2 (PRC2) a H3K27 trimethylase that normally induces transcriptional repression. The most commonly mutated gene was *EZH2*, which encodes the catalytic component of the complex. *EZH2* is also mutated in follicular lymphoma, but in contrast to the highly recurrent Y641 mutations observed in FL that are gain of function,[42] the mutations in T-ALL occur in other sites in *EZH2* and are predicted to disrupt the catalytic SET domain and result in loss of function.

These pathways – hematopoietic development, signaling and epigenetic regulation – are also frequently mutated in AML. In addition, the transcriptional profile of ETP ALL is highly similar to that of normal hematopoeitic stem cells, and that of high risk AML but *not* the normal human ETP. This suggests that ETP ALL may represent a stem cell or progenitor leukemia, and recent data examining biphenotypic leukemias have identified similar mutations in a small number of cases,[43] suggesting that the entity of ETP ALL may extend beyond leukemias nominally of T-cell (e.g cCD3+) lineage. Moreover, these findings suggest that non-ALL regimens, either myeloid-directed, targeted or epigenetic therapies, should be pursued in this disease.

Clonal heterogeneity in ALL

Genomic profiling of serial ALL samples has shown that the majority of ALL cases exhibit substantial changes in genetic alterations from diagnosis to relapse. Relapse in ALL commonly arises from the emergence of a minor subclone that shares some genetic features, and also harbors distinct genetic alterations from the predominant clone at diagnosis. Less commonly, the predominant clones at diagnosis or relapse are identical or share no commonality. Thus at diagnosis, individual patients harbor multiple genetically distinct clones that share a common clonal origin, that then respond differently to the selective pressure of anti-leukemic therapy, and this hypothesis is supported by recent xenograft models of ALL that have compared the genomic alterations in engrafted tumors with the primary sample and traced the clonal evolution of tumors.[44,45] This has important clinical implications, as among the lesions that may not be detected at diagnosis by profiling of the by leukemia clone, yet emerge at relapse are alterations of *IKZF1*. Thus, while many patients with *IKZF1* alteration at high risk of relapse may be identified by genomic profiling of bulk leukemic samples by standard approaches, others will require highly sensitive methods, for example quantitative DNA or RNA PCR, to identify these alterations (which may be deletions or mutations) at very low levels at the time of diagnosis. Moreover, the full range of genetic alterations contributing to relapse remains to be defined.

Conclusions and future directions

Genome sequencing will identify all somatic genetic alterations present in ALL genomes within the next few years. At present, these studies are focused on characterizing somatic genetic alterations in coding genes, but it will also be important to identify of all inherited variations contributing to leukemogenesis and to determine the role of non-coding genomic variation in leukemia development. An additional important area of study is sequencing of ALL in older children and adult with ALL who typically have an inferior outcome to childhood leukemia.

Several genetic alterations are of clear clinical importance for risk stratification or therapeutic targeting, including detection of *IKZF1* alterations and identification of patients with kinase-activating alterations that may benefit from targeted TKI therapy. It is likely that next generation sequencing approaches will rapidly transition from being a research to clinical diagnostic tool in many laboratories. Meanwhile, many groups are pursuing focused genetic testing of individual lesions, and screening approaches to identify pathway dysregulation, such as flow cytometric assays to identify activated kinase signaling in B-ALL. It is likely that these approaches will improve current risk stratification and ultimately improve outcome for patients with high risk ALL.

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PROFESSIONAL APPOINTMENTS:

1983-1986	Fellowship in Hematology-Oncology, American University of Beirut Medical Center, Beirut, Lebanon
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1995-2001	Assistant Professor (tenure track), Department of Pediatrics, The University of Texas M. D. Anderson Cancer Center, Houston, TX
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2001-2003	Associate Professor (tenure), The University of Texas M. D. Anderson Cancer Center, Houston, TX
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PROFESSIONAL SOCIETY MEMBERSHIPS:

1995-2004	merican Association for Cancer Research
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HONORS AND AWARDS:

Clinical Trainees Research Award UT M. D. Anderson Cancer Center

1996	PRS Research Award:Testing novel therapeutic approaches in a SCID mouse model of human leukemia. UT M. D. Anderson Cancer Center
2009	AACR team science award
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PUBLICATIONS:

Original Articles

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50. Canalli A, Yang H, **Jeha S**, Hoshino K, Sanchez-Gonzalez B, Brandt M, Pierce S, Kantarjian H, Issa JP, Garcia- Manero G. Aberrant DNA methylation of a cell cycle regulatory pathway composed of p73, p15 and p57KIP2 is a rare event in children with acute leukemia. Leuk Res 29:881-885, 2005.
51. Pui CH, Pei D, Sandlund JT, Campana D, Ribeiro RC, Razzouk B, Rubnitz JE, Howard SC, Hijiya N, **Jeha S**, Cheng C, Downing JR, Evans WE, Relling MV, Hudson M. Risk of Adverse Events after Completion of Therapy for Childhood Acute Lymphoblastic Leukemia. J Clin Oncol 23:7936-7941, 2005.
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53. Yee KW, Cortes J, Ferrajoli A, Garcia-Manero G, Verstovsek S, Wierda W, Thomas D, Faderl S, King I, O'Brien S, **Jeha S**, Andreef M, Cahill A, Sznol M, Giles FJ. Triapine and cytarabine

is an active combination in patients with acute leukemia or myelodysplastic syndrome. Leuk Res 30:813-822, 2006.

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*48. Chen SH, Pei D, Yang W, Cheng C, **Jeha S**, Evans W, Pui CH, Relling M. Genetic variations in GRIA1 on chromosome 5q33 related to asparaginase hypersensitivity in childhood acute lymphoblastic leukemia (ALL). Blood 114(22)51,2009

*49. Wayne A, Bhojwani D, **Jeha S**, Stetler-Stevenson M, Pui CH, McDevitt J, FitzGerald D, Kreitman R, Kaucic K, Pastan I. Phase I clinical trial of the anti-CD22 immunotoxin CAT-8015 (HA22) for pediatric acute lymphoblastic leukemia (ALL). Blood 114(22)345, 2009

50. Brennan R, Helton K, Inaba H, Metzger M, Howard S, Rubnitz J, Ribeiro R, Sandlund J, **Jeha S**, Pui CH, Bhojwani D. Characteristics and implications of spinal epidural lipomatosis in children with hematologic malignancies. ASPHO 2010

51. Anghelescu D, **Jeha S**, Relling MV, Sandlund JT, Cheng C, Pei D, Hinds P, Hankins, Pui CH. Gabapentin use for neuropathic pain/peripheral neurotoxicity secondary to chemotherapy for childhood ALL. International Pediatric Pain Symposium, Mexico 2010

* 52. Bhojwani D, Pei Ding P, Sandlund J, **Jeha S,** Ribeiro R, Rubnitz JE, Raimondi SC, Shurtleff S, Onciu M, Cheng C, Coustan-Smith E, Bowman P, Howard SC, Metzger ML, Inaba H, Leung WH, Evans WE, Campana D, Relling MV, Pui CH. Excellent outcome for *ETV6/RUNX1*-positive childhood acute lymphoblastic leukemia (ALL) with contemporary therapy. Abstract # 495: Blood 116(21)220, 2010

*53. **Jeha S**, Pei Deqing P, Campana D, Bowman P, Sandlund J, Kaste S, Ribeiro R, Rubnitz JE, Coustan-Smith E, Cheng C, Metzger ML, Bhojwani D, Inaba H, Raimondi SC, Onciu M, Howard SC, Leung WH, Downing JR, Evans WE, Relling MV, Pui CH. Improved prognosis for older adolescents with acute lymphoblastic leukemia. Abstract # 498: Blood 116(21)221, 2010

54. Hijiya N, Paul J, Borowitz MJ, Thomson B, Isakoff M, Silverman LB, Steinherz PG, Kadota R, Pressey JG, Shen V, Chu R, Cooper T, **Jeha S, Razzouk BI, Rytting ME, Barry E, Carroll WL, Gaynon P. Phase 2 results of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Abstract # 866: Blood 116(21)378, 2010

55. Wayne A, Bhojwani D, Richards K, Stetler-Stevenson M, Silverman LB, **Jeha S**, Pui CH, McDevitt J, FitzGerald DJ, Kreitman RJ, Lechleider RJ, Pastan I. Complete remissions in 3 of 12 patients with pediatric acute lymphoblastic leukemia (ALL) during phase I testing of the anti-CD22 immunotoxin Moxetumomab pasudotox. Abstract # 3246: Blood 116(21)1331, 2010

56. Plourde PV, **Jeha S**, Silverman LB, Nachman JB, Rheingold SR, Dahl GVH, Raetz A, Mercedes T, Corn T. L-asparaginase (L-ASP)-related toxicities with Erwinia L-ASP in a large compassionate-use protocol. Proceedings of the Am Soc Clin Oncol 2011.

*** oral presention**

ORGANIZATION OF NATIONAL OR INTERNATIONAL CONFERENCE/SYMPOSIA

Chair, AYA 1999 Symposium: Adolescent and Young Adult Issues in Oncology, UT M. D. Anderson Cancer Center, Houston, TX, September 24, 1999

Chair, AYA 2001 Symposium: Issues in Adolescents & Young Adult Leukemias, UT M.D. Anderson Cancer Center, Houston, TX, September 7-8, 2001

Chair, Satellite Symposium: Pediatric Trials – Design, Development and Demand, American Society of Pediatric Hematology/Oncology (ASPH/O), Seattle, Washington, May 1, 2003

Moderator, Oral Session - Acute Lymphocytic Leukemias: Novel and Targeted Therapies, 48th Annual Meeting of the American Society of Hematology, Orlando, Florida, December 11, 2006

Organizer, Ponte di Legno Childhood ALL Workshop, Atlanta, GA. December 5-7, 2007.

Session Chair: Acute Lymphoblastic Leukemia, 32nd Congress of the International Society of Hematology (ISH), Bangkok, Thailand, October 22nd, 2008

Moderator, Opening Session: Third Regional Congress of Cancer and Blood Disorders of Childhood. Amman, Jordan. April 15, 2010

Session Chair: Towards Improving Pediatric Oncology Service in Alexandria. 1st Annual Scientific Congress of Alexandria Pediatric Oncology Board (Alex-POB), Alexandria Faculty of Medicine, Alexandria, Egypt, October 30, 2010.

Moderator, Oral Session - Acute Lymphoblastic Leukemia: Therapy, excluding Transplantation: Clinical Trials. 54th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 9, 2012.

INVITED LECTURES AND PRESENTATIONS

Invited Speaker: PIXY321 in children with bone marrow failure. Texas Pediatric Hematology/Oncology Consortium, Houston, Texas, February 28, 1992

Seminar: SCID Mouse as a Model for Human Leukemias, Division of Laboratory Medicine, Topics in Laboratory Medicine, UT M. D. Anderson Cancer Center, Houston, Texas, June 6, 1995

Seminar: SCID Mouse as Model to Study Leukemia Biology and Develop New Therapies, Bioimmunotherapy Research Seminar, UT M. D. Anderson Cancer Center, Houston, Texas, December 1, 1996

Plenary Session: Updates of Pediatric Leukemia Studies, Third Middle East Oncology Congress meeting (COMO III), Beirut, Lebanon, May 1, 1997

Plenary Session: Pediatric Acute Myelogenous Leukemia in Children, National Arab American Medical Association meeting, Damascus, Syria, June 25, 1997

Invited Speaker: Pediatric Leukemia Diagnosis and Management, European Pan Arab Pediatric Subspecialties Course, Beirut, Lebanon, October 25, 1997

Grand Rounds: Update on pediatric leukemia studies. American University of Beirut Medical Center, Beirut, Lebanon. October 28, 1997

Seminar: Advances in Treating Pediatric Hematologic Malignancies. Pediatric Oncology Day, UT M. D. Anderson Cancer Center, Houston, Texas, June 18, 1998

Invited Speaker: Managing Fever and Neutropenia in Children with Leukemia. Columbia Medical Center East, El Paso, Texas, July 10, 1998

Plenary Session: Lessons from Pediatric Leukemias, 4th Middle East Oncology Congress (COMOIV), Beirut, Lebanon, April 30, 1999

Grand Rounds: Malignancies in the Adolescent and Young Adult, Gulf Coast Medical Center, Wharton, Texas, September 17, 1999

Plenary Session: Cancer in the Adolescent and Young Adult, The U.S. experience, XI Congress of Turkish Pediatric Oncology Group, Izmir, Turkey, April 28, 2000

Plenary Session: The Adolescent and Young Adult Program at M. D. Anderson Cancer Center. XI Congress of Turkish Pediatric Oncology Group, Izmir, Turkey, April 29, 2000

Grand Rounds: The Adolescent and Young Adult Program at M. D. Anderson Cancer Center. Pediatric Grand Rounds, University of Texas Houston Medical School, Houston, Texas, May 30, 2000

City Wide Hematology Conference: Role of Intensification in Childhood ALL Cure, Colegio Jalisciense de Hematologia, A.C., Guadalajara, Mexico, July 27, 2000

Grand Rounds: Treatment of Childhood ALL, ISSSTE, Guadalajara, Mexico, July 28, 2000

Educational Symposium: Tumor Lysis Syndrome in Pediatric Cancer, American Society of Hematology (ASH) Annual Meeting, San Francisco, California December 1, 2000

Grand Rounds: Recent Advances in Management of Tumor Lysis Syndrome. University of Arkansas at Little Rock, August 31, 2001

Grand Rounds: Tumor Lysis Syndrome. Pediatric Grand Rounds, Driscoll Children's Hospital, Children's Medical Center of South Texas, Corpus Christi, Texas February 22, 2002

Grand Rounds: Advances in the Management of Tumor Lysis Syndrome, Hematology Oncology Grand Rounds, Dartmouth-Hitchcock Medical Center, Hanover, NH, February 28, 2002

Pediatric Grand Rounds: Pediatric Phase I Studies. UT M. D. Anderson Cancer Center, Houston, Texas, March 18,2002

Citywide Hematology Conference: Advances in the Management of Tumor Lysis Syndrome, Bone Marrow Transplant Citywide Conference, University of Texas Health Science Center, San Antonio, Texas May 9, 2002

Educational Symposium: New Initiatives in Pediatric ALL, 8th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 11, 2002

Seminar: Clofarabine Initiatives in Cancer Therapy, St. Jude Children's Research Hospital, September 5, 2002

Invited Speaker: Adolescents with ALL: Falling Between the Cracks, Leukemia Towards The Cure, Global Organization Against Leukemia (GOAL) Meeting, Miami, Florida, September 19, 2002

Invited Speaker: New Initiatives in Pediatric ALL, Leukemia 2002-towards the cure, Global Organization Against Leukemia (GOAL) Meeting, Miami, Florida, September 20, 2002

Invited Speaker: New Initiatives in Pediatic Leukemias, Cancer 2002-An International Symposium, King Faisal Research Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia, October 2002

Presenter: Phase I study of clofarabine in pediatric leukemia. 44th annual meeting of the American Society of Hematology (ASH), San Diego, California, December 2002.

Invited Speaker: Advances in the Management of ALL. Doernbecher Children's Hospital, OHSU, Portland, Oregon, March 18, 2003

Invited Speaker: ALL in the Adolescent. NCI sponsored State Of The Science (SOTS) Symposium on Acute Lymphoblastic Leukemia, Washington, DC, May 12, 2003

Grand Rounds: Challenges in Childhood Leukemia Treatment, Scott and White Hospital Grand Rounds, Temple, Texas, September 17, 2003

Plenary Session: Childhood Leukemias, 5th International Medical Conference, Santiago, Panama, October 4, 2003

Educational Symposium: Expanding Clinical Options for the Treatment of Relapsed or Refractory Leukemia. 17th Annual Meeting of the American Society of Pediatric Hematology/Oncology (ASPHO), San Francisco, April 29,2004

Invited Speaker: Childhood acute leukemias. City wide hematology conference. Guadalajara, Mexico, May 20, 2004.

Presenter: Clofarabine therapy for the treatment of relapsed or refractory pediatric acute leukemias. 40th annual meeting of the American Society of Clinical Oncology (ASCO), New Orleans, Louisiana, June 7, 2004.

Invited Speaker: New Targets and New Drugs in Leukemia. International Society of Pediatric Oncology (SIOP), Oslo, Norway, September 19, 2004

Invited Speaker: Pediatric/adolescent/adult AML-any defined boundaries? Leukemia 2004-towards the cure, Global Organization Against Leukemia (GOAL) Meeting, Houston, Texas, October 7, 2004

Invited Speaker: Update on Pediatric leukemias, the XXth Annual Conference of Saint George Hospital University Medical Center, Beirut, Lebanon, November 19, 2004

Presenter: Phase II trials of clofarabine in relapsed or refractory pediatric leukemia. 46th annual meeting of the American Society of Hematology (ASH), San Diego, California, December 6, 2004.

Invited Speaker: Advances in the treatment of childhood leukemia. Doernbecher Children's Hospital, Portland, Oregon, January 5, 2005.

Pediatric Grand Rounds: Challenges in pediatric leukemia developmental therapeutics. Sloan Kettering Cancer Center, NY, NY, January 6, 2005.

Invited Speaker: Novel Purine Analogues in ALL. . 9th Annual Winter Oncology Conference, Whistler, British Columbia, Canada, Feb 20, 2005

Invited Speaker: Treatment of Acute Leukemias. Children's Hospital of Orange County (CHOC), Orange County, CA. April 13, 2005

Presenter at city wide hematology conference hosted by the Children's Hospital of Los Angeles (CHLA). Challenges of treating Pediatric Leukemia. Los Angeles, CA. April 13, 2005.

Invited Speaker. Advances and challenges in pediatric leukemia therapy. Children's Hospital of San

Diego, San Diego, CA. April 14, 2005.
Invited Speaker. Challenges in the treatment of acute lymphoblastic leukemia. New York Presbyterian Columbia University, NY. May 5, 2005
Invited Speaker. Role of leukemia biology in diagnosis and treatment. Methodist Children's Hospital, San Antonio, TX. August 26, 2005
Guest Speaker. Novel approaches in leukemia therapy. Hispanic Medical Society of San Antonio meeting. San Antonio, TX. August 26, 2005.
Seminar. Overview of clofarabine trials in children and adults-Future directions. Stanford University, Stanford, CA. September1 14, 2005
Invited Speaker. New nucleoside analogs in development for leukemia. UCSF, San Francisco, CA. September 13, 2005
Invited Speaker. Current options and future strategies for relapsed leukemia. Oakland Children's Hospital, CA. September 13, 2005
Invited Speaker. New approaches in leukemia therapy. University of Louisville, KY. November 18, 2005
Invited Speaker. Challenges in drug development. Rainbow Babies and Children's Hospital, Cleveland, OH. November 28, 2006.
Invited Speaker. Therapeutic options for relapsed leukemia. Wake Forest University Baptist Medical Center, Winston-Salem, NC. February 9, 2006
Invited Speaker. Strategies for drug development in Pediatric Leukemia. Vanderbilt University Medical Center, Nashville, TN. February 27, 2006.
Invited Speaker. Acute leukemias therapy: current challenges and future direction. Quarterly Blood Club Meeting, Richmond, VA. March 6, 2006.
Invited Speaker. New strategies for treatment of relapsed and refractory leukemia. Virginia Commonwealth University, Richmond, VA. March 6-7, 2006.
Invited Speaker. Current progress and remaining challenge in the treatment of leukemia. University of Kentucky, Lexington, KY. May 4, 2006.
Educational Symposium. ALL therapy: Recent advances and future directions-a US perspective. SIOP, Geneva, September 21, 2006.
Invited Speaker. ALL in children and adults: what have we learned? Mission Hospitals Clinical Cancer Conference, Ashville, NC. November 2, 2006.
Invited Speaker. Novel strategies in the treatment of ALL. MUSC, Charleston, SC. December 14, 2006.
Invited Speaker. New agents for relapsed ALL. St. Jude-Asia Forum in Pediatric Oncology. Singapore. March 9, 2007.
Invited Speaker. Current strategies in the treatment of childhood ALL. The 41st Middle East Medical Assembly (MEMA), American University of Beirut, Lebanon. May 10, 2007.
Invited Speaker. Management of relapsed ALL. The 41st Middle East Medical Assembly (MEMA), American University of Beirut, Lebanon. May 11, 2007.
Invited Speaker. Overview of Total XVI study. Baton Rouge, LA. June 26, 2007
Keynote Speaker. New approaches to treatment of relapsed leukemia. Second Regional Congress of Cancer & Blood Diseases of Childhood, Jordan. September 7, 2007
Keynote Speaker. St. Jude's International Outreach Program in the Middle East: Future vision. Second Regional Congress of Cancer & Blood Diseases of Childhood, Jordan. September 8, 2007
Invited Speaker. Clofarabine for treatment of childhood ALL. The 34th Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) meeting, Calabria, Italy. October 22, 2007.
Invited Speaker, Pediatric oncology advances in 2007: Novel strategies for relapsed childhood leukemia, Chemotherapy Foundation Symposium XXV, Mount Sinai School of Medicine, New York, NY, November 6, 2007.
Special Seminar. Childhood ALL: Remaining Challenges. Greehey Children's Cancer Research Institute, University of Texas Health Science Center, San Antonio, TX. November 30, 2007.
Invited Speaker. St Jude International Outreach in the Middle East. KACCH, Kuwait. January 14, 2008.
Hematology Grand Rounds. Novel Therapeutic Strategies in ALL. Vanderbilt University School of Medicine, Nashville, TN. January 23, 2008.
Pediatric Grand Rounds. Acute Lymphoblastic Leukemia: diagnosis, management, and new therapies. ETSU Quillen College of Medicine, Johnson City, TN. February 6, 2008.
Invited Speaker. Relapsed Leukemia: Novel approaches. Tulane Cancer Center, New Orleans, LA. February 11, 2008.
Hematology Grand Rounds. Rational and Results of Total Therapy for Childhood ALL. M. D. Anderson Cancer Center, Houston TX. March 26, 2008.
Invited Speaker. Highlights of St Jude Total XV Study: Results and Plans. The 19th Annual Meeting of the International BFM Study Group, Glasgow, UK. April 5, 2008
Invited Speaker. Clofarabine: Results of US studies and future plans. The 48th Annual Scientific Meeting of the British Society for Haematology, Glasgow, UK. April 7, 2008
Invited Speaker. Acute Lymphoblastic Leukemia in Adolescents and Young Adults. The 49th Annual Meeting of Mexican Hematology Association (AMEH), Monterrey, Nuevo Leon, Mexico. May 2, 2008.
Invited Speaker. Acute Lymphoblastic Leukemia: New and evolving strategies for relapsed pediatric patients. The 21st Annual Meeting of American Society of Pediatric Hematology/ Oncology (ASPHO), Cincinnati, Ohio. May 15, 2008
Grand Rounds. Advances in Acute Lymphoblastic Leukemia. The Children's Hospital at Albany New England Medical Center, Albany, NY. May 20, 2008.
Grand Rounds. Acute Lymphoblastic Leukemia. Tufts Medical Center. Boston, MA. May 21, 2008
Invited Speaker. Acute Lymphoblastic Leukemia: Advances in therapy and remaining challenges. Boston Association of Pediatric Hematology/Oncology Nurses (APHON) Chapter meeting, Cambridge, Massachussets. May 22, 2008.
Invited Speaker. Strategic Planning for Managing Acute Leukemia in Relapsed Patients. Cook Children's Health Care System, Fort Worth, TX. June 19, 2008.
Invited Speaker. Acute Lymphoblastic Leukemia: Update St. Jude Total Therapy Studies. Cook Children's Health Care System, Fort Worth, TX. June 20, 2008.
Invited Speaker. ALL in the adolescents and young adults: what have we learned? 4th International Conference Leukemia 2008, Houston, TX. September 26, 2008.
Invited Speaker. Clofarabine in the therapy of pediatric leukemias: the US experience. SIOP, Berlin. October 4, 2008.
Education Session: Treatment of childhood acute lymphoblastic leukemia, 32nd Congress of the International Society of Hematology (ISH), Bangkok, Thailand, October 19th and October 20th, 2008.
Invited Speaker: Biologic studies of acute lympholastic leukemia. 32nd Congress of the International Society of Hematology (ISH), Bangkok, Thailand. October 21st, 2008.
Invited Speaker: Management of ALL in adolescents and young adults. Second Regional Meeting of the Lebanese Society of Hematology and Blood Transfusion, Beirut, Lebanon. October 24, 2008.
Invited Speaker: Management of relapsed ALL with focus on extramedullary relapse and new agents. Second Regional Meeting of the Lebanese Society of Hematology and Blood Transfusion, Beirut, Lebanon. October 24, 2008.
Hospital information sessions, Country Cares. Acute Lymphoblastic Leukemia. St. Jude Children's Research Hospital, Memphis, TN. January 16, 2009.
Invited Speaker: New therapeutics in relapsed leukemias. 3rd St. Jude-Viva Forum, Singapore. March 5, 2009.
Invited Speaker: Acute Lymphoblastic Leukemia. First Annual Mack/Khoury Pediatric Hematology/ Oncology Conference, LSU Health Sciences Center Shreveport, Feist-Weiller Cancer Center, Shreveport. May 16, 2009.
Invited Speaker: Diagnosis and management of childhood leukemias. South African Chidrens Cancer Study Group (SACCSG) meeting. Durban, South Africa. May 22nd, 2009.
Invited Speaker: New strategies in the management of relapsed leukemia. 50th National Congress of the AMEH (Agrupacion Mexicana para el studio de la Hematologia). Morelia, Michoacán, Mexico. August 20th, 2009.
Invited Speaker: Prevention and treatment of acute lymphoblastic leukemia of the central nervous system. 50th National Congress of the AMEH (Agrupacion Mexicana para el studio de la Hematologia). Morelia, Michoacán, Mexico. August 20th, 2009
Seminar: Risk-adapted therapy of acute lymphoblastic leucemia. Hospital d'Enfants, University Hospital Center Ibn Sina. Rabat, Morocco. October 6, 2009
Seminar: Acute lymphoblastic leukemia in the adolescents and young adults. Hospital 20 Aout 1953. Casablanca, Morocco. October 7, 2009.
Fellows Rounds: Rationale for modern ALL Therapy. St. Jude Children's Research Hospital, Memphis, TN. January 11,2010
Grand Rounds: Lessons Learned from St Jude's Total Studies. Children Cancer Hospital 57357. Cairo, Egypt. February 1, 2010
Special Seminar: Management of CNS Leukemia. Children Cancer Hospital 57357. Cairo, Egypt. February 2, 2010
Special Seminar: Novel Strategies for relapsed Leukemia. Children Cancer Hospital 57357. Cairo, Egypt. February 3, 2010
Invited Speaker: The role of MRD in managing children with ALL. Third Regional Congress of Cancer and Blood Disorders of Childhood. Amman, Jordan. April 16, 2010
Invited Speaker: New Agents for ALL. Third Regional Congress of Cancer and Blood Disorders of Childhood. Amman, Jordan. April 17, 2010
Symposium on Leukemia and Lymphoma: Pediatric Hematologic Malignancies. University of Arkansas for Medical Sciences, Little Rock, Arkansas. September 17, 2010.
Visiting Professor: Case presentation and roundtable discussion. National Children's Hospital Juan P. Garrahan, Buenos Aires, Argentina. September 26, 2010.
Visiting Professor: Case presentation and roundtable discussion. Argentinean Group of Acute Leukaemia Therapy (GATLA). Buenos Aires, Argentina. September 27, 2010.
Invited Speaker: "New Therapies for Relapsed/Refractory Leukemia" . Argentinean Hematological Society (SAH), Buenos Aires, Argentina. September 27, 2010.
Invited Speaker: Plenary Symposium "Management of relapsed/refractory leukemia". XII Brazilian Congress of Pediatric Oncology, Curitiba, Brasil September 30, 2010.
Round table presenter and participant: Advances in ALL and AML. XII Brazilian Congress of Pediatric Oncology, Curitiba, Brasil September 30, 2010.
Symposium speaker: Update on advances in the treatment of pediatric acute leukemias, a US perspective. 7th Bi-annual Childhood Leukemia Symposium, Antalya, Turkey. October 4, 2010.
Meet the Professor: ALL in the adolescent and young adult. Sixth International Conference Hematologic Malignancies Houston 2010. Houston, TX, October 13, 2010.
Invited Speaker: Acute Lymphoblastic Leukemia: Key elements towards cure. 1st Annual Scientific Congress of Alexandria Pediatric Oncology Board (Alex-POB), Alexandria Faculty of Medicine, Alexandria, Egypt, October 30, 2010.
Invited Speaker: Developing a Leukemia Program in the Middle East. 1st Annual Scientific Congress of Alexandria Pediatric Oncology Board (Alex-POB), Alexandria Faculty of Medicine, Alexandria, Egypt, October 30, 2010.
Invited Speaker: Management of Pediatric Lymphomas. 1st Annual Scientific Congress of Alexandria Pediatric Oncology Board (Alex-POB), Alexandria Faculty of Medicine, Alexandria, Egypt, October 31, 2010.
Visiting Professor and Invited Speaker: Management of pediatric leukemia. Sor Maria Ludovica Pediatric Hospital. LaPlata, Argentina. March 14, 2011
Invited Speaker: Current strategies for the management of refractory and relapsed leukemia. Citywide Hematology Conference. Rosario, Argentina, March 15, 2011
LLH&BMTCT conference: Isolated testicular ALL relapse. St. Jude Children's Research Hospital, Memphis, TN. April 12, 2011
Invited Speaker: Current Treatments in Acute Lymphoblastic Leukemia. King Fahad Specialist Hospital, Dammam, Saudi Arabia. April 16, 2011
Invited Speaker: Advances in treatment of childhood ALL. 44th Middle East Medical Assembly, at the American University of Beirut, Lebanon. May 8, 2011.
Invited Speaker by Tennessee Cancer Coalition-TC2: Current trends in pediatric clinical trials. 7th Annual Summit on the Burden of cancer in TN, Franklin, TN. June 17, 2011
Invited Speaker: Issues and strategies for addressing end of life care for children with cancer. 2011 Summit on cancer in Tennessee: Spotlight on Cancer Prevention and Control, Franklin, TN. June 17, 2011
Invited Speaker by the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). Meet the Professor: Current treatment strategies for frontline ALL. Nagoya, Japan. November 4, 2011
Invited Speaker by the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). Update

on drug development in childhood hematologic malignancies. Nagoya, Japan. November 5, 2011

Invited Speaker. . Management of relapsed and refractory acute lymphoblastic leukemia. Congresso Brasileiro de Hematologia e Hemotherapia. HEMO 2011. Sao Paulo, Brasil. November 12, 2011

Invited Speaker. New drugs in relapsed and refractory AML. Congresso Brasileiro de Hematologia e Hemotherapia. HEMO 2011. Sao Paulo, Brasil. November 12, 2011

Danny Thomas Lecture Series: Early T-cell Precursor ALL-Insight from the Pediatric Cancer Genome Project. St. Jude Children's Research Hospital, Memphis, TN. May 11, 2012

Grand Rounds: Acute Lymphoblastic Leukemia: What does it take to get closer to 100? Children's Hospital of Illinois, Peoria, IL. September 6th, 2012

Residents Rounds: Diagnosis and supportive care of a child with leukemia: role of the primary care provider. University of Illinois College of Medicine at Peoria, IL. September 7th, 2012

Invited Speaker: Childhood ALL: History and Future. 3rd Regional Pediatric Hematology-Oncology Symposium for the Primary Care Provider. Spalding Pastoral Center, Peoria, IL. September 8th, 2012

Invited Speaker: Treatment of High-Risk and Relapsed Acute Lymphoblastic leukemia. 3rd Annual Meeting of the Argentinian Society of Hematology. Buenos Aires, Argentina. October 4th, 2012

Invited Speaker: Role of Clofarabine in Pediatric ALL: Questions Answered and Remaining Challenges. The 6th Regional Meeting of the Lebanese Society of Hematology. Beirut, Lebanon. October 12rh

Invited Speaker: Personalized ALL Therapy; Redefining Risk Groups. The 6th Regional Meeting of the Lebanese Society of Hematology. Beirut, Lebanon. October 12rh

Domestic affiliates Nov 3 TOTXVI How did we get there?

Nov 13home of the Lebanese Ambassador Antoine Chedid and Mrs. Nicole Chedid Washington DC

EDITORIAL BOARD:

Section Editor: Pediatric Hematologic Malignancies. Current Hematologic Malignancy Reports (2006-2009)

Editorial Board Member. Journal of Clinical Oncology (2009-2012)

AD HOC REVIEWER (Journals)

Acta Haematologica
American Journal of Hematology
Blood
Cancer
Haematologica
Journal of Clinical Oncology
Journal of Pediatric Hematology and Oncology
Leukemia
Leukemia and Lymphoma
Pediatric Blood and Cancer
Pediatric Hematology/Oncology
Annals of Saudi Medicine

ABSTRACTS REVIEW:

The American Society of Hematology 49th Annual Meeting, 2007.
The American Society of Hematology 54th Annual Meeting, 2012

GRANT REVIEW:

FDA Grant Review: Member of Review Panel for the FDA Office of Orphan Products Development Grant Program. Rockville, Maryland, July 29, 2005.
FDA Grant Review: Member of Review Panel for the FDA Office of Orphan Products Development Grant Program. Rockville, Maryland, June 20, 2006.
Grant Reviewer: Leukaemia Research Fund, UK. September 2007

OTHER PROFESSIONAL ACTIVITIES:

Advisory Board member, Rasburicase, Sanofi-Synthelabo, 1999-2003

Consultant, Grupos Cooperativo Del Occidente de Mexico (invited by investigators in Western Mexico to help them design a unified protocol for childhood ALL in the region), 2000-2003

Chair, Clofarabine Pediatric Leukemia Expert Panel (formed to plan strategy for clofarabine development in children in consultation with the FDA), 2001

Advisory Board member, ILEX, 2001-2003

Consultant for License Application of Rasburicase to the US Food & Drug Administration, Sanofi-Synthelabo, Great Valley, PA, 2001

Advisory Board member, Pharmion, 2002-2003

Advisory Board member, Bioenvision, 2002-

Advisory Board member: Abelcet, Memphis, TN, November 11, 2003

Consultant, ILEX for clofarabine NDA filing with the US Food and Drug Administration, 2004

Clinical expert, ODAC meeting leading to clofarabine approval in US, December 1st, 2004

Consultant, Bioenvision for submission of clofarabine NDA to the European Medicines Evaluation Agency (EMEA), 2004

Advisory Board member: Post marketing studies for rasburicase. Sanofi, Washington, DC, September 22, 2004

Advisory Board member, Oncospar: Evidence based management of ALL in late adolescence and young adults, Chicago, IL, September 2004

Advisory Board member, Marqibo: Clinical Trial Protocols for the Treatment of Acute Lymphoblastic Leukemia (ALL), Houston, Texas, October 7, 2004

Advisory Board member: Clinical development of Dacogen. Houston, Texas, October 9, 2004

Advisory Board member, Enzon: Clinical Development of a PEGylated Recombinant Asparaginase, New York, NY. Feb 15, 2005

Advisory Board, Genzyme: Pediatric development of clofarabine. Boston, MA, Sep 16-18, 2005.

Advisory Board, Biocryst: Clinical Development of Forodesine. Clearwater, FL, January 21, 2006.

Clinical expert, European Medicines Evaluation Agency (EMEA) meeting leading to clofarabine approval in Europe, London, England, February 22, 2006.

Advisory Board, Enzon: Novel Therapeutic Concept Targeting Innate Immnunity. NJ March 8, 2006.

Virtual Pediatric Oncology Drug (vPOD) member: a not-for profit entity formed of scientists from leading academic institutions in pediatric oncology research and leaders from government, industry and philantropy; focused on planning scientific priorities for the Institute of Medicine of the National Academies and expediting drug discovery and development in pediatric oncology. 2006

Advisory Board, Enzon: Translating asparaginase depletion in the adult ALL population. Chicago, IL, January 20, 2007.

Advisory Committee: Second Regional Congress of Cancer & Blood Diseases of Childhood, 2007.

International Scientific Advisory Board for the State of Kuwait Ministry of Health, 2008-to present

International Advisory Board of the Pan Arab Journal of Oncology (PAJO), journal of the Arab Medical Association Against cancer (AMAAC). November 2007 to present

Advisory Board Member, Micromet AG: Development of blinatumomab (MT103) in childhood ALL. Stuttgart,

January 13, 2009.

Member of the Data Safety Monitoring Committee for Protocol: CHNY-06-532 (Clofarabine in combination with cytarabine and total body irradiation followed by allogeneic stem cell transplantation in children with acute lymphoblastic leukemia and acute non-lymphoblastic leukemia, PI Mitchell Cairo) 2009-to present

Consultant Genzyme on the development of clofarabine in the pediatric population in China. May 2010

Member Therapeutic Advances in Childhood Leukemia and Lymphoma TACL Steering & Prioritization Committee, July 2010-2011

Advisory Board Member, Genentech and Roche: GA101 Global Pediatric Hematology Advisory Board. Miami, FL. Sep 14-15, 2010

Advisory Board Member, Hana Biosciences, Inc. Development of Marqibo (liposomally encapsulated vincristine sulfate) in pediatric patients. Orlando, FL. Dec 6, 2010

Advisory Board Member, SeattleGenetics. SGN19a in Pediatric ALL. Chicago, IL June 3rd, 2011

Advisory Board Member, Genzyme. Optimizing clofarabine combinations in relapsed pediatric ALL. Boston, MA. November 18, 2011

Advisory Board Member, Amgen. Blinatumomab (AMG 103) Pediatric ALL Scientific Advisory Board. Paris, France. October 15th, 2012

INSTITUTIONAL SERVICE:

1995-2003	Member, New Agents Group, Department of Pediatrics, UT M. D. Anderson Cancer Center
1996-2001	Member, Clinical Research Committee, UT M. D. Anderson Cancer Center
1998-1999	Member, Supportive Care Committee, Department of Pediatrics, UT M. D. Anderson Cancer Center
1998-2003	Chair, Adolescents and Young Adults Committee, UT M. D. Anderson Cancer Center, TX
1998-2001	Chair, Clinical Research Committee II, UT M. D. Anderson Cancer Center
1999-2003	Member, Research Administration Scientific Advisory Committee, UT M. D. Anderson Cancer Center
1998-2003	Member, Middle East Business Development Task Force, UT M. D. Anderson Cancer Center
1999-2003	Member, Outpatient Task Force, Department of Pediatrics, UT M. D. Anderson Cancer Center
2000-2003	Member, Subcommittee for Clinical Research Billing, UT M. D. Anderson Cancer Center
2002-2003	Member, Leukemia Tissue Bank Committee, UT M. D. Anderson Cancer Center
2002-2003	Chair, New Agents Working Group, Division of Pediatrics, UT M. D. Anderson Cancer Center
2002-2003	Member, Blue Ribbon Committee, UT M. D. Anderson Cancer Center. A committee appointed by the Dr Mendelson, MDACC president, to evaluate how clinical research is performed at M.D. Anderson, and to recommend ways to enhance the clinical research program.
2004-2007	Member, Continuing Medical Education (CME) `Committee, St. Jude Children's Research Hospital
2004-2009	Member, Clinical Protocol Scientific Review & Monitoring Committee(CPSRMC), St. Jude Children's Research Hospital
2004-2005	Member, International Outreach Program Advisory Committee, St. Jude Children's Research Hospital

2004-2005 Member, Protocol Prioritization Committee, St. Jude Children's Research Hospital
2005-2005 Member, Affiliate Committee Task Force, St. Jude Children's Research Hospital
2005-2006 Member, Conflicts of Interest and Commitment Task Force, St. Jude Children's Research Hospital
2005-2007 Member, BMT Division Director Search Committee, St. Jude Children's Research Hospital
2006-2009 Vice-Chair, Clinical Protocol Scientific Review & Monitoring Committee(CPSRMC), St. Jude Children's Research Hospital
2007-2010 Member, Pharmacy & Therapeutics Committee, St. Jude Children's Research Hospital
2007-2011 Member, Incidents & Events Task Force
2008-2011 Member, Faculty Appointments and Promotions Committee
2009-2010 Member, Hematology Task Force
2009-2011 Member, Faculty Mentoring Program Task Force
2010-2011 Director, Translational Therapeutics for Childhood Cancer (TTCC)
2003-to date Member, Developmental Therapeutics Working Group, St. Jude Children's Research Hospital
2005-to date Member, Credentials Committee, St. Jude Children's Research Hospital
2006-to date Medical Director, Middle East-St Jude International Outreach Program
2011-to date Member, Pharmacogenetics Oversight Committee (POC)

GRANT SUPPORT

Grants and Contracts

(1) Previous

Principal Investigator, Study of the activity of different dose schedules of oral and intravenous 9-Aminocamptothecin in a SCID mouse model of human leukemia. (Pharmacia, Inc.) 12/1995-12/1996, $18,812

Collaborator, The Adolescent and Young Adult Program (Children's Art Project,UT M. D. Anderson Cancer Center) 5/1998-4/1999, $86,000.

Collaborator, Study of the activity of different dose schedules of DX-8951f in a SCID mouse model of human AML. (Daiichi Pharmaceutical Corporation) 12/1998-6/2000, $79,460

Collaborator, The Adolescent and Young Adult Program (Children's Art Project, UT M. D. Anderson Cancer Center) 5/1999-12/2000, $208,000.

Collaborator, Various Donors Fund for Adolescent & Young Adult Clinical Research, UT M. D. Anderson Cancer Center, 9/1999-8/2001, $123,000.

Principal Investigator, Evaluation of NX 211 activity in SCID mouse model of human AML (Stephen Friedman Myeloma Fund) 2/2000-2/2001, $50,000.

Collaborator, Kimberly Patterson Fund for Leukemia Research, 7/2000-6/2001, $28,000.

Collaborator, Interactive media on banking sperm before cancer therapy (National Cancer Institute)
8/2000-7/2004, $498,497

Principal Investigator. Cancer and Body Image in Adolescents and Young Adults. UT M. D. Anderson Cancer Center, 1/2001-1/2002, $27,712.

Collaborator, Adele Pittman Endowment Development/Child & Adult Leukemia, 10/2001-12/2002, $100,000.

Collaborator. Asparaginase production at SJCRH. AP4/NCI, 07/01/05-06/30/06, $16,000 (5% effort).

Collaborator. Asparaginase production at SJCRH. CCAC/SJCRH, 07/01/05-06/30/06, $30,000 (5% effort)

(2) Active

SIGMA TAU Pharmaceuticals, Inc. (Collaborator)	$1,067,992	5%
Aspar PK-PD T16	09/01/2008-08/31/2016	

Collaborator. Implement assays to compare the pharmacokinetics and pharmacodynamics of PEG-asparaginase given in higher dose (3500 or 3000 units/m^2) versus those with PEG-asparaginase given in conventional dose (2500 units/m^2) in the continuation phase of Total XVI and correlate with assays for anti-asparaginase antibodies (PI Relling)

Funded Protocols

(1) Previous
Principal Investigator, Phase II study of SR 29142 (urate oxidase) in patients with hyperuricemia, 1/1997-12/1999, $27,000 (Sanofi Wintrop)
Co-Investigator, P99-401, Phase II liposomal vincristine for pediatric and adolescent patients with relapsed tumors, 7/2000-7/2001, $81,250 (INEX Pharmaceutical Corporation)

Principal Investigator, Compassionate use of SR 29142 for prevention of treatment of hyperuricemia,
7/2000-9/2002, $138,500 (Sanofi-Synthelabo)

Principal Investigator, P00-276, A randomized, double-blind, placebo-controlled study to evaluate the effect of weekly procrit on anemia and quality of life in children with malignant solid tumors or Hodgkin's disease undergoing myelosuppressive immunotherapy, and P00-277, A randomized, double-blind, placebo-controlled study to evaluate the effect of weekly procrit on anemia and quality of life in children with acute lymphocytic leukemia or non-Hodgkin's lymphoma undergoing myelosuppressive immunotherapy, 10/2000–10/2002, $219,600 (Ortho-Biotech)

Principal Investigator, ID99-383, Phase I study of CL-F-ARA-A (Clofarabine) in pediatric patients with solid and hematologic malignancies, 9/2001-9/2003, $400,000 (Ilex Oncology Incorporated)

Principal Investigator, ID02-108, A phase II open label study of CLOFAREX□ in pediatric patients with refractory or relapsed acute lymphoblastic leukemia., 6/2002 – 6/2003, $154,745 (Ilex Oncology Incorporated)

Principal Investigator, ID02-117, A phase II open label study of CLOFAREX□ in pediatric patients with refractory or relapsed acute myelogenous leukemia, 6/2002 – 6/2003, $154,745 (Ilex Oncology Incorporated)

Principal Investigator, ID02-303, A randomized trial to assess the effectiveness of Elitek (Rasburicase) versus Allopurinol in reducing hyperuricemia and improving renal function in moderate to high risk adult patients with leukemia or lymphoma, 1/2003-6/2003, $1,618,000 (Sanofi-Synthelabo)

SANOFI-AVENTIS	(PI:Jeha)	$204,600	5%
2003-0936 (EFC5339)		10/2004 -10/2008	

Evaluation of single agent rasburicase in treatment/prevention of hyperuricemia associated with tumor lysis syndrome in adult and pediatric patients with lymphoma/leukemia/solid tumor malignancies at their first relapse or refractory disease.

GENZYME CORPORATION	(PI:Jeha)	$90,424	5%
CLOLAR		3/2006-5/2010	

A phase I/II dose-escalation study of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute leukemias

EUSA Pharma	(PI:Jeha)	$5,700	1%
ERWASE		6/2006-6/2011	

Erwinia asparaginase in children with hematologic malignancies who are allergic to E-coli asparaginase
(2) Active

SANOFI AVENTIS	(PI:Jeha)	$11,640	1%
RASBU-L-02990		3/1/2009-2/28/2012	

Rasburicase re-challenge immuno-monitoring study.

OPEN PROTOCOLS

Principal Investigator

TOTXVI: Total therapy study XVI for newly diagnosed patients with acute lymphoblastic leukemia

ERWASE: Compassionate use of Erwinase for pediatric patients with acute lymphoblastic leukemia or Non-Hodgkins Lymphoma

ALERAS: A multicenter registry of anti-rasburicase antibodies in patients retreated with rasburicase in the context of relapsing leukemia/lymphoma who experienced subsequent hypersensitivity reaction(s) or loss of uricolytic activity: an immunomonitoring observational study

Co-Investigator

ALLR17: A study of therapy for pediatric relapsed or refractory acute lymphoblastic leukemia

RELHEM: A pilot pharmacokinetic, pharmacodynamic and feasibility study of sorafenib in combination with cytarabine and clofarabine in patients with refractory or relapsed hematologic malignancies
AML 08: A phase III randomized trial of clofarabine plus cytarabine versus conventional induction therapy and a phase II study of natural killer cell transplantation in patients with newly diagnosed acute myeloid leukemia

CD22AB: A Phase I, multicenter, dose escalation study of CAD8015 in children, adolescents, and young adults with refractory CD22+ acute lymphoblastic leukemia or Non-Hodgkin's lymphomas

NECTAR: A Phase I trial of NECTAR in T-ALL relapse: A joint study of POETIC and TACL
PG4KDS: Clinical implementation of pharmacogenetics

GAIT09: The effects of ankle foot orthroses on gait efficiency in children with acute lymphoblastic leukemia and foot drop

VTE1: A three month prospective open label study of therapy with Fragmin (Dalteparin sodium injection) in children with malignancies and venous thromboembolism

EDUCATIONAL COURSES/MENTORING

1995-1196 Teaching and supervising Xiao-BoCao (Postdoctoral Fellow), and Christina Marie Zeppieri and Guozhong Jin (Research Assistant II) in conducting SCID mouse experiments. UT M. D. Anderson Cancer Center, Houston, TX

1996-1997 SICU Lectures Series, Oncologic Emergences in Children with Leukemia
UT M. D. Anderson Cancer Center, Houston, TX

1998 Supervising and mentoring visiting physician from France, Norbert Vey
UT M. D. Anderson Cancer Center
Research project involved testing the activity of different dose schedules of the topoisomerase inhibitor DX-8951f in SCID mice engrafted with human leukemia. Dr Vey returned to France having gained expertise in designing and conducting animal studies. He presented his work at the ASH meeting and at the ASCO meeting. Final manuscript was published in Clinical Cancer Research in 2000

1999 harmD Board Review Course, Pediatric Leukemias and Lymphomas, UT M. D. Anderson Cancer Center, Houston, TX, September22, 1999

2002 ercepting Lisa Mc Donald for her clinical experience and helping her develop and refine her clinical judgment and skills as a Pediatric Nurse Practitioner. She is currently a PediatricLeukemia Nurse Practitioner at Ut M. D. Anderson Cancer Center

2003 Preceptor for Lisa McDonald, Pediatric Nurse Practitioner.

2002-2005 Advances in the Treatment of Pediatric Hematologic Malignancies. Leukemia lectures series for Spain, UT M. D. Anderson Cancer Center, Houston, Texas, November 5, 2002. May 7, 2003. September 29, 2003. May 31, 2004. June 25, 2005.

2004 Virtual Slide Lecture: Expanding Clinical Options for the Treatment of Relapsed or Refractory Pediatric Acute Leukemia. CD-ROM/Web enduring continuing education activity, Meniscus.

2006 Contributed and reviewed Chapters and Test Questions to the 3rd edition of American Society of Hematology Self-Assessment Program (ash-sap).

2006 Leukemia & Lymphoma Society education program (invited speaker)- Focus on Childhood Cancers: Childhood Leukemia and Lymphoma, New Options for Treatment

2006-2008 Mentoring Damon Reed, Pediatric Hem/Onc Fellow, St Jude

2008 Mentored medical student Fulvia Brugnoletti, referred by Prof Vincenzo Leuzzi, Instituto di Neuropsichiatria, Rome, Italy. Fulvia spent 3 months at St Jude preparing her thesis on neurotoxicity associated with leukemia therapy. In addition to drafting her thesis during her visit, she also completed a case report in collaboration with Drs Inaba, Morris, and Laningham.

2007 Leukemia & Lymphoma Society education program (950 participants called into the teleconference from US, Canada, Puerto Rico, Denmark, India, Indonesia, Lebanon, Mexico, and Kenya)- Childhood Leukemia and Lymphoma: An update on current and emerging therapies.

2009-2011 Member Scholarship Oversight Committee for Sara Federico, MD (Michael Dyer's lab)

2010 The Leukemia & Lymphoma Society Focus on Childhood Cancer telephone/webcast program: a live educational teleconference reaching out to an audience of over 1000 families of childhood cancer patients, as well as health care professionals nationally and internationally. Presentation covered following topics:
- Current treatment options for pediatric leukemia and lymphoma
- Follow up care after treatment ends
- Clinical trials and emerging therapies for treatment of relapsed childhood blood cancers
- Quality of life issues for patients and caregivers
- Followed by a 25 minute Q & A session (May 4, 2010)

2007-todate Monthly Leukemia Middle East Teleconference-Review and discuss consults from several
countries in the Middle-East and North Africa

2008-todate Mentor to Deepa Bhojowani, Assistant Member in
- Design and conduct of early phase trials
- Collaborations with the NCI and TACL (Therapeutic Advances in Childhood Leukemia and Lymphoma)
- The design of ALL R18 (St Jude study for ALL in first relapse)

2009-todate Member, Graduate Student Committee for Harpreet Singh, MD (Richard Williams' lab)

2009-todate Mentor to Hiroto Inaba, Assistant Member in design and conduct of early phase trials

Treatment of Childhood Acute Lymphoblastic Leukemia

Lesson Learned and Future Directions

Sima Jeha, MD

St. Jude Children's Research Hospital, Memphis, USA

Risk assignment

The treatment of childhood acute lymphoblastic leukemia (ALL) is based on the concept of tailoring the intensity of therapy to a patient's risk of relapse. Steady progress in the development of treatment strategies for childhood ALL was accomplished by optimizing the dosage and schedule of administration of agents developed over 30 years ago, with the addition of central nervous system (CNS) prophylaxis, in serial clinical trials using outcome predictors to stratify therapy. A risk classification approach based on age and leukocyte count at diagnosis was adapted at a National Cancer Institute (NCI) sponsored workshop held in 1993[1]. This classification has since been modified with improved understanding of the immunology and molecular pathways involved in ALL, current risk classification typically include age, leukocyte count at diagnosis, blast cell immunophenotype and genotype, as well as early treatment response. The degree of reduction of the leukemic cell clone early during remission induction therapy as measured by minimal residual disease (MRD) has shown greater prognostic strength than any other individual biological or host related feature [2,3]. Although MRD positivity is strongly associated with known presenting risk features, it has independent prognostic strength, and has played an increasingly important role in risk stratification of ALL in contemporary regimens. There is strong concordance between the assessment of MRD by flow cytometry and by PCR methods. About half of all patients show a disease reduction to 10^{-4} or lower after only 2 weeks of remission induction, and these patients appear to have an exceptionally good treatment outcome. Persistence of MRD of 10^{-4} or more at 4 months from diagnosis is associated with an especially dismal outcome. Current childhood ALL therapy emphasizes early and vigorous assessment of the risk of relapse in individual patients, so that only high-risk patients are treated aggressively, with less toxic therapy reserved for cases at lower risk of failure [2]. Accordingly, patients are divided into three risk groups low-, intermediate-, and high-risk (also referred to as standard-, high-, and very high-risk categories in other risk classification schema).

PROGNOSTIC FACTORS IN CHILDHOOD ALL

Factor	Favorable	Intermediate	Unfavorable
Age (years)	1 to 9	>10	<1 and MLL+
WBC ($x10^9$/L)	<50,000	≥50,000	
Immunophenotype	Precursor-B	T-cell	
Genetic/molecular	Hyperdiploidy>50 Trisomies 4,10 and17 DNA index ≥1.16 t(12;21)/*ETV6-CBFA2*	Diploid t(1;19)/*TCF3-PBX1*	t(9;22)/*BCR-ABL1* t(4;11)/*MLL-AF4*
CNS status	CNS1	CNS2 Traumatic with blasts	CNS3
MRD by flow	$<10^{-4}$ day 15 induction	10^{-4}>end of induction<10^{-2}	>10^{-2} end of induction >10^{-4} at 20 weeks

Systemic therapy

Treatment of ALL typically spans 2-2.5 years and consists of a brief remission-induction phase followed by intensification (or consolidation) therapy to eliminate residual disease, and then prolonged continuation treatment to maintain remission. Addition of a tyrosine kinase inhibitor has greatly improved the remission induction rate and the duration of disease-free survival of patients with Philadelphia positive (Ph+) ALL [4]. All patients also require treatment directed to the CNS early in the clinical course to prevent relapse due to leukemic cells sequestered in this site. The benefit in long-term survival of using 4 or more drugs during induction is widely accepted in higher risk patients

but less clear in lower risk patients [5]. Based on reports of more potent in-vitro antileukemic activity and better CNS penetration [6], dexamethasone has replaced prednisone in some induction and many continuation regimens [7,8].

Delayed intensification, pioneered by the Berlin-Frankfurt-Münster (BFM) consortium, consists of using drugs similar to those used in remission induction therapy after a three months period of a less intensive, interim maintenance chemotherapy [3]. The Children's Cancer Group (CCG) confirmed the efficacy of delayed re-induction therapy in low-risk cases [67], and showed that double-delayed intensification with a second re-induction at week 32 of treatment, improved outcome in patients with intermediate-risk disease [9]. An augmented intensification regimen consisting of the administration of additional doses of vincristine and asparaginase during the myelosuppression period following delayed intensification, and sequential escalating-dose parental methotrexate followed by asparaginase (Capizzi methotrexate), improved the outcome of high-risk patients whose disease had responded slowly to initial multiagent induction therapy [10]

Continuation or maintenance phase consists of 2 to 2.5 years of low intensity metronomic chemotherapy designed to eradicate any residual leukemic cell burden. Weekly low-dose methotrexate and daily oral mercaptopurine form the backbone of most continuation regimens. Adjusting chemotherapy doses to maintain neutrophil counts between 0.5 and $1.5x10^9$/L has been associated with a better clinical outcome [2, 11]. Overzealous use of mercaptopurine, to the extent that neutropenia necessitates chemotherapy interruption, reduces overall dose intensity and is counterproductive [12]. Many groups add regular pulses of vincristine and corticosteroids to this regimen although the benefit of these pulses in the context of contemporary therapy has not been established [13].

Genetic polymorphisms of drug transporters, receptors, targets and drug-metabolizing enzymes, and concomitant administration of drugs that induce cytochrome P450 enzymes can influence the efficacy and toxicity of antineoplastic agents [14]. Interindividual variability in the pharmacokinetics and pharmacodynamics of many antileukemic agents might partially explain the heterogeneity in treatment response among patients with specific genetic abnormalities and the difference in outcome by age group.

CNS directed therapy

The CNS acts as a pharmacologic sanctuary, poorly penetrated by conventional doses of systematically administered chemotherapeutic agents [15]. The incidence of CNS leukemia as an initial site of relapse became progressively more common as more effective chemotherapeutic regimens resulted in longer duration of hematologic remissions in the 1960s. Radiation therapy was the first modality successfully used to prevent CNS relapse [16]. The effectiveness of 2400 cGy cranial radiation as preventive therapy was offset by substantial late effects in long-term survivors, including learning disabilities, multiple endocrinopathy, and an increased risk of second malignancies. Subsequent trials demonstrated that, in the context of intensive systemic and intrathecal therapy, cranial irradiation can be reduced [17] or even omitted altogether [18]

Future directions

As cure rate approach 90%, there remain subsets of ALL that carry an adverse prognosis. Individualizing therapy on the basis of germline genetic status may help optimize treatment, and expanding the application of pharmacogenomics will allow further individualized therapy. While optimizing the use of old drugs continues through serial studies, new formulations of existing agents are being tested to improve the efficacy and reduce the toxicity of the parent compounds. Such modifications include improving drug transport and delivery, or altering the molecular structure to improve the therapeutic index. Ongoing trials are studying the benefit of the two novel nucleoside analogs, clofarabine and nelarabine, in high risk ALL and T-cell ALL respectively [19, 20]. MRD measurements has emerged as a powerful and independent prognostic indicator for gauging the intensity of therapy and should allow reduction of treatment intensity for patients at low risk of relapse. Further intensification of current regimens is unlikely to dramatically improve survival for all high risk patients. . In addition to

New Agents for ALL (to list a few)

Nucleoside analogues
- -Clofarabine
- -Nelarabine

PNP inhibitors
- -Forodesine

Liposomal conjugates
- -Liposomal vcr/araC
- -Marqibo

Asparaginase Preparations
- -Peg-asparaginase
- -Erwinia preparations
- -GRASPA

Methotrexate analogues
- -Talotrexin
- -Pralatrexate

Immunotherapy
- -Rituximab
- -Alemtuzumab
- -Epratuzumab
- -Moxetumomab
- -Inotuzumab ozogamicin
- -Blinatumomab
- -NK CD19
- -CAR modified T-cells

Tyrosine Kinase inhibitors
- -Imatinib, Nilotinib, Dasatinib
- -Bosutinib
- -
- -Sunitinib

Aurora Kinase inhibitors
- -MK-0457, PHA-739538, XL-228

Other targets
- -Notch
- -Histone deacetylase: Vorinostat, Panobinostat
- -PI3Kinase
- -Meck
- -Heat shock protein-90
- -Farnesyltransferase
- -DNA methyltransferase
- -Mammalian target of rapamycin
- -Proteasome pathway
- -Survivin
- -FLT3
- -NFκβ Bortezomib
- -CDK
- -BCL2

refining leukemia classification, studies of global gene expression help identify potential molecular targets for therapy. Ultimately, these emerging technologies should lead to a new era of individualized molecular medicine, which results in more effective and less toxic regimens It remains to be determined whether the success in targeting BCR-ABL with tyrosine kinase inhibitors will translate to other pathways. The development of monoclonal antibodies and cellular immunotherapy that exploits the expression of leukemia-associated antigens to stimulate the antitumor or activity of cytotoxic T-lymphocytes or natural killer cells offers a new modality of targeted therapies that are under investigation. Combining our current knowledge with emerging technology will help design effective risk-targeted therapies based on biological features of leukemic cells, host genetics, and early response to therapy.

References

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4. Schultz KR, Bowman WP, Aledo A, et al: Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group Study. J Clin Oncol 2009;27:5175-5181.
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9. Hutchinson RJ, Gaynon PS, Sather H, et al : Intensification of Therapy for Children With Lower-Risk Acute Lymphoblastic Leukemia: Long-Term Follow-Up of Patients Treated on Children's Cancer Group Trial 1881. J Clin Oncol 2003;1790-1797.
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11. Chessells M, Harrison G, Lilleyman JS, et al : Continuing (maintenance) therapy in lymphoblastic leukaemia: lessons from MRC UKALL X. Br J Haematol 1997;98:945-951.
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13. Conter V, Valsecchi MG, Silvestri D, et al: Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial. Lancet 2007;369:123-131.
14. Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature 2004;429:464-468.
15. Pinkel D: Five-year follow-up of Total Thearpy" of childhood acute lymphocytic leukemia. JAMA 1971;216:648-652.
16. Hustu HO, Aur RJA, Verzosa MS, et al: Prevention of central nervous system leukemia by irradiation. Cancer 1973;32:585-597.
17. Pui CH, Howard SC: Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol. 2008;9:257–268
18. Pui CH, Campana D, Pei D, et al: Treatment of Childhood Acute Lymphoblastic Leukemia Without Prophylactic Cranial Irradiation. N Engl J Med 2009; 360:2730-2741
19. Jeha S, Gaynon PS, Razzouk BI, et al: Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 24:1917-1923, 2006.
20. Berg SL, Blaney SM, Devidas M, et al: Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol 2005;23:3376-3382.

ICLLM 2013

Infections in Hematological Malignancies

Dear Attendee of the 4th International Congress on Leukemia Lymphoma Myeloma:

It is with great enthusiasm and a warm welcome that we invite you to attend our Symposium, "**Meeting the Challenge of Emerging Pathogens in Patients with Hematological Malignancies: Rational Approaches to Diagnosis, Treatment, and Prevention**."

Infectious diseases are major causes of morbidity and mortality in patients with hematological malignancies. The achievements in infectious diseases supportive care have resulted in the ability of patients to undergo curative cytotoxic cancer chemotherapy, hematopoietic stem cell transplantation, radiation therapy, and intense immunosuppression with unprecedented durable remissions and remarkably improved outcome. These advances of infectious diseases supportive care also have contributed substantially to the improved survival, outcome, and reduction of suffering and pain due to infectious complications. This Symposium, "Meeting the Challenge of Emerging Pathogens in Patients with Hematological Malignancies: Rational Approaches to Diagnosis, Treatment, and Prevention," will review the epidemiology, clinical manifestations, strategies, and challenges for managing emerging bacterial, fungal and viral infectious diseases in patients with hematological malignancies. While the prodigious achievements in infectious diseases supportive care that will be reviewed here have greatly improved outcome, there are new formidable microbial challenges that continue to threaten and undermine the successes. Among these are the inexorable rise of multidrug resistant bacteria, emergence of invasive fungal infections, and development of refractory viral infections.

Dr. Thomas J. Walsh of Weill Cornell University Medical Center in New York City, USA will review the impact of the global dissemination of multidrug resistant bacteria on strategies for management of neutropenic and HSCT patients. Dr. Maria N. Gamaletsou of National and Kapodistrian University of Athens, Greece will discuss the changing patterns of invasive fungal infections in patients with hematological malignancies. Finally, Dr. Nikolas V. Sipsas, also of the National and Kapodistrian University of Athens, will analyze approaches to emergent respiratory and systemic viral infections in patients with lymphoma, myeloma, and leukemia. In summary, we believe that this Symposium will prove an important foundation for understanding and management of the bacterial, fungal and viral pathogens that complicate the course of our patients with hematological malignancies.

Sincerely,
Thomas J. Walsh and Hamdi Akan
Scientific Chairs

CURRICULUM VITAE

Thomas J. Walsh, M.D.

Thomas J. Walsh, M.D. is the Director of the Transplantation-Oncology Infectious Diseases Program of Weill Cornell Medical Center of Cornell University, New York, NY and Professor of Medicine, Pediatrics, and Microbiology & immunology. Dr. Walsh received his M.D. degree from the Johns Hopkins University School of Medicine and subsequently pursured 10 post-doctoral years of training in infectious diseases, oncology, pharmacology, medical mycology, and cell biology. He then joined the staff of the National Cancer Institute in Bethesda, MD, where he established a world-renowned program of translational research in antifungal pharmacology, innate host defenses, and molecular diagnostics of life-threatening and debilitating mycoses of immunnocompromised children and adults. He now continues this work with substantially expanded responsibilities in research, training, and patient care as Director of the Transplantation-Oncology Infectious Diseases Program, where his team studies and treats an expanded scope of medically important fungal, bacterial, and viral infections in pediatric and adult immunocompromised patients.

The extensive body of laboratory and clinical investigations conducted and reported by Dr. Walsh and his colleagues has become a paradigm for infectious diseases translational research in advancing important pharmacological interventions systematically from *in vitro* to *in vivo* systems, to phase-I-II studies, and to ultimately phase-III clinical trials. These laboratory investigations and clinical research have advanced the fields of antifungal pharmacotherapy and Immunopharmacology, established new standards of care, and saved the lives of immunocompromised patients worldwide. In response to a major unmet medical need, Dr. Walsh and his colleagues also established a consortium that systematically studied the safety, tolerability, and pharmacokinetics of the entire class of systemic antifungal agents used in pediatric oncology and other immunodeficient children during the past 20 years in order to provide this important group of compounds to seriously ill patients.

Dr. Walsh has served as councillor and president of the Medical Mycology Society of the Americas, Councillor of International Immunocompromised Host Society, as well as Chair and Councillor of Division F (Medical Mycology) of the American Society for Microbiology. He serves on the editorial boards of several major biomedical journals. Dr. Walsh also has served his nation by deploying with medical response teams in times of national or regional disasters over the past two decades.

Dr. Walsh and his staff also serve as an international resource for the care of seriously ill children and adults with life-threatening invasive fungal infections and multidrug resistant bacterial infections. Dr. Walsh has called upon to care for patients in 196 medical institutions throughout the United States as well as in 28 countries around the world. Dr. Walsh also is a dedicated mentor and inspiring teacher. Under Dr. Walsh's mentorship, he has trained more than 150 physicians, scientists, pharmacists, microbiologists, students, nurses, and veterinarians from more than 30 countries. Many of these trainees are now continuing to make important contributions in the field of antimicrobial pharmacology, innate host defenses and microbiology in diagnosis treatment and prevention of life-threatening infections in immunocompromised children.

Global Threat of Multidrug Resistant Bacteria in Patients with Hematological Malignancies

Thomas J. Walsh, M.D.[1] Maria N. Gamaletsou, M.D.[2], and Nikolaos V. Sipsas, M.D.[2]

[1] *Weill Cornell Medical Center of Cornell University, New York, USA*

[2] *Laikon General Hospital and Medical School, National and Kapodistrian University of Athens, Greece*

Global Emergence of Carbapenem-resistant Enterobacteriaceae

Enterobacteriaceae cause approximately one-fourth of all healthcare-associated infections. These organisms include *Escherichia coli, Klebsiella* spp., and *Enterobacter* spp. Historically Enterobacteriaceae were reliably susceptible to carbapenems, even when resistant to other antimicrobial classes.

During the past decade, there has been a global emergence of carbapenem-resistant Enterobacteriaceae (CRE) [1-4]. These carbapenemases confer resistance to all cephalosporins such as cefepime and ceftazidime, to all extended spectrum penicillins, such as piperacillin-tazobactam, and to all carbapenems, such as meropenem and imipenem.

Klebsiella pneumoniae carbapenemase (KPC) producing bacteria were initially described in hospitals of New York City and Israel [2]. Subsequent reports now described these organisms in multiple cities throughout the developed nations. There are now reports of CRE infection in more than 35 states in the United States and more than 30 countries reporting these infections. The Center for Diseases Control and Prevention in 2006-2007 reported that 21% of *Klebsiella pneumoniae* isolates from NYC were carbapenem-resistant. Carbapenem resistance among Enterobacteriaceae in the USA is most commonly caused by KPC [1, 2]. These organisms express the plasmid-based gene bla_{KPC}, which encodes a broad spectrum carbapenemase.

Further adding to this public threat of multidrug resistance has been the emergence of New Delhi Metallo-beta-lactamase-1 (NDM-1) in Enterobacteriaciae as a new antibiotic resistance mechanism in India, Pakistan, Iran, and the United Kingdom [5, 6]. From an historical perspective, clones of CRE historically have resided in hospitals or long-term care facilities. However, the NDM-1 containing Enterobacteriaciae now also now have the capability of thriving in the community and quickly spreading across countries and continents in relation to accessible, rapid global travel. Among the conditions favoring these organisms are profligate antibiotic use and poor infection control procedures. The rapid global transmission of NDM-1 from New Delhi demonstrates a local problem of resistance can rapidly become a worldwide health crisis.

Clinical Manifestations and Consequences of CRE Infections.

Patel and colleagues reported from Sinai Hospital in New York City the demographic and clinical characteristics of patients with carbapenem-resistant *Klebsiella pneumoniae* infection [7]. Among 99 infections caused by KPC, the mean age of the population was 61 years with a wide SD of ± 15% with 59% males. There were 56 bacteremias and 34 intra-abdominal infections, 15 of which had secondary bacteremia. Other infections included urosepsis, ventriculitis, osteomyelitis, empyema, and deep sinus infection.

Using a two matched case-control analysis in these patients, KPC infection was independently associated with recent organ or hematopoietic stem-cell transplantation (P =.008), receipt of mechanical ventilation (P=.04), longer length of stay before infection (P =.01), and exposure to cephalosporins (P =.02) and carbapenems (P <.001) [7]. KPC infection also was independently associated with increased death during hospitalization (48% *vs* 20%; P <.001) and increased death from infection (38% *vs* 12%; P <.001). Mechanical removal of the focus of infection, such as debridement and drainage, was independently associated with patient survival (P =.002).

Notably, administration of antibiotics with *in vitro* activity against KPC was not associated with patient survival. This finding may be related to a delay in diagnosis of life threatening infections, such

that by the time KPC was identified, the hemodynamic consequences of untreated KPC infection were irreversible.

Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies.

Satlin and colleagues at Weill Cornell Medical Center in New York hypothesized that expansion of KPC and other CRE organisms into patients with hematologic malignancies was a serious threat to survival and would have serious implications for empirical antimicrobial therapy [8]. As Enterobacteriaceae are the most common causes of Gram-negative blood stream infections in this patient population, a CRE phenotype would have potentially lethal consequences. All of the recommended empirical antimicrobial agents for the initial management of fever and neutropenia in patients with hematological malignancies have no *in vitro* or *in vivo* activity against CRE. Such patients would be expected to have a high risk of mortality as they would not be receiving effective therapy for 24-48 hours while the CRE was being identified.

These investigators, therefore, studied the emergence of CRE in patients with hematologic malignancies in a large, oncology-hematopoietic stem cell transplant (HSCT) center located in an endemic area (2007-2010) in New York City. Eighteen patients with hematologic malignancies developed bloodstream infections (BSIs) caused by CRE during the study period. Fourteen of these BSIs were caused by *Klebsiella pneumoniae*, three by *Enterobacter cloacae*, and one was polymicrobial. Initial empirical antimicrobial therapy was active in only two patients (11%). Moreover, a median of 55h elapsed between culture collection and receipt of an active agent. Ten (56%) of the 18 patients died. Nine (69%) of the 13 neutropenic patients also died. Accounting for this strikingly elevated mortality, a median of 4 days elapsed between time of culture collection and death.

Among the CRE isolates that were analyzed for carbapenemase production, β-lactamase genes, and outer membrane porin deletions, carbapenem resistance mechanisms included bla_{KPC} in most cases, while CTX-M-15 production with an absent outer membrane porin protein was found in one isolate. Among the isolates that were further characterized by multilocus sequence typing and pulsed-field gel electrophoresis (PFGE), no isolate had ≥95% homology on PFGE, indicating a heterogeneous, non-outbreak population of isolates. Such an heterogeneous group of CRE BSI isolates suggests that infection control measures alone will not be sufficient to curtail this spread into the population of hematological malignancies.

These findings indicate that CRE infections are emerging in patients with hematological malignancies and are associated with ineffective initial empirical therapy, long delays in administration of active antimicrobials, and high mortality rates. The mortality rate of 69% in neutropenic patients with CRE is consistent with earlier data in the 1960's and 1970's when monotherapy with gentamicin was being used for treatment of febrile neutropenic hosts. The mortality of the CRE bacteremic neutropenic patients were also compatible with earlier studies three decades ago that in the absence of immediate, effective, broad-spectrum, empirical antimicrobial therapy, approximately 50% of neutropenic patients with Gram-negative bacteremia died within 3 days of presentation.

Developing Solutions for Diagnosis, Treatment, and Prevention of CRE Infections in Patients with Hematological Malignancies.

In predicting risk of CRE bacteremia in patients with hematological malignancies, prior exposure to carbapenems is not a reliable determinant. Satlin and colleagues demonstrated that the absence of recent carbapenem exposure does not preclude the development of CRE BSI in patients with hematologic malignancies. The majority of CRE BSIs that occurred during neutropenia were not "breakthrough" infections. These infections principally occurred as the initial BSI during neutropenia. Indeed, the most common setting for CRE bacteremia in these patients was the new onset of fever and neutropenia.

The two most common possible risk factors in patients with hematological malignancies predicting CRE bacteremia are (1) exposure to a non-oncology unit, such as a surgical unit or an ICU, elsewhere in the hospital that is known to have CRE infection, and (2) previous or ongoing exposure to a fluoroquinolone or cephalosporin. That patients with hematological malignancies presented with CRE bacteremia is consistent with studies in non-oncology patients where exposure to fluoroquinolones and cephalosporins were important risk factors. These broad spectrum compounds most likely eliminate or reduce the competing endogenous microbiome in the alimentary tract to permit acquisition, colonization, and ultimately infection with CRE pathogens.

Given the continued expansion of CRE into the

highly vulnerable population of patients with hematological malignancies, new diagnostic, therapeutic, and preventive strategies are critically needed [9-11]. Surveillance cultures of mucosal surfaces may provide early warning of patients with hematological malignancies who would be colonized with CRE. Among the possible strategies currently being studied for surveillance of mucosal surfaces of high risk patients with hematological malignancies are selective chromophore agar-based media for CRE, rapid PCR systems for the bla_{KPC} gene, and mass spectroscopic systems, such as Matrix Assisted Laser Desorption Ionization Time of Flight (MALD-TOF). Once patients are found to be colonized, they are placed on isolation and specific plans are implemented for including antimicrobial agents active against CRE if they become febrile.

There are limited options for specific treatment of CRE bacteremias. Amikacin, tigecycline, and polymyxin B were active against the majority but not all of the CRE isolates from the study of Satlin et al. Of course, these agents are not commonly used for empirical therapy of fever and neutropenia in patients with hematologic malignancies. The rates of tigecycline and polymyxin B susceptibility to CRE isolates are globally declining. Recent foreboding reports from Greece and China of increasing polymyxin and tigecycline resistance among CRE isolates augurs for diminished utility of these antimicrobial agents. Aminoglycosides are also not consistently active *in vitro* against CRE. Some centers describe susceptibility of CRE to aminoglycosides to be as low as 10%.

Once potentially active agents, such as polymyxin B or colistin with tigecycline or an aminoglycoside are initiated against documented CRE bacteremia, several limitations ensue. First, emergence of resistance may occur during therapy to one or both agents. Second, these agents are not potently microbicidal against CRE. As bactericidal agents are critical for successful therapy of neutropenic patients, breakthrough bacteremias may develop when the plasma concentrations of the agents reach trough in the dosing interval. Third, as nephrotoxic agents, polymyxin B, colistin, and aminoglycosides may not be well tolerated in patients with hematological malignancies who may have underlying renal dysfunction and who may be receiving concomitant nephrotoxic agents, such as foscarnet or amphotericin B.

The development of CRE is occurring in the context of multiple micro-evolutionary events that presage increasing antimicrobial resistance. Among Enterobacteriaciae development of plasmid-based genes encoding extended spectrum beta-lactamases (ESBLs) has created widespread use of carbapenems to treat infections caused by these organisms. *Pseudomonas aeruginosa* continues to emerge resistant by multiple molecular mechanisms in hospitals and chronic care facilities. *Acinetobacter baumanii*, which is frequently pan-resistant due to multiple integron-resistant regulated genes encoding proteins mediating high level resistance to most classes of antimicrobial agents. The problems also of resistant Gram-positive bacteria, such as MRSA and VRE, pose additional challenges to patients with hematological malignancies. While there is a small armamentarium of antimicrobial agents for resistant Gram-positive bacteria, there is a serious dearth of potent agents for the multidrug resistant Gram-negative bacteria.

Despite portentous global trends of increasing multidrug resistant pathogens, there is a paucity of new antimicrobial agents being developed. A recent review discusses recent developments in targeting beta-lactamases and beta-lactam combinations [12]. Among the new β-lactam-β-lactamase inhibitor combinations in late-stage (phase II and beyond) clinical trials are ceftolozane-tazobactam, ceftazidime-avibactam, ceftaroline-avibactam, and imipenem-cilastatin-MK-7655. Ceftolozane is an antipseudomonal cephalosporin and tazobactam is designed to protect it against ESBLs. Avibactam and MK-7655 are non-β-lactam diazabicyclooctane inhibitors, which inhibit class A carbapenemases and class C enzymes.

There is a crisis in the development of new antimicrobial agents that threatens the public health of all patients, especially those with hematological malignancies, where infections are treated through well-established algorithms. Although new agents are being developed that show activity against CRE, other multidrug resistant bacteria will continue to emerge with different mechanisms of resistance. There needs to be a global effort directed to improved surveillance, infection control measures, and new antimicrobial agents, in order to better protect our patients with hematological malignancies.

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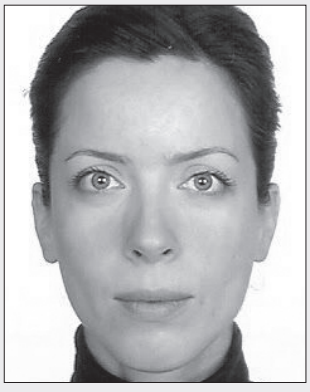

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PUBLICATIONS
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Invasive Fungal Infections in Patients with Hematological Malignancies

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Invasive fungal infections (IFIs) are important causes of morbidity and mortality in patients with hematological malignancies. The risk for IFIs in patients with hematological malignancies varies as a function of underlying neoplastic process and degree of immunosuppression.

Risk factors for development of IFIs in patients with hematological malignancies

Neutropenia is a key risk factor for the development of invasive fungal infections. Neutropenia may develop as the result of chemotherapy, radiation, bone marrow failure (myelodysplasia and aplastic anemia), and by replacement of hematopoietic cells in the bone marrow by malignant cells. In the classic description of the inverse relation between risk of infection and degree of neutropenia, Bodey *et al.* underscored the role of profound neutropenia (ANC<100) in leukemia patients for increasing the risk for infection. In a classic study of patients receiving treatment for acute leukemia Gerson *et al.* later demonstrated that the risk of invasive aspergillosis is directly related to the duration of neutropenia in patients with acute leukemia. After 14 days of neutropenia, the risk of aspergillosis increased in direct relation to the duration of neutropenia. Neutropenia is also a surrogate marker for other risk factors for IFIs. For example, mucositis associated with intensive chemotherapy increases the risk for translocation of *Candida* spp. across the alimentary tract.

Lymphocytopenia in hematological malignancies increases the risk for fungal infections associated with impaired cell mediate immunity (CMI). Fludarabine, which is a lymphotoxic compound primarily affecting CD4+ lymphocytes and corticosteroids markedly increase the risk of infection caused by *Pneumocystis jirovecii* and *Cryptococcus neoformans*.

In addition to their effects on CMI, corticosteroids markedly alter the distribution, trafficking and functions of neutrophils, monocytes, and lymphocytes. Corticosteroids also impair oxidative function and hyphal damage capacity of neutrophils and impair phagocytosis of macrophages. The risk of infections caused by invasive filamentous fungi, such *Aspergillus* spp. and the *Mucorales,* is significantly increased in these patients receiving a prednisone equivalent of 0.5 mg/kg for longer than 30 days. Among allogeneic HSCT recipients, corticosteroid therapy for GVHD is a major risk factor for invasive Aspergillosis and filamentous fungal infections.

Among the humanized immunosuppressive biological agents, alemtuzumab (Campath-1H; anti-CD52 humanized monoclonal antibody that targets normal and most malignant T-lymphocytes) is associated with severe lymphopenia and an increased risk for opportunistic infections, including *Pneumocystis jirovecii* pneumonia. TNF-alpha inhibiting agents, including infliximab, etanercept, and adalimumab, increase the risk for infections caused by intracellular pathogens, such as *Histoplasma capsulatum*.

Candidiasis

Candida species are a component of the endogenous microbiome that invade the bloodstream through disruptions in anatomical barriers. The alimentary tract is the principal portal of entry in patients with acute leukemia.

Oropharyngeal and esophageal candidiasis. Invasive candidiasis in patients with hematological malignancies may present initially as oropharyngeal and esophageal candidiasis. Therapy for oropharyngeal candidiasis includes clotrimazole troches or oral fluconazole. Esophageal candidiasis typically presents as odynophagia. The differential diagnosis include herpes simplex virus, cytomegalovirus (principally in HSCT recipients), and bacteria. Fluconazole is use as initial therapy for esophageal candidiasis, while an echinocandin is used in refractory cases. *Candida glabrata* and *Candida krusei* may emerge resistant to fluconazole and cause recurrent symptoms of odynophagia.

Candidemia. Candida albicans historically was the

most common *Candida* species isolated from blood. With the advent of triazole and echinocandin prophylaxis and therapy, there has been a major shift in the causes of candidemia toward non-*albicans Candida* spp.

A recent prospective, multicenter study specifically designed to investigate the epidemiology, risk factors, and outcome of candidemia among hospitalized patients with hematological malignancies found that most infections (87.5%) were caused by non-*Candida albicans* species, with *C. parapsilosis*, being most common. Independent risk factors for the development of candidemia were the presence of CVC, hypogammaglobulinemia, and high APACHE II score. Twenty-eight-day crude mortality was 45%. Patients with candidemia had significantly lower survival than those without candidemia. Among patients with candidemia, an elevated APACHE II score was an independent risk factor for death, while recovery from neutropenia was independently associated with improved survival.

Among the different *Candida* species, *Candida krusei* is always resistant to fluconazole. *Candida glabrata* may emerge as breakthrough infection with resistance to all triazoles. *Candida tropicalis* bloodstream infection often has a severe course with cutaneous dissemination, myalgias, renal failure, and hemodynamic collapse. *Candida parapsilosis* is mostly associated with vascular catheters and may emerge during the course of echinocandin therapy.

Recent studies indicate that removal of central vascular catheters in patients with hematological malignancies does not improve outcome. This finding suggests that the likely portal of entry is the alimentary tract. If a multi-lumen catheter is not immediately removed, antifungal therapy should be administered parenterally through all lumens. As candidemia in neutropenic patients may be complicated by chronic disseminated candidiasis of liver, spleen, and kidney, and eyes, ophthalmologic examination and CT scan of the abdomen is recommended upon recovery from neutropenia.

Chronic disseminated candidiasis. Chronic disseminated candidiasis (hepatosplenic candidiasis) may persistent with new fever after recovery from neutropenia. Following resolution of neutropenia, elevated alkaline phosphatase and development of numerous target lesions in the liver and spleen develop. An open liver biopsy is advisable but may not be feasible. Antifungal therapy with fluconazole or echinocandin is initiated with anticipation of treatment for several months until resolution of lesions. The presence of persistent lesions does not preclude further chemotherapy.

Treatment of Invasive Candidiasis. As most patients with hematological malignancies are receiving fluconazole prophylaxis, an echinocandin (anidulafungin, caspofungin, or micafungin) is recommended as the initial therapy of invasive candidiasis in neutropenic patients with hematologic malignancies. For non-neutropenic stable patients with uncomplicated candidemia an initial course of echinocandin followed by fluconazole is reasonable if the organism proves to be *C. albicans*.

Aspergillosis

The sino-pulmonary tract is the most common portal of entry of Aspergillus spp. and other filamentous fungi. Profound and persistent neutropenia, repeated cycles of prolonged neutropenia, concomitant corticosteroid therapy, and graft versus host disease (GVHD) increase the risk of development of invasive sino-pulmonary aspergillosis (ISPA). Other risk factors in HSCT recipients include lymphopenia, GVHD, CMV disease, and respiratory viral infections.

ISPA may initially only manifest as fever. More advanced infection presents sinus pain or congestion, cough, pleuritic chest pain, and hemoptysis. Invasive pulmonary aspergillosis (IPA) includes nodules, halo sign, bronchopneumonia, lobar consolidation, wedge-shaped segmental pneumonia, and cavitary lesions. CNS aspergillosis may present as focal neurological deficits. Early diagnosis of aspergillosis is important for improved outcome. Recovery of organism from bronchoalveolar lavage, percutaneous needle aspirate, and biopsies, in sino-pulmonary lesions is advised but may have limited sensitivity. Serum galactomannan detected by double sandwich ELISA improves early detection of aspergillosis and complements CT scans. Serial quantitation of galactomannan antigenemia also predicts response to antifungal therapy. Serum (1→3)-β-D-glucan may also detect invasive aspergillosis and other invasive mold infections. PCR-based detection of Aspergillus DNA in BAL fluid may be useful for the diagnosis of IPA. Aspergillus fumigatus followed by Aspergillus flavus are the most common species causing invasive aspergillosis. Aspergillus terreus is observed with increasing frequency at several hematological malignancies centers, and is notable for being resistant to amphotericin B.

Treatment of invasive aspergillosis. Voriconazole is the preferred agent for initial therapy of ISPA and disseminated aspergillosis. For patients for whom voriconazole is contraindicated, liposomal amphotericin B (LAmB) is used instead. Posaconazole is approved for use as prevention of invasive

aspergillosis in patients with acute leukemia and in HSCT recipients.

The combined data from laboratory animal studies, case controlled studies, and a recently completed prospective randomized controlled trial support the use of voriconazole and echinocandin in the treatment of invasive aspergillosis. The rationale is that echinocandins target a unique site of cell wall biosynthesis while triazoles target synthesis of the fungal cell membrane. Patients who recover from an episode of ISPA are at risk for relapse of infection during subsequent immunosuppression. Secondary prophylaxis is indicated in those patients who undergo additional cycles of cytotoxic chemotherapy or HSCT.

Mucormycosis

The agents of mucormycosis (zygomycosis) include the following members of the order Mucorales: *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* (formerly *Absidia*) *corymbifera*. Risk factors for mucormycosis among patients with hematological malignancies include prolonged neutropenia, corticosteroids, diabetic mellitus, iron overload, and GVHD. Mucormycosis in patients with hematological malignancies typically manifests as pulmonary, sinus, sino-orbital, rhino-cerebral, or cutaneous disease. Patients with pulmonary mucormycosis may present with cough, hemoptysis, pleuritic pain, and single or multiple pulmonary nodules, which also may demonstrate a reverse halo sign. In rhino-cerebral disease, fever, facial pain and headache are common symptoms. Contiguous extension may lead to orbital involvement with proptosis and extraocular muscle paresis, involvement of hard palate, and extension into the brain. Invasion of the veins draining the ethmoid sinuses and orbits may lead to cavernous sinus thrombosis. An eschar over the palate or nasal turbinates is suggestive of mucormycosis, but other filamentous fungi can produce similar findings. Occasionally, isolated primary cutaneous disease may follow minor trauma.

Treatment of mucormycosis. There are three cornerstones of therapy for mucormycosis: lipid formulation of amphotericin B or conventional deoxycholate amphotericin B; early and aggressive surgical debridement; and reversal of immunosuppression, as well as correction of hyperglycemia in diabetic patients.

Fusarium infections

Fusarium species in patients with hematological malignancies cause sino-pulmonary and disseminated infection. Prolonged neutropenia is the most common risk factor. The portal of entry is most frequently respiratory but may also be from periunguinal and soft tissue infection. Fungemia with positive blood cultures occurs in approximately one-half of cases during neutropenia. Multiple hematogenously disseminated cutaneous lesions are common and usually reveal the organism in biopsy. Other sites of infection in the process of dissemination include CNS, bone, joints, eyes, and liver. Initial localized manifestations include onychomycosis, paronychiae, and cellulitis. Early identification of localized skin disease and debridement may be life-saving.

Treatment of fusariosis. Fusarium species, which include *Fusarium solani* species complex and *Fusarium oxysporum* species complex, have variable *in vitro* susceptibility to amphotericin B and to voriconazole. Initial therapy consists of both amphotericin B and voriconazole for spectrum (not synergy) while awaiting susceptibility results. Although interpretive breakpoints have not been established, readings of >4μg/ml usually signify lack of response ("resistance") to the antifungal agent. Survival from disseminated fusariosis is critically dependent on resolution of neutropenia. Granulocyte transfusions have been life-saving in selected patients until recovery from neutropenia.

Scedosporium infections

Scedosporium apiospermum and *Scedosporium prolificans* are the principal pathogenic species. In neutropenic patients, *S. apiospermum* causes sinopulmonary disease, and dissemination to the central nervous system infection. *S. apiospermum* is clinically and histologically indistinguishable from aspergillosis. Voriconazole is the preferred fist line antifungal agent against this organism.

Treatment of Scedosporium infections. As *S. apiospermum* is often resistant to amphotericin B but susceptible to voriconazole and posaconazole, establishing a microbiological diagnosis is important. *Scedosporium prolificans*, by comparison, causes a similar spectrum of disease as *Aspergillus* but is resistant to all systemically available antifungal agents. Reversal of immunosuppression and surgical resection are the keys to the management of infections caused by *S. prolificans*.

Dematiaceous moulds

These organisms are distinguished as dark-walled molds contain melanin in their cell walls which

confers a black, brown, or olive-green pigment in culture. Infections caused by these dematiaceous moulds is sometimes termed phaeohyphomycosis. Among patients with hematological malignancies, sinusitis, pneumonia, central nervous system infection, fungemia, soft tissue infection, and disseminated disease may develop. As a group, these organisms have a strong predilection to cause central nervous system infection. Among the most common organisms are Alternaria spp., Bipolaris spp., Ochroconis gallopava, Cladophialophora (Xylohypha or Cladosporium) bantiana, and Exophiala (Wangiella) dermatitidis, and Exserohilum rostratum. The recent outbreak of fungal meningitis caused by Exserohilum rostratum in the United States in association with exposure to contaminated methylprednisolone solution demonstrates the morbidity cause by these organisms.

Treatment of infections caused by dematiaceous moulds. Treatment consists of systemic antifungal therapy and surgical excision of localized disease when feasible. Based upon susceptibility profiles and clinical reports, voriconazole is the primary agent for therapy. Amphotericin B and posaconazole may be alternatives. However, as antifungal susceptibility profiles vary according to species, guidance by an expert infectious diseases and mycoses is advisable.

Cryptococcosis

As host defense against cryptococcal infection is principally dependent on cell-mediated immunity, patients with isolated neutropenia are rarely infected with *C. neoformans*. Instead, patients receiving corticosteroids, those with lymphopenia, and those suffering from GVHD are at greatest risk. As the respiratory tract is the principal portal of entry, patients may present initially with pneumonia or may have concomitant CNS infection. Although meningitis is the most common presentation of cryptococcal infection, other manifestations include primary pneumonia, fungemia, and cutaneous and visceral dissemination.

Risk factors for poor outcome include elevated cerebrospinal fluid opening pressure, a low glucose level, less than 20 leukocytes/ml, a positive India ink preparation, culture of cryptococci from extraneural sites, and high titers of cryptococcal antigen in serum and cerebrospinal fluid. Central nervous system complications include development of a mass lesion, obstructive hydrocephalus requiring shunting, and visual loss, especially cortical blindness related to elevated intracranial pressure.

Treatment of cryptococcosis. Initial therapy consists of deoxycholate amphotericin B (0.7 mg/kg daily) plus 5-flucytosine (100 mg/kg daily) for the first 2 weeks, followed by maintenance fluconazole therapy (400 mg daily). Liposomal amphotericin 5 mg/kg/d may also be used in lieu of deoxycholate amphotericin B. As fluconazole is well-tolerated, continuing therapy with this agent through immunosuppressive therapy is reasonable.

Pneumocystis pneumonia (PCP)

Patients defective CMI and T-cell immunity are at risk for PCP. Corticosteroid therapy is the most common predisposing factor in patients with hematological malignancies. PCP can have a more fulminant course with more rapid progression to respiratory failure. Patients treated with corticosteroids may develop initial clinical manifestations of PCP during steroid taper. Although diffuse bilateral interstitial pulmonary infiltrates are the most common manifestation of PCP, unilateral, segmental or patchy infiltrates may also develop. Extrapulmonary infection is uncommon in patients with PCP and hematological malignancies.

Bronchoalveolar lavage is indicated in patients with hematological malignancies who present with these findings. Diagnosis of PCP relies on microscopic visualization of the organism. Immunofluorescent staining using monoclonal antibodies is more sensitive than cell wall staining methods, such as silver staining or Wright-Giemsa. Where available, PCR on BAL fluid may also facilitate diagnosis. Serum (1→3)-β-D-glucan recently has been shown to be a sensitive circulating biomarker for PCP.

Treatment of PCP. The treatment of choice for PCP is trimethoprim/sulfamethoxazole (trimethoprim: 15 mg/kg daily in 3 divided doses) (TMP/SMX). For patients intolerant of TMP/SMX, intravenous pentamidine, primaquine-clindamycin, and dapsone-trimethoprim are acceptable alternatives. Although response rates are significantly lower than with that of TMP/SMX, atovaquone may be used for treatment of mild to moderate PCP. For patients with moderate to severe PCP (PaO_2 < 75 mmHg), corticosteroids should be administered. As TMP/SMX is highly effective as prophylaxis against PCP, it should be administered to patients at risk using any one of several oral regimens. Among those patients found to benefit are children with acute lymphoblastic leukemia, adult and pediatric patients with allogeneic HSCT, patients with CNS tumors receiving high-dose corticosteroid therapy, those receiving Fludarabine, and patients receiving combination corticosteroid therapy.

Mycoses caused by other fungal pathogens.

Trichosporonosis. Trichosporon species may emerge as breakthrough infections in neutropenic patients receiving amphotericin B. Trichosporonosis in profoundly neutropenic patients typically manifests with refractory fungemia, funguria, cutaneous lesions, renal failure, pulmonary lesions, and chorioretinitis. Disseminated trichosporonosis may yield a false positive cryptococcal latex antigen test because of cross-reactivity with the polysaccharide capsule of *C. neoformans*. *In vitro* and experimental infections indicate that most *Trichosporon* species are inhibited, but not killed, by achievable serum levels of conventional amphotericin B. Fluconazole and voriconazole have superior activity in experimental infections and are the preferred antifungal agents.

Malassezia infections. Malassezia furfur fungemia is often associated with lipid-containing parenteral nutrition administered through a central venous catheter in immunocompromised patients or premature infants. Clinical manifestations include persistent fungemia and pulmonary infiltrates. Blood culture recovery is enhanced by addition of olive oil or other long chain fatty acids to the culture plates. Discontinuation of lipid infusions and removal of the central catheter are essential. As *Malassezia furfur* is resistant to amphotericin B therapy, fluconazole therapy is the drug of choice. Among neutropenic patients and patients treated with corticosteroids, a folliculitis resembling disseminated candidiasis may occur. This localized process does not imply disseminated infection.

Endemic dimorphic fungi. These organisms include *Histoplasma capsulatum, Coccidioides* spp., *Blastomyces dermatitidis*, and *Penicillium marneffei. Histoplasma capsulatum* is found in central US, and in areas of northern Mexico. *Coccidioides* is endemic in the southwestern U.S. *P. marneffei* is endemic in Southeast Asia. Endemic dimorphic fungi are so named because of their characteristic geographic distribution. These fungi are dimorphic, existing in nature in the mycelial stage and converting to the yeast stage at body temperature. Impaired cell-mediated immunity and a geographic exposure are the key risk factors. Endemic mycoses in the central U.S. include histoplasmosis and blastomycosis. For histoplasmosis fever, pulmonary infiltrates, and hypoxia with dissemination to liver, spleen, lymph nodes, bone marrow, adrenal glands, mucocutaneous tissues, gastrointestinal tract, and central nervous system may occur. The chest radiograph may show a miliary reticulonudular pattern that is suggestive of disseminated tuberculosis. A rapid diagnosis of histoplasmosis can be made by Giemsa staining of a peripheral blood smear or bone marrow aspirate demonstrating characteristic intracellular yeast forms. Blood cultures may be positive for small yeast-like cells. Severe pulmonary or disseminated histoplasmosis should be treated with an amphotericin B formulation. Prolonged therapy with itraconazole may be initiated after stabilization of disease.

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CURRICULUM VITAE

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Dr Nikolaos V. Sipsas received his medical degree from the National and Kapodistrian University of Athens in Greece. He did his post-doctoral thesis, in History of Medicine at the Medical School of the Zurich University in Switzerland, and in Infectious Diseases at the Athens University Medical School, Greece. Then he was trained in Internal Medicine at the Athens Naval Hospital and the Athens University Laikon Hospital. He was subsequently trained as a research fellow in Infectious Diseases at Massachusetts General Hospital in Boston. He is currently attending physician at the Department of Medicine and the Infectious Disease Unit at the Laikon General Hospital, in Athens, Greece and Associate Professor at the Athens University Medical School. He is a reviewer in peer-reviewed journals in Infectious Diseases and Internal Medicine and he has authored more than 60 peer-reviewed manuscripts.

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Emergence of Respiratory and Systemic Viral Infections in Patients with Hematological Malignancies

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INTRODUCTION

Over the past several decades, there has been substantial progress in the treatment of hematological malignacies. Research has provided a new array of chemotherapeutic agents, while modern treatment modalities, including hematopoietic stem cell transplantation (HSCT), have been successfully introduced into the clinical practice. Unfortunately, the majority of these treatment options cause a profound suppression of innate and/or acquired immunity. Neutropenia in particular, remains as the most prominent chemotherapy-induced immune defect, making the patients vulnerable to infections. Infections are an important complication of hematological malignancies, especially after chemotherapy or during HSCT procedures and contribute significantly to morbidity and mortality. Besides the risk of developing bacterial and fungal infections, there is a substantial risk of primary viral infection and reactivation.

Respiratory viruses can cause severe pneumonia after chemotherapy and/or HSCT, with high morbidity and mortality. Historically, their clinical significance in patients with hematological malignancies has been underestimated, but nowadays they are increasingly recognized as common causes of upper respiratory infection (URI), lower respiratory tract infection (LRTI), and are frequently associated with bacterial or fungal co-infections. Common respiratory viruses affecting patients with hematological malignancies include respiratory syncytial virus (RSV), influenza and parainfluenza viruses, adenoviruses, rhinoviruses, and coronaviruses. More recently, newly identified viruses such as human metapneumoviruses (HMPV), new strains of coronaviruses, and bocavirus have also been detected in symptomatic HSCT recipients. Respiratory viruses can be acquired in the community or during hospitalization.

Heavy immunosuppression of patients with hematological malignancies can lead to reactivation of latent viruses, including herpes viruses (varicella-zoster virus [VZV], herpes simplex virus [HSV], human herpes virus 6 [HHV-6], Epstein Barr virus [EBV] cytomegalovirus [CMV]), polyomaviruses, and adenovirus. These systemic viral infections occur usually in HSCT recipients, after conditioning or later, due to the administration of immune-suppressive agents.

In this review we address the problem of viral infections that are associated with high morbidity and mortality in the immunocompromised patient with hematological malignancy, and we provide a practical guideline for their treatment.

Respiratory viral infections in patients with hematological malignancies

Respiratory viruses cause acute illness in the general population and are responsible for hospitalizations of elderly patients and patients with underlying medical conditions. These viruses are also a common cause of severe respiratory disease in patients with hematological malignancies and/or HSCT. Community-acquired respiratory viruses have a significant impact on the morbidity and mortality of the hematological patient, causing a variety of diseases ranging from self-limited upper respiratory tract illnesses to life-threatening lower respiratory tract infection and occasionally disseminated disease. Disease manifestations are dependent on the specific virus, the type of chemotherapy, immunosuppressive therapy, and transplant, as well as the net state of immunosuppression. Pneumonia following infection with these viruses may be primarily viral, bacterial, fungal, or mixed in origin.

Nosocomial transmission of respiratory viruses is common, and widespread outbreaks have occurred in hematology units with sometimes devastating consequences. Prevention of transmission of respiratory viruses in a hospital setting, especially in units caring for patients with hematological malignancies is considered a basic standard of care

for the hospitals. Strict enforcement of infection control measures is mandatory to prevent spread within a hospital ward; such measures include respiratory isolation of infected patients, handwashing before and after contact with patients, and educational efforts targeting healthcare workers and family members.

With regard to diagnosis, prompt and accurate identification of the respiratory viral pathogen is of paramount importance for the management of infection, because it allows for timely implementation of virus-specific infection control maeasures, the initiation of appropriate antiviral therapy, and for potential modifications of immunosuppressive therapy or rescheduling of HSCT. Proper collection of specimens is critically important for accurate identification of viruses in clinical samples. Different diagnostic methods have been used, but during recent years, the use of multiplex PCR technique is becoming the standard of care, it may detect multiple respiratory viruses from a single, readily obtained specimen.

Management of respiratory viral infections has been controversial. With the exception of influenza infections for which neuramidase inhibitors have been shown to be effective, there are no established treatments. There is a paucity of well-designed, randomized, controlled, clinical studies for the treatment of respiratory viral infections among patients with hematological malignancies. There are only a few studies, mostly retrospective and from single centers, and "expert opinions" that guide physicians on the therapy of these serious and sometimes fatal infections in patients with hematological malignancies and/or HSCT.

Respiratory Syncytial Virus (RSV) Infection

Respiratory syncytial virus is a paramyxovirus causing respiratory infection in patients with hematological malignancies, especially those who have undergone HSCT. Infection with RSV affects approximately 2% to 17% of HSCT recipients but usually is not a severe illness. However, outbreaks of fatal infections have been reported in transplant recipients. RSV infection is seasonal, occuring in the fall, winter, and spring, with an attack rate up to 10% during winter time. Risk factors for RSV infection among patients with hematological malignancies include HSCT (especially allogeneic HSCT with mismatched/unrelated transplant), male sex, advanced age, cytomegalovirus seropositivity, and pre-engraftment status.

RSV is detected in clinical specimens, including nasal washes, nasopharyngeal swabs, and bronchoalveolar lavages. The "gold standard" for diagnosis of RSV infection is viral culture (conventional or shell vial), but this technique is time consuming with low sensitivity. Other methods include detection of viral antigens via direct immunofluorescence and molecular detection of viral RNA. HSCT recipients with symptoms of common cold (ie, fever, nasal congestion / rhinorrhea sore throat / cough) during winter should be tested for RSV and other respiratory viruses.

Patients with RSV usually present with symptoms of an upper respiratory tract infection (eg, rhinorhhea, nasal/sinus congestion, sore throat, caugh, and otitis media), which progress rapidly to lower respiratory tract infection (tracheobronchitis, pneumonia), and finally to respiratory failure, necessitating admission to an intensive care unit and mechanical ventilation. RSV infection among HSCT recipients is associated with significant morbidity, and mortality ranging from 7% to 83% in patients with LRTI.

Treatment of RSV infection

The targets of the treatment of RSV infection are viral replication, coinfections, lung inflammation and respiratory failure. Available therapies that have been used for treatment of RSV infections are limited to ribavirin, intravenous polyclonal (IVIG) and RSV-specific immunoglobulin (RSV-IVIG), and palivizumab (PVZ). Ribavirin is a guanosine analog that is active against RNA and DNA viruses. It is available in aerosol, intravenous, and oral forms. PVZ is an RSV-specific monoclonal antibody derived from murine antibodies and directed against the F glycoprotein of RSV. Early initiation of ribavirin therapy, preferably in the aerosolized form, before development of RSV advanced LRI is nesecary in high risk patients with hematological malignancies and/or HSCT. In patients with established RSV LRI, initiation of combination therapy with aerosolized ribavirin and IVIG or PVZ) before the onset of respiratory failure and need for mechanical ventilation may reduce mortality, but this remains controversial.

Prevention of RSV

Chemoprophylaxis in susceptible patients may be considered, especially in outbreak situations when horizontal transmission is occurring. Polyclonal or monoclonal immunoglobulins and palivizumab can be used for the prevention of RSV infection. Currently, there is no vaccine that can prevent RSV infection.

Influenza and parainfluenza viruses

Transmission of parainfluenza and influenza

viruses is by direct droplet spread or aerosolized respiratory secretions. During community outbreaks, influenza, especially type A, and parainfluenza viruses have been reported as a frequent cause of severe and fatal pneumonia in HSCT recipients. Neuraminidase inhibitors, including oseltamivir and zanamivir are effective for the treatment of influenza, when they are used early. Ribavirin has antiviral effects against parainfluenza virus *in vitro* and has been used for the treatment of lower respiratory tract disease in immunocompromised hosts. Studies have reported decreased viral load and clinical improvement in immunocompromised children with severe parainfluenza virus infection after treatment with aerosolized ribavirin.

Human metapneumovirus infections

Human metapneumovirus (hMPV) belongs to the *Paramyxoviridae* family. It has been disovered in 2001, but it causes respiratory tract infections in humans for at least 60 years with a worldwide distribution. hMPV should always be considered as a potential cause of respiratory illness in immunocompromised patients. hMPV is transmitted by direct or close contact with contaminated secretions, with an incubation period of three to five days. The virus can cause upper and lower respiratory tract infection in patients of all age groups, but symptomatic disease most often occurs in young children or older adults. hMPV usually causes mild, self-limited infections in children and adults. However, among immunocompromised patients hMPV infections may be more severe and the course more prolonged due to poor clearance of virus. Clinical manifestations in this situation can range from bronchiolitis to severe pneumonia and acute respiratory distress syndrome. Immunocompromised hosts appear to acquire infection at the same frequency as immunocompetent individuals. In studies of upper and lower respiratory tract infection in patients with hematologic malignancies, 3% - 9% percent of episodes were associated with hMPV infection. Reverse transcriptase PCR on nasopharyngeal specimens is the most sensitive method for diagnosis of hMPV infection.

Ribavirin is active against hMPV *in vitro* and reduces viral replication in animal models. However, there are no clinical data on the treatment of hMPV; therefore, treatment is supportive and varies with the clinical manifestations.

Other respiratory viruses

Infections from human bocavirus, human coronavirus, and other newly identified viruses such as WU/KI viruses are less likely to cause severe problems in patients with hematological malignancies and/or HSCT, compared with the well-described viral pathogens above.

Systemic Viral Infections in Patients with Hematological Malignancies

Adenovirus

Adenonirus, belonging to the Adenoviridae family of DNA viruses, is a common cause of infections in the general population. In patients with hematological malignancies and/or HSCT *Adenonirus* disease may be life threatening. Reactivation within the recipient and horizontal transmission are most common routes of acquisition of the virus. *Adenonirus* infections affect mainly (20%-25%) pediatric populations undergoing HSCT than adults (9%). Risk factors include low numbers of CD3(+) T cells, graft-versus-host disease and the associated use of immunosuppressive agents (cyclosporine-A, methotrexate, steroids, mycophenolate mofetil), and use of serotherapy in conditioning regimens, including agents such as antithymocyte globulin or alemtuzumab.

Adenonirus can cause severe respiratory disease, hepatitis, and colitis in patients with hematological malignancies and/or HSCT, with a reported mortality of 8%-26%. Other manifestations of the infection include hemorrhagic cystitis and keratoconjunctivitis. Disseminated disease with multiorgan failure can also occur. Regarding diagnosis, adenoviral load detection by PCR should be performed weekly for optimal timing of preemptive treatment and careful monitoring of the response to treatment. Ribavirin and cidofovir are agents used in the treatment of *Adenonirus*. Most evidence for efficacy against *Adenonirus*, however, is present for cidofovir. Cidofovir *in vitro* has been shown to be active against all *Adenonirus* subtypes. Probenecid and hyperhydration should be started concurrently to limit cidofovir nephrotoxicity. Ribavirin has *in vitro* activity against some, but not all, *Adenonirus* subtypes. There are case reports suggesting therapeutic efficacy of ribavirin in patients with *Adenovirus* infection refractory to other antivirals. Administration of *Adenovirus*-specific cytotoxic T-cells should be considered for patients who do not adequately respond to cidofovir and/or alternative antivirals.

Preemptive treatment with cidofovir [1 mg/kg 3 times per week (alternatively 5 mg weekly)] can be started when the adenoviral load exceeds a certain critical level, depending on the risk group. Treatment starts when the load exceeds 100 copies/mL (in low-risk patients), or 1000 cp/mL (intermediate-risk patients). Treatment with cidofovir

should always be initiated with a viral load > 10.000 copies/mL, or when there are symptoms and signs of disease irrespective of the load. Moreover, immunosuppressive therapy should be tapered as soon as possible. Discontinuation of therapy should be considered when adenoviral load has been < 400 copies/mL for 2 consecutive weeks and immunosuppression has been reversed.

Herpes simplex virus

Most HSV infections in patients with hematological malignancies and/or HSCT are caused by viral reactivation in seropositive patients. The rate of reactivation is as high as 70%, and it is equal after autologous or allogeneic transplantation. The median time to onset of HSV disease is 2-3 weeks.

Clinical manifestations of HSV-1 infections include primarily severe mucositis and infrequently esophagitis. Occasionaly, HSCT recipients develop HSV-1 viremia, and subsequent viral infection of other organs including: the trachea (tracheobronchitis), lungs (pneumonitis), liver, CNS, adrenal glands, or gastrointestinal tract. Reactivation of HSV-2 can cause lesions in the genital or perineal area and accounts for 10% - 15% of all HSV infections in HSCT recipients.

Prophylaxis with acyclovir is a standard of care in transplant recipients and has strikingly reduced the incidence of all herpetic infections in this vulnerable patient population. In seropositive HSCT recipients intravenous (5 mg/kg IV twice daily) or oral acyclovir (800 mg twice daily) from marrow infusion until engraftment, prevents reactivation of HSV.

Cytomegalovirus

CMV infections in patients with hematological malignancies and/or HSCT are due to viral reactivation. The risk of reactivation of CMV is 70 - 80 % for seropositive allogeneic HSCT recipients and only 40 % for seropositive autologous or syngeneic HSCT recipients. The risk of seronegative HSCT recipients to acquire CMV infection from blood transfusion or seropositive bone marrow is 40%. Clinical manifestations of CMV infections in patients with hematological malignancies and/or HSCT include protracted fever not responding to antibiotics, interstitial pneumonitis, enteritis, esophagitis, hepatitis, retinitis, and encephalitis. During the last decades, the widespread use of prophylaxis or preemptive antiviral therapy reduced the frequency and severity of CMV disease, but mortality remained as high as 18.3% in seronegative of HSCT recipients from a CMV-seropositive donor.

Various antivirals agents have been used for CMV prophylaxis including ganciclovir, foscarnet, acyclovir, and valacyclovir. Intravenous ganciclovir has been the most effective, but its use is limited by bone marrow toxicity. A more widely accepted approach to minimize toxicity of antiviral prophylaxis is preemptive therapy, based upon active screening for CMV with quantitative PCR assays or the antigenemia assay. Ganciclovir (5 mg/kg IV twice daily) and foscarnet (90 mg/kg IV twice daily) are equally effective as preemptive therapy of CMV infection in allogeneic HSCT recipients.

Varicella zoster virus

VZV reactivation is common among patients with hematological malignancies, especially among HSCT recipients, with an incidence up to 20-40%. The risk factors for VZV reactivation include recent VZV infection, VZV seropositivity, GvHD, absolute lymphopenia, and intensive conditioning with agents such as anti-thymocyte globulin. VZV infection affects mainly pediatric patients (up to 90 % during the first post-transplant year) and may be complicated by disseminated cutaneous lesions (25 %), post-herpetic neuralgia (25 %), scarring (20 %), and bacterial superinfection (15 %). Dissemination complicates mainly allogeneic HSCT (45%) involving the lungs, liver, and CNS, and is associated with a death rate of at least 5 %. Acyclovir at a dose of 800 mg twice daily, administered for a period of 2-12 months after allogeneic HSCT reduces the risk of VZV infection.

Epstein-Barr virus

The spectrum of EBV infection among patients with hematological malignancies and/or HSCT includes oropharyngeal viral excretion, fever and neutropenia, oral hairy leukoplakia, aplastic anemia, meningoencephalitis, and posttransplant lymphoproliferative disorder (PTLD). PTLD is due to the lack of EBV-specific T lymphocytes resulting in a polyclonal or monoclonal B cell proliferation, usually of donor origin. Risk factors for PTLD include receipt of allogeneic matched unrelated, mismatched, or T-cell depleted transplants, treatment with antithymocyte globulin, chronic GvHD, and T cell depletion. The incidence of PTLD varies from <1 % among matched related allogeneic HCT recipients to up to 18 % among high-risk patients. Clinical manifestations of PTLD range from an indolent infectious mononucleosis-like syndrome to fulminant disseminated disease, including gastrointestinal tract and CNS involvement.

The prevention of PTLD largely relies upon reduction in immunosuppression, when this is feasible.

Quantitative EBV viral load surveillance should be incorporated into the routine evaluation of patients at high risk for PTLD. Preemptive treatment with a single infusion of rituximab given when EBV viral load exceeds 1000 copies/mL has been advocated as a strategy for prevention of PTLD and clearance of EBV-DNA from the peripheral blood; however, the appropriate threshold value of EBV-DNA copuy number for this intervention has not been well studied.

Management of PTLD includes reduction of immunosuppression, immunotherapy with rituximab, chemotherapy, radiation therapy, or a combination of these. In patients with refractory disease adoptive immunotherapy with EBV-specific cytotoxic T cells, is an option in some centers.

Human herpesvirus- 6

Reactivation of human herpesvirus-6 (HHV-6) has been documented in 40% - 60 % of HSCT recipients, usually within the first month after transplantation. Risk factors associated with HHV-6 viremia are cord blood transplantation, conditioning regimen, administration of anti-CD3 monoclonal antibodies, and acute GvHD. Clinical syndromes associated with HHV-6 reactivation include rash, fever, interstitial pneumonitis, encephalitis, and myelosuppression. In particular, HHV-6 encephalitis appears to be significant, life-threatening complication. Most cases of HHV-6 encephalitis develop in patients receiving transplant from an unrelated donor, particularly cord blood, typically around the time of engraftment. Symptoms are characterized by short-term memory loss and seizures. Magnetic resonance imaging typically shows limbic encephalitis. Prognosis for HHV-6 encephalitis is poor. There is no known form of prophylaxis for HHV-6 infection.

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Pediatric Acute Myeloid Leukemia

Acute myeloid leukaemia (AML) is genetically very heterogenous, which has been described recently in children and adults (Creutzig, Blood 2012, Döhner, Blood, 2010). Today AML has become a curable disease in children and adolescents with survival rates in the range of 70%. However, there are subtypes with a favourable outcome and survival rates in the range of 90% (core binding factor leukemias and acute promyelocytic leukemia [APL]), as well as unfavourable subtypes with survival rates below 40% (mainly those with complex karyotypes or with rare adverse cytogenetics). Therefore, different therapeutic interventions are required which consider more individual risk factors and potential therapeutic targets. New, highly sensitive diagnostic methods including immunophenotyping, cytogenetics and molecular genetics are necessary. Some approaches are different in pediatric and adult AML.

Ursula Creutzig (Medical High School Hannover, Germany) will focus on the differences in the genetic characterization and therapeutic approach in paediatric and adult AML. Gertjan Kaspers (VU University Medical Center, the Netherlands) will speak about the very interesting subtype of acute promyelocytic leukemia and differences in treatment strategies in children compared to adults with APL. Cure in AML is not possible without an adequate supportive care strategy. Thomas Lehrnbecher (Johann Wolfgang Goethe-University, Frankfurt, Germany) will present new informations about supportive care during high intensive chemotherapy for paediatric patients with AML.

We hope that this session will provide you with important and new informations about the diagnosis and treatment of AML in children and adolescents.

Ursula Creutzig, MD

CURRICULUM VITAE

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Prof. Ursula Creutzig was Pediatric Hematologist/Oncologist at the University of Münster until the end of 2011 and is now engaged at the Medical High School in Hannover. Her major interests are the acute myeloid leukemias. Since 1978 she started as coordinator under the chairmanship of Professor G. Schellong and since 1993 she chaired the cooperative therapy studies AML-BFM (Acute Myeloid Leukemia in childhood - Berlin Frankfurt Münster). She is professor for pediatric oncology at the University of Münster. Since 1992 she was also scientific manger of the German Society of Pediatric Oncology and Hematology and since 1997 editor of the national guidelines for pediatric hematology and oncology. She was coordinator of the German Competence Net pediatric hematology and oncology. Prof. Creutzig has published extensively about clinical results in childhood AML.

New Recommendations for the Genetic Characterization and Therapeutic Approach in Paediatric AML*

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Acute myeloid leukemia (AML) occurs in all ages but the frequency increase with age. There are differences in the genetic characterization and therapeutic approach in paediatric and adult AML. Therefore, this paper will focus on the main differences between adults and children with AML and the standards for the management, diagnosis, response assessment, and treatment in childhood AML. These standards have been recently proposed by an international expert panel of the 'International BFM Study Group' AML Committee.1

Childhood AML is a rare and heterogeneous disease (incidence of 0.7 /100.000 children below 15 years). With intensive therapy together with effective supportive care survival rates are now in the range of 70%. There is a broad overlap in the diagnostic and treatment recommendations for AML for children and adults, however, there are also important differences, which require age-specific recommendations.

In 2008, new molecular genetics have been implemented in the new World Health Organization (WHO) classification of AML.[2] These changes, and the definition of new diagnostic and prognostic markers and their associated targeted therapies are included in the recommendations of the international adult and pediatric AML groups.[1,3]

The WHO 2008 classification contains most, but not all, cytogenetic subgroups specific to children. The most important differences in genetic background between children and adults include:[1]

More patients with *de novo* AML and less patients with secondary (MDS-related) AML in children.

Higher proportion of patients with the favourable core-binding factor (CBF) leukaemias t(8;21) and inv(16) in children. More patients with t(9;11) in childhood.

AML (megakaryoblastic) with t(1;22) is typically found in infants.

The adverse karyotypes/mutations t(7;12)(q36;p13)/t(7;12)(q32;p13) and t(5;11)(q35;p15.5)/*NUP98/NSD122* are found in especially in infants and in children with normal karyotype, respectively.[4]

Myeloid proliferations related to Down syndrome are seen in children only. Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder) are found in 5% of the newborns with Down syndrome.[5] There is a 400-fold increased risk for acute megakaryoblastic leukaemia (myeloid leukemia associated with Down syndrome = ML-DS) during the first

4 years of life in children with Down syndrome.

The definition of the subclass of acute leukemias of ambiguous lineage (mixed phenotype acute leukemias – MPALs) is more stringently now. It is based mainly on detailed immunophenotypic criteria or presence of t(9;22)(q34;q11.2)/*BCR-ABL1* or t(v;11q23)/*MLL* rearrangement.[2,6,7]

Overview on the diagnostic recommendations for children[1]

At diagnosis: Morphology, cytochemistry, immunophenotyping, molecular- and cytogenetics of the bone marrow aspirate are required. In the event of a dry tap or of a suspected underlying myelodysplastic syndrome (MDS), a bone marrow trephine biopsy has to be performed in addition. All patients should have a cerebral spinal fluid examination for evidence of CNS involvement (which should be postponed in case of APL or hyperleukocytosis). To differentiate between AML with a low blast count and MDS, serial bone marrow aspirates and trephine biopsies are required, as well as detailed cytogenetic analyses.

Immunophenotyping: The mandatory minimal panel required to fulfill WHO and EGIL criteria for AML includes CD34, CD117, CD11b, CD11c, CD13, CD14, CD15, CD33, CD64, CD65, iMPO, i-lysozyme, CD41, CD61 and for MPAL: CD19, iCD79a, iCD22, CD10, iCD3.

Fusion genes: Routine evaluation should include the evaluation of prognostically relevant genetic aberrations by cytogenetics/FISH including at least the following fusion genes at diagnosis: *RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA* and *MLL* rearrangements. Other rare fusion genes are mainly seen in adverse risk patients.

Furthermore, the evaluation of a prognostically relevant and potentially targetably selected set of molecular genetic markers is recommended: *FLT3*-ITD*, WT1, C-KIT, CEBPA* [double mutation], *NPM1* and further specific MLL-abnormalities with favorable or very poor prognosis e.g. *MLL-(AF1Q, AF6, AF10)*.

Minimal residual disease (MRD): Measurements should be incorporated in the context of clinical trials and used, if appropriate, for treatment stratification.

Treatment:[1]

Treatment of childhood AML requires an intensive anthracycline- and cytarabine-based therapy employing at least 4 to 5 courses. Children with AML should be treated within controlled clinical trials.

One or two courses of induction therapy comprising 3 days of an anthracycline and 7–10 days of cytarabine should be applied.

Haematopoietic stem cell transplantation (HSCT): Auto-HSCT is not recommended for children with AML in 1st remission (CR). Allo-HSCT in 1st CR is not beneficial in childhood AML with favorable risk factors. In other risk groups, the benefit of allo-HSCT must be balanced against toxicity. Allo-HSCT in 2nd CR is generally considered.[8]

Central nervous system (CNS) treatment needs to consist of intrathecal treatments with cytarabine or methotrexate or in combination with steroids, although the optimal number of administrations is unknown.

G-CSF cannot be recommended as routine practice in either adults and children, as the data are conflicting, and recent studies raise doubt about the beneficial role of G-CSF.[9-11]

Down syndrome: Newborns with Down syndrome who have transient leukemia with severe clinical symptoms secondary to leukemic infiltrates should receive supportive care and consideration should be given to the use of low-dose cytarabine.[12]

Myeloid leukaemia in Down syndrome (ML-DS): These patients should receive reduced-intensive chemotherapy and particular attention should be given to the high risk of severe infections. HSCT is not indicated in 1st CR in ML-DS.[13]

Relapsed AML: Children with relapsed AML should be treated with reinduction chemotherapy followed by allo-HSCT.

Prevention of early death: For patients with initial hyperleukocytosis and symptomatic coagulopathy and/or leukostasis, emergency strategies should be initiated to reduce the risk of fatal hemorrhage and leukostasis.

*The recommendations given here are elucidated in detail in the BLOOD paper: *Creutzig U et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel, on behalf of the AML Committee of the International BFM Study Group. Blood. 2012;120:3187-320*

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CURRICULUM VITAE

Biosketch Gertjan J.L. Kaspers, MD PhD

Professor Gertjan Kaspers (born March 22, 1963, married and 2 children) became pediatric oncologist/haematologist in 2000, after being trained in several hospitals including GOSH (London, UK), AMC and VU University Medical Center (VUmc; Amsterdam, NL) with a fellowship from the Dutch Cancer Society. Since 2000, he has been a staff member of the Department of Pediatrics at the VUmc in Amsterdam, the Netherlands. He chairs the Division of Pediatric Oncology/Hematology since 2002 and has been a full Professor of this division since 2006. He was Deputy Chair of the Department of Pediatrics from August 2010 until end of December 2012. From January 2013 onwards, he is one of the medical directors of Princess Máxima Center for Pediatric Oncology, the novel Dutch national center for children with cancer, that will open in 2016. His main clinical and translational research focusses on leukemia, and at a national level also at brain (stem) tumors. He (co-) chaired and chairs several clinical studies on innovative treatment of childhood leukaemia, with a focus on acute myeloid leukemia, including acute promyelocytic leukemia. He is a member of several national and international organisations, including the International Society of Pediatric Oncology, European Haematology Association, American Association for Cancer Research and American Society of Hematology. Within the Netherlands, he is a member of the Supervisory Board of the Dutch Childhood Oncology Group (DCOG), and chairman of the Disease Committee "Myeloid Malignancies". Within the DCOG, he chairs the protocol committees "Relapsed AML 2001/01", "ICC APL Study 01", and "newly diagnosed AML". He is chairman of the Relapsed AML Working Group of the International BFM Study Group since 1999, and chaired the AML committee of that group from 1999-2007. He (co-) edited a series of books on Drug Resistance in Leukemia and Lymphoma, and is first editor of a recent book titled "Innovative Leukemia and Lymphoma Therapy". He (co-) authored more than 200 international publications on pediatric oncology. Finally, he is involved in several "outreach" projects, especially with University Hospitals in Eldoret (Kenya), Blantyre (Malawi) and Yogyakarta and Manado (Indonesia), aiming at improved outcome for children with cancer in low-income countries.

Amsterdam, February 2013

Differences in Treatment Between Pediatric and Adult Acute Promyelocytic Leukemia

Gertjan J.L. Kaspers

Pediatric Oncology/Hematology

VU University Medical Center, Amsterdam, The Netherlands

Acute leukemia is the most frequent type of cancer in children, with acute myeloid leukemia (AML) comprising up to 20% of cases. Acute promyelocytic leukemia (APL) contributes to 5-30% of the latter patients, with the higher incidences observed in populations from Hispanic and Mediterranean origin. The median age at presentation is similar to that of other AML subtypes (7-9 years), but APL has been reported in even the first year of life. It can arise de novo or be therapy related (t-APL). The characteristics and outcome of t-APL appear similar to those of de novo APL (Beaumont et al. 2003; Gregory Jr & Feusner, 2003).

APL is characterized by chromosomal rearrangements of 17q21 involving the gene encoding the Retinoic Acid Receptor Alpha (RARα), which is most commonly fused to the PML gene (ProMyelocytic Leukemia) as a result of the t(15;17)(q22;q21) translocation. In a minority of cases (<5%), RARα is fused to an alternative partner, which in the pediatric setting is most commonly nucleophosmin (NPM1) resulting from the t(5;17)(q35;q21) translocation. This subtype and that involving NuMA as a result of t(11;17)(q13;q21) are sensitive to retinoic acid; whereas APL involving PLZF and STAT5b as a result of t(11;17)(q23;q21) and interstitial deletion of chromosome 17 respectively, are resistant to all-trans retinoic acid (ATRA). These ATRA resistant subtypes of APL are extremely rare in children, and should be treated as a regular type of AML (Mistry et al. 2003, Grimwade et al. 2000).

While the outcome of APL patients with the PML-RARα fusion treated with extended courses of ATRA in combination with anthracycline–based chemotherapy is generally favorable, pediatric patients more commonly present with hyperleukocytosis, as compared to their adult counterparts. Thus, approximately 35-40% of children with APL fall within a high risk group defined by a presenting WBC ≥10 x 10^9/L, which is associated with more often M3v morphology and presence of FLT3 length mutations, and which predicts for poorer outcome. The latter is due both to an increased risk of induction death, particularly as a result of hemorrhage and a higher risk of the APL differentiation syndrome, as well as a significantly higher rate of relapse (Gregory Jr & Feusner 2003, Tallman et al. 2002). Using ATRA and anthracycline–based chemotherapy protocols followed by maintenance with ATRA, 6-MP and methotrexate, relapse rates for patients with a WBC <10 x 10^9/L at diagnosis are typically 10% or less, while rates may exceed

20% for patients with a WBC ≥10 x 10^9/L (Biondi et al. 1994; de Botton et al. 2004; Ortega et al. 2005). Several more recent reports have described the treatment of pediatric AML, the two largest by Testi et al. (2005) and Creutzig et al. (2010). These and other studies showed or at least suggested that ATRA is beneficial in all phases, maintenance treatment is beneficial, and the cumulative dose of anthracyclines can be reduced to less than 400 mg/m^2 without an excess of relapses.

Treatment of pediatric APL in the last 5-10 years, based on the previously mentioned studies, has been done in most Western countries according to International Consortium Childhood (ICC) APL Study 01, or the concurrent protocol of the Children's Oncology Group (COG). Both protocols can be characterised by a risk-group adapted chemotherapy, ATRA at induction, consolidation and maintenance, limited use of anthracyclines, use of intermediate dose cytarabine, prophylactic intrathecal cytarabine, minimal residual disease (MRD) monitoring during the two years of maintenance treatment and the first year thereafter, and preemptive therapy for molecular relapse. The COG protocol however prescribed one additional course of arsenic trioxide (ATO). Results are being awaited, but overall survival seems excellent, and children dying because of refractory or relapsed disease rare. In adults, different protocols are being used, which sometimes apply a very high cumulative dose of anthracyclines on the one hand, but also a combination of ATRA and ATO without any chemotherapy on the other hand. Especially in China and other Asian countries, it also seems that single-agent ATO is being used.

Some differences in the treatment and its side-effects between pediatric and adult APL will be discussed below.

1. Dose and administration of ATRA

It seems that children are more susceptible to the side-effects of ATRA. Therefore, the daily dose of ATRA that is being used in children is 25 mg/m^2, which is much lower than the 45 mg/m^2 which is typically used in adults. The studies reported by Testi et al. (2005) and Creutzig et al. (2010) reported excellent outcome with this reduced dose of ATRA. Since children are more likely not to be able or willing to swallow the capsules containing ATRA, it is important to know that the capsules can be opened and the liquid be given to young children with soft ice cream or yoghurt. There are also guidelines to administer ATRA through nasogastric tube, however this mode of administration should only be used in exceptional circumstances. Alternatively, the use of liposomal ATRA can be considered. Manipulation of ATRA capsules should be done carefully because ATRA is teratogeneic.

2. Side-effects of ATRA

The type of side-effects is essentially the same in children and adults, however the incidence seems to be higher in the pediatric population. This is especially true for headache and pseudotumor cerebri. Moreover, since the incidence of high-risk APL is higher in children, that is also true for the ATRA syndrome, also known as the retinoic acid or APL differentiation syndrome.

3. Use of anthracyclines

Children are more susceptible to anthracycline-induced cardiotoxicity, a late effect of which the risk increases with higher cumulative doses. There is not really a safe dose, but the risk increases above cumulative doses of 300 mg/m^2 and becomes a real issue with doses above 450 mg/m^2. In many protocols for adult APL and in some protocols for pediatric APL, these cumulative doses are even above 600 mg/m^2. This justifies the development of protocols specific for the pediatric population, among other reasons to do so. It should be emphasized that acute cardiotoxicity is associated with an increased risk for late cardiotoxicity, and that iv push of anthracyclines seems to be associated with a higher risk of acute cardiotoxicity. This can be explained by higher peak plasma levels with iv push. Therefore, in children anthracyclines must be given as an iv infusion of at least one hour.

4. Use of cytarabine

In several protocols for adults and also in some protocols for children, cytarabine is not being used. There are two reasons why using this drug in pediatric APL is justified. First, the reduced doses of anthracyclines used in pediatric protocols probably should be compensated by other therapy, and cytarabine is an obvious option in view of its activity in AML. Second, it has been demonstrated in adults that cytarabine improved outcome in APL (Ades et al. 2006).

5. Outcome

Since children have a higher incidence of high-risk APL, the relapse rate is possibly somewhat higher. However, overall survival in most recent studies in both adults and children is about 90%.

Perspectives

In view of the high rate of overall survival, it is attempting to explore possibilities to omit toxic parts of chemotherapy. Anthracyclines and (prolonged) maintenance therapy are obvious examples. Reports from China and other countries in that region of the world on cure by ATRA plus ATO are encouraging. Recently, Lo-Coco et al. reported at the Annual Meeting of the American Society of Hematology (2012), that in more than 100 adult patients with standard-risk APL, treatment with ATRA plus ATO was at least as effective as conventional chemotherapy plus ATRA, albeit it with short-term follow-up. Together with the likely renewed availability of gemtuzumab ozogamicin in the future, it may be possible to apply treatment to both children and adults that does not contain conventional chemotherapy. That would likely lead to less toxic treatment on the short- and long-term, although possible late effects of ATRA and especially ATO must be investigated carefully.

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CURRICULUM VITAE

Thomas Lehrnbecher is Professor of Pediatrics and works since 2001 as a Pediatric Hematologist and Oncologist in the Johann Wolfgang Goethe-University, Frankfurt, Germany. He started his career in the Children´s Hospital in Würzburg, followed by a fellowship at the Pediatric Oncology Branch of the National Cancer Institute, USA, where he trained in infectious diseases in immunocompromised children. The main areas of Dr.Lehrnbecher´s research are invasive fungal infections, genetic markers of susceptibility for infections, and adoptive immunotherapy. He has published his work in journals such as *Clinical Infectious Diseases*, *Journal of Infectious Diseases*, *Blood, Journal of Clinical Oncology and The Lancet Oncology.* Dr.Lehrnbecher currently chairs the sections "Infection in the immunocompromised child" of the German Society of Pediatric Infectious Diseases and "Supportive Care" of the International Society of Pediatric Oncology.

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• since 2001	Consultant, Department of Pediatric Hematology and Oncology, Johann Wolfgang Goethe-University, Frankfurt, Germany (Head: Prof. Dr. T. Klingebiel)
• 1999-2000	Consultant, Children´s Hospital, University of Würzburg, Germany
• 1996-1999	Post-doctoral fellow, laboratory Stephen Chanock, MD Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
• 1990-1995	Fellow, Children´s Hospital, University of Würzburg, Germany (Head: Prof. Dr. H. Bartels)
• 1988-1990	Fellow, Institute of Biochemistry, University of Würzburg, Germany (Head: Prof. Dr. W. Sebald)
Education and training	
• 2007	Board exam "Pediatric Hematology and Oncology"
• 2005	Diploma of Pediatric Infectious Diseases (German Society for Pediatric Infectious Diseases)
• 2005	Professorship, Johann Wolfgang Goethe-University, Frankfurt, Germany
• 1996	Board exam for general pediatrics
Awards	
• 2011	Nesbit Award for Clinical Science
• 2006	Oldtimermarkt-Medienpreis for innovative therapy
MEMBERSHIP and AFFILIATION	• German Society of Pediatrics • German Society of Pediatric Oncology and Hematology (GPOH) • German Society of Pediatric Infectious Diseases (DGPI) • Pau Ehrlich Society (PEG) • German Society of Mycology (DMycG) • International Society of Pediatric Oncology (SIOP) • Histiocyte Society • • Chairman of the committee „Infections in the Immunocompromised Child" of the German Society of Pediatric Infectious Diseases • Deputy Section Head „Infections in Cancer Patients" of the Paul-Ehrlich-Society • Infectious Disease Working Party of the European Group for Blood and Marrow Transplantation • Chairman of the working party "Supportive Care" of the International Society of Pediatric Oncology • Chairman for Germany of the International Study on Langerhans • cell Histiocytosis • Committee of clinical trials in children with AML (AML-BFM trials) • Committee of clinical trials in children with Hodgkin Disease (HD-BFM-trials)

Supportive Care Strategies for Pediatric Patients with Acute Myeloid Leukemia

Thomas Lehrnbecher

Pediatric Hematology and Oncology, Johann Wolfgang Goethe-University, Frankfurt, Germany

Therapy for acute myelogenous leukemia (AML) is one of the most intensive treatment modalities in pediatric oncology, and most children experience one or more infectious complications during treatment. Non-pharmacological anti-infective measures such as restriction of social contacts and food have never been tested in larger randomized trials, and consequently vary widely between the centers. Although the use of the hematopoietic growth factor G-CSF results in a significant decrease of the duration of neutropenia, a randomized trial in pediatric AML failed to demonstrate an impact on the incidence of febrile neutropenia or microbiologically documented infections. The cumulative incidence of bacteremia with viridans group streptococci is approximately 40% and is associated with use of high-dose ARA-C. Most experts recommend high awareness and to consider to include glycopeptides in the first-line empirical therapy in these patients. Current data are insufficient to support routine vancomycin prophylaxis in this setting. Although some data suggest a potential benefit of fluoroquinolones as antibiotic prophylaxis, the prophylactic use of these compounds remains controversial, since the use of fluoroquinolones results in an increase in antimicrobial resistance and the compounds are not licensed for use in children. Due to a high incidence of invasive fungal infections in children with AML (>10%), antifungal prophylaxis is generally recommended. Since the dosage of posaconazole, which significantly reduced the incidence of aspergillosis and mortality in adults with AML, has not yet been defined for young children, itraconazole, voriconazole, micafungin, or liposomal amphotericin B may be used instead. However, these compounds have limitations, such as variable absorption or multiple potential drug-drug interactions, or can only be administered intravenously.

ICLLM 2013

Myelodysplastic Syndromes

"Dr Deeg will present an update on hematopoietic cell transplantation in patients with MDS. He will summarize recent developments of conditioning regimens and analyze the impact of cytogenetics on transplant outcome. He will also discuss the importance of clonal heterogeneity and clonal evolution as a feature of relapse of MDS after transplantation, and options for post-transplant management of relapse."

"Good afternoon. We are presenting now a session on Myelodysplastic Syndromes (MDS), divided into three presentations, one, by Dr Boultwood, on molecular aspects of the pathogenesis of MDS, one by Dr Bowen, on non-transplant management of MDS, and one by Dr Deeg , on the indications for and the results with transplantation for MDS. I hope that at the conclusion of our session you will have an up-to-date overview of many aspects of the rapidly evolving field of basic and clinical research in MDS".

Curriculum Vitae

1. Qualifications and Career History

Name and date of birth	Jacqueline Boultwood, BSc (Hons), PhD. d.o.b 11/7/62
Address	Leukaemia and Lymphoma Research Molecular Haematology Unit, Nuffield Department of Clinical Laboratory Sciences, Oxford University, John Radcliffe Hospital, Headington, Oxford, OX3 9DU.
Nationality	British
Higher Education	
1980 - 1983	BSc (Hons) Zoology (2:1), University of Swansea.
1983 - 1987	PhD: Detection of differentiation specific and oncogene mRNAs in human tumour cells and tissues. CRC Thyroid Tumour Biology Research Group, Department of Pathology, University of Wales College of Medicine, Cardiff.

Job Description

I am Director (and Principal Investigator) of the LLR Molecular Haematology Unit. I have held the title of University Reader in Molecular Haematology since 2004. I am responsible for the scientific direction of our research group (including the LLR Unit) and for the supervision of members of staff. My current funding employs a total of six members of staff. These comprise the following three LLR Specialist Programme staff members: Dr Andrea Pellagatti (Senior Research Associate), Dr Bon Ham Yip (Postdoctoral Research Assistant), Mr Martin Attwood (Research Assistant), and the following members of staff employed via project grants: Dr Hamid Dolatshad (Postdoctoral Research Assistant), Ms Marta Fernandez-Mercado (Research Assistant) and Mr Chaitanya Vuppusetty (Research Assistant). An additional Research Assistant will be appointed later this year (EU FP7 funded). I also supervise Hannah Smith, St Hilda's College Oxford, a DPhil student.

Current Appointment

October 2004 - to date	University Reader in Molecular Haematology, Nuffield Department of Clinical Laboratory Sciences, LRF Molecular Haematology Unit at the University of Oxford.
April 2003- December 2011	Co-director of LRF Molecular Haematology Unit at the University of Oxford. Salary scale: Grade 10S Grade 10 Stage 09.
January 2012 – to date	Director of LLR Molecular Haematology Unit at the University of Oxford. Salary scale: Grade 10S Grade 10 Stage 09.

Immediate Past Appointments

November1987-November 1988	Member of Scientific Staff, LRF Leukaemogenesis Laboratory, MRC Radiology Unit, Chilton, Didcot, Oxon.
November 1988-March 1995	Postdoctoral Research Assistant (RS1A), LRF Molecular Haematology Unit at the University of Oxford.
March 1995-1998	Senior Postdoctoral Research Assistant (RSII), LRF Molecular Haematology Unit at the University of Oxford.
July 1995 – April 2003	Deputy Director of LRF Molecular Haematology Unit at the University of Oxford.
January 1998- October 2004	University Research Lecturer, Nuffield Department of Clinical Laboratory Sciences, LRF Molecular Haematology Unit at the University of Oxford.

2. Advanced Study and Research, including publications and grants etc.
i. Research achievements of the LLR Molecular Haematology Unit at Oxford University
Introduction: Research Interests of the LLR Unit

The LLR Molecular Haematology Unit was established in the late 1980s with the study of the molecular mechanisms involved in disease initiation and progression in the myelodysplastic syndromes (MDS) as its central objective. The MDS comprise a group of clonal myeloid disorders showing frequent evolution to AML. The cytogenetic analyses of MDS are characterised by the loss of genetic material and our studies have focused on the investigation of patients with loss of the long arm of chromosome 5 [del(5q)], the most common cytogenetic abnormality found in MDS. I identified the commonly deleted region (CDR) of the 5q- syndrome and demonstrated that patients with the 5q- syndrome show haploinsufficiency of the ribosomal gene RPS14. We subsequently showed that p53 activation (secondary to haploinsufficiency of RPS14) underlies the anaemia in the 5q- syndrome.

Our work has been instrumental in the elucidation of the molecular basis of the 5q- syndrome and in the determination of the disease mechanism that underlies this disorder. We are currently performing a series of translational studies concerning the use of p53 inhibitors and enhancers of translation in cultured erythroblasts from patients with the 5q- syndrome. It is widely acknowledged that we are one of the leading groups in the study of the 5q- syndrome and I have published two invited reviews on this subject in the journal Blood.

Several years ago I initiated a major project concerning global gene expression profiling in MDS that has yielded valuable insights into the molecular pathogenesis of MDS, and has identified new prognostic markers for this disease. Our array-based studies of MDS have proven most fruitful, and I have established an international reputation in this field.

The Chronic Myeloid Leukaemia group of the International Cancer genome Consortium, of which I am a member, is using whole-exome sequencing to identify somatically acquired point mutations in patients with MDS. We have recently reported frequent mutation of the splicing factor SF3B1 in patients with MDS with particular enrichment in patients whose disease was characterised by ring sideroblasts. Our results provided the first evidence that alterations in the major splicing components play a critical role in the pathogenesis of MDS. We are currently investigating the effects of SF3B1 mutations on global gene expression and RNA splicing in MDS.
Recent Research Achievements: 2009-2012

a) Molecular pathogenesis of MDS, including the 5q- syndrome
A p53-dependent mechanism underlies macrocytic anaemia in a mouse model of human 5q- syndrome and in the human 5q- syndrome

Our group has been working in close collaboration with Dr McKenzie at the LMB, Cambridge over several years to generate a mouse model of the 5q- syndrome based upon the CDR that we had defined in the human. We recently created a mouse model for the human 5q- syndrome that displays the main features of the human disease, using large-scale chromosomal engineering.80 The Cd74-Nid67 interval (mouse chromosome 18) deleted in this mouse model is syntenic with the CDR of the human 5q- syndrome43 and contains the RPS14 gene. Haploinsufficiency of the Cd74-Nid67 interval caused macrocytic anaemia, prominent erythroid dysplasia and monolobulated megakaryocytes. These effects were associated with defective bone marrow progenitor development, the appearance of bone marrow cells expressing high amounts of the tumour suppressor p53 and increased bone marrow cell apoptosis. Notably, intercrossing the Cd74-Nid67-deleted mice with p53-deficient mice completely rescued the progenitor cell defect, restoring haematopoietic stem cell bone marrow populations. This mouse model supports a critical role for RPS14 in the pathogenesis of the 5q- syndrome and is groundbreaking in that it suggests that a p53-dependent mechanism underlies the pathophysiology of this disorder.80 This work was published in Nature Medicine in 2010.

We have since shown activation of p53 and deregulation of the p53 pathway (secondary to haploinsufficiency of RPS14) in the human 5q- syndrome.82 It is known that ribosomal stress resulting from reduced expression of key ribosomal proteins leads to activation of the p53 pathway, with consequent increased apoptosis. Our recent data80,82 strongly suggests that this mechanism underlies the anaemia that characterises the 5q- syndrome, thus providing a potential new target for therapeutic intervention. This work was published in Blood. 82

The effects of the translation enhancer L-leucine on RPS14-deficient erythroid cells

We and others have previously shown that the 5q- syndrome is a disorder of aberrant ribosome gene expression and biogenesis.70 It is well

recognised that defective ribosome biogenesis can result in a reduction in the efficiency of mRNA translation. We have recently shown that RPS14-deficient erythroblasts and cultured erythroblasts from MDS patients with the del(5q), show reduced levels of mRNA translation, and that the translation enhancer L-leucine increased the erythroid differentiation, cell proliferation and translation efficiency of these cells. It is probable that translation insufficiency contributes to the erythroid defect observed in the 5q- syndrome and these data support the development of an exciting new strategy for the treatment of MDS with the del(5q) based on improving translation efficiency by L-leucine or other agents.107 We published this work in Leukemia. 107

b) Gene expression profiling of CD34+ cells in MDS using microarray technology

Deregulated gene expression pathways in myelodysplastic syndrome haematopoietic stem cells

We have performed global gene expression profiling and pathway analysis on the CD34+ cells of 183 MDS patients.81 Among the most significantly deregulated gene pathways in early MDS are immunodeficiency, apoptosis and chemokine signalling, whereas advanced MDS is characterised by deregulation of the DNA damage response, the cell cycle and checkpoint pathways. Particular karyotypic abnormalities in MDS show different haematological or clinical features, and gene expression profiling is a method to explore this relationship. We have demonstrated that patients with the major karyotypic abormalities found in MDS: trisomy 8, –7/del(7q) and del(5q,) show deregulation of distinct gene pathways.81 The deregulated pathways identified give new insights into the molecular pathogenesis of MDS thereby providing new targets for therapeutic intervention.81 We published this work in Leukemia. 81

Identification of gene expression based prognostic markers in the hematopoietic stem cells of patients with myelodysplastic syndromes

We have recently identified a new valuable gene expression profiling-based signature for assessing prognosis in MDS. We suggest that gene expression profiling-based signatures correlating with clinical outcome may significantly contribute to a refined risk classification of MDS. A paper on this work is under revision in the Journal of Clinical Oncology.109

c) Mutation analysis of MDS and other myeloid malignancies

Frequent mutation of the polycomb-associated gene ASXL1 in myeloid malignancies: MDS, AML and CML

We have identified frequent mutation of the chromatin remodeller ASXL1 in myeloid malignancies. ASXL1 mutations were observed in 62/300 patients (21%). The mutation frequency is high in late MDS (31%).83 Gene expression profiling showed that the most significantly deregulated pathway in patients with mutation of ASXL1 was retinoic acid receptor activation.83 We have recently shown that mutation of ASXL1 is also a frequent event in chronic myeloid leukaemia.86 These findings suggest that ASXL1 may function as an important new tumour suppressor gene in a wide range of malignancies of the myeloid lineage, including MDS, AML and CML. Moreover, our study shows that ASXL1 mutations are the commonest known mutations in advanced MDS, suggesting an important role in disease progression. We published this work in Leukemia. 83, 86

Inactivating mutations of the histone methyltransferase EZH2 in myeloid disorders

Abnormalities of chromosome 7q are common in myeloid malignancies but no specific target genes have been identified. I collaborated with Professor Nick Cross, Salisbury, in a SNP array-based study that resulted in the identification of inactivating mutations of the histone methyltransferase EZH2 in a range of myeloid disorders including MDS. Homozygous EZH2 mutations were found in 9 of 12 cases with 7q acquired UPD. Screening of a total of 614 cases with myeloid disorders revealed 51 EZH2 mutations in 42 cases, most commonly in MDS/MPD (27/219; 16%) and myelofibrosis (4/30; 13%).87 These data suggest that EZH2 acts as a tumour suppressor in myeloid malignancies. We published this work in Nature Genetics. 87

SETBP1 mutations in atypical chronic myeloid leukemia

In a collaborative study using whole-exome sequencing we recently identified a recurrent mutation of SETBP1 in 25% of patients with atypical CML (aCML). Mutated SETBP1 represents a novel type of oncogene which is specifically present in aCML and closely related diseases. These data allow a better understanding of the molecular pathogenesis of this disease and provide evidence that SETBP1 mutation might be a new biomarker for future diagnosis and classification of aCML. A paper on this work is under revision in Nature Genetics. 108

Frequent mutation of the splicing factor SF3B1 in MDS

The Chronic Myeloid Leukaemia group of the International Cancer genome Consortium, of which I am a member, has identified frequent mutation of the SF3B1 gene in MDS using next generation sequencing.95 SF3B1 encodes a core component of the RNA splicing machinery. Approximately 28% of all MDS patient harbor mutations of SF3B1, and thus this represents the most common gene mutation identified in MDS.95,96 Mutations were found in over 70 % of patients whose disease is characterised by ringed sideroblasts, including both RARS and RCMD-RS.95,96 The close association between SF3B1 mutation and ring sideroblasts is consistent with a causal relationship, and makes this the first gene to be strongly associated with a specific feature of MDS. We showed that SF3B1 mutations are independent predictors of favourable clinical outcome and their incorporation into stratification systems might improve risk assessment in MDS.96

The discovery of SF3B1 mutation is a major advance in MDS research and may result in the development of new treatment options for this disorder. Others have recently identified mutations in other splicing factors in MDS (in 45-85% of all patients) and it is now clear that genetic alterations of the major splicing components play a key role in the pathogenesis of MDS. This work was published in the N Engl J Med and Blood. 95,96

A novel BRCA1-mRNA splicing complex required for maintenance of genomic stability is mutated in multiple cancer types.

We have identified a novel, DNA damage induced, BRCA1 complex containing BCLAF1, SF3B1 and other key components of the splicing machinery. These data suggests that regulation of mRNA splicing by the BRCA1-mRNA splicing complex may play an important role in the development of multiple cancer types. A paper based on this work is under revision in Nature.110

Targeted gene sequencing as a front-line diagnostic test for myelodysplastic syndromes

As part of the International Cancer genome Consortium, we sequenced coding regions from 111 genes implicated in myeloid cancers across 738 patients with MDS using a high-throughput, low-cost protocol. Targeted gene sequencing identified oncogenic mutations or copy number changes in three quarters of MDS patients and this work greatly illuminates the genomic landscape of MDS. Since this can be performed for low cost on DNA from peripheral blood, there is considerable potential to develop such approaches as a front-line diagnostic test for MDS. A paper based on this work has been submitted to the N Engl J Med.

ii. Publications

I have published 107 papers in peer-reviewed journals and I am the first or last author of 56 of these. My h-index is 32. My publications in prestigious international journals including, Nature Genetics, Nature Medicine, NEJM, PNAS, Blood and Leukemia, illustrate my major interest and achievement in MDS genetics over the years. I have provided the citation for some key papers.

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105. Will B, Zhou L, Vogler TO, Ben-Neriah S, Schinke C, Tamari R, Yu Y, Bhagat TD, Bhattacharyya S, Barreyro L, Heuck C, Mo Y, Parekh S, McMahon C, Pellagatti A, Boultwood J, Montagna C, Silverman L, Maciejewski J, Greally JM, Ye BH, List AF, Steidl C, Steidl U, Verma A. (2012) Stem and progenitor cells in myelodysplastic syndromes show aberrant stage-specific expansion and harbor genetic and epigenetic alterations. Blood 120(10):2076-86.
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110. Papaemmanuil E, Schnittger S, Kim D-W, Boultwood J, Rossi F, Gaipa G, De Martini GP, Francia di Celle P, Jang HG, Fantin VR, Bignell G, Magistroni V, Haferlach T, Pogliani EM, Campbell P, Chase AJ, Tapper WJ, Cross NCP, Gambacorti-Passerini C. SETBP1 mutations in atypical chronic myeloid leukemia. Nature Genetics (under revision).
111. Pellagatti A, Benner A, Mills KI, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, Jädersten M, Verma A, McDonald E-J, Killick S, Hellström-Lindberg E, Bullinger L, Wainscoat JS, Boultwood J. Identification of gene expression based prognostic markers in the hematopoietic stem cells of patients with myelodysplastic syndromes. Journal of Clinical Oncology (under revision)
112. Savage KI, Gorski JJ, Barros EM, Irwin GW, McDade SS, Manti L, Pellagatti A, McCance DJ, McCluggage WG, Schettino G, Salto-Tellez M, Boultwood J, Richard DJ, Harkin DP. A novel BRCA1-mRNA splicing complex required for maintenance of genomic stability is mutated in multiple cancer types. Nature (under revision)

iii. Books

1. Boultwood, J. (ed). Gene isolation and mapping protocols. (1996) Methods in Molecular Biology. Totowa, N.J., USA, Humana Press.
2. Boultwood, J., and Fidler, C.(ed). Molecular analysis of cancer. (2001) Methods in Molecular Medicine. Totowa, N.J., USA, Humana Press.

Book Chapters

1.Boultwood, J. (1994). Physical mapping of the human genome by pulsed field gel electrophoresis, in Harwood A (ed): Methods in Molecular Biology. Totowa, NJ, Humana Press.

2. Boultwood, J. (1996). Molecular diagnosis of the 5q- chromosome in malignant myeloid disorders, in Cotter F (ed): Methods in Molecular Biology. Totowa, NJ, Humana Press.
3. Fidler, C., Boultwood, J. (1996). Isolation of cDNAs using the YAC screen method, in Boultwood J (ed): Methods in Molecular Biology. Totowa, NJ, Humana Press.
4. Boultwood, J. (1998) Genome mapping, in Walker, J. and Rapley, R. (eds.): Methods in Molecular Biology. Totowa, N.J., Humana Press.
5. Boultwood, J., and Wainscoat, J.S. (2005) Molecular pathogenesis of the myelodysplastic syndromes in Provan D and Gribben J (eds) Molecular Haematology. Blackwells Science, Oxford.
6. Boultwood, J., and Wainscoat, J.S. (2008) Molecular analysis of the 5q- syndrome in Steensma D and Bennet J (eds) Myelodysplastic syndromes: Pathobiology and Clinical Management. Informa Healthcare, New York, USA.

iv. Invited Commentaries
1. Boultwood, J, Wainscoat, JS. (2004) The 5q- syndrome. Haematologia, 89: 257.
2. Boultwood J, Wainscoat JS. (2005) High-mobility group A (HMGA) genes: from solid to liquid tumours? Leukemia, 19: 195-6.
3. Boultwood, J, Wainscoat JS. (2008) The molecular basis of the 5q- syndrome. Guest Editorial, MDS News (The MDS Foundation Newsletter).

v. Grants held during past five years
The total grant income held
The total grant income I have held (either as main grant holder or co-applicant) at Oxford University over the past 5 years is in excess of £7 million pounds. I wrote and am the main grant holder of all the grants shown below in which my name is shown in bold.
1. Dr A Pellagatti, Dr J Boultwood
FP7-HEALTH-2012-INNOVATION-1 Proposal title: Early warning signals of ageing in human stem cells and age-related disorders, Coordinator Dr Anne-Claude Gavin, EC contribution requested for Oxford: Euro 549,623. 5 years (January 2013-December 2017)
2. Dr J Boultwood, Dr A Pellagatti, Professor JS Wainscoat
LLR project grant: SF3B1 mutation and pathogenesis of the myelodysplastic syndromes: RNA splicing and gene expression analysis (February 2012-January 2015) £171,322
3. Dr J Boultwood (PI) , (Director of LLR Unit)
Leukaemia and Lymphoma Research (formally LRF) Molecular Haematology Unit Specialist Programme Grant, University of Oxford. 3 years (March 2011-March 2014) £850,000.
4. Dr J Boultwood, Professor JS Wainscoat (Co-Directors and PIs of LRF Unit)
LRF Molecular Haematology Unit Specialist Programme Grant, University of Oxford. £1 million. (March 2006-March 2009) (and term extended to March 2011 with additional £670,000 funding). Total 5 years
5. Professor D Roberts, Professor D Anstee, Dr J Boultwood, Professor D Collett, Professor A Nandi, Dr A Nathwani, Dr W H Ouwehand, K Robson, Professor JS Wainscoat.
National Institute for Health Research (NIHR) Programme Grant: Erythropoiesis in Health and Disease. 5 years (June 2010-June 2015) £3.49 million.
6. Dr ANJ McKenzie, Professor Wainscoat, Dr J Boultwood
LRF Project Grant: Investigation of Rps14, microRNA miR-145,p53 and clonal survival in a novel mouse model of 5q-syndrome. 3 years, (September 2010- September 2013) £163,450.
7. Dr J Boultwood, Andrea Pellagatti, Paresh Vyas, Professor JS Wainscoat
KKLF Project grant: An investigation of the role of ASXL1 in the myelodysplastic syndromes and acute myeloid leukaemia. 18 months (August 2010-February 2012) £87,912.
8. Dr J Boultwood, Andrea Pellagatti, Paresh Vyas, Professor JS Wainscoat
LRF Project grant: An investigation into the role of ABCB7 in normal and RARS erythropoiesis using a lentiviral-based approach.3 years (November 2009-November 2012) £186,426.
9. Dr J Boultwood, Dr C Fidler, Professor JS Wainscoat
KKLF Project grant: Identification of DNA copy number changes and acquired UPD associated with disease evolution in CML using SNP array analysis. 2 years (March 2007-March 2009) £94,000.
10. Dr J Boultwood, Professor JS Wainscoat, Professor M Cazzola, Professor E Hellstrom Lindberg
LRF Project grant: An investigation of the molecular basis of pure sideroblastic anaemia using SNP and expression array analysis. 3 years (November 2006-November 2009) £135,000.
11. Professor JS Wainscoat, Dr C Fidler, Dr J Boultwood
LRF Project grant: Acquired uniparental disomy in the 5q- syndrome and MDS. 3 years (June 2006-June 2009) £150,000.
12. Dr CSR Hatton, Professor D Y Mason, Dr J Boultwood, Professor JS Wainscoat
Julian Starmer Smith Lymphoma Fund Project grant: Gene expression in lymphoid tumours. 3 years (March 2004-March 2007) £130,639.
13. Dr A Peniket, Dr J Boultwood, Professor JS Wainscoat.
LRF Funding of Cell Banks: Oxford Haematology Specimen Archives. April 2005 £33,378.
14. Dr ANJ McKenzie, Professor Wainscoat, Dr J Boultwood
LRF Project Grant: Chromosomal engineering to produce a model of the human 5q- syndrome. 3 years (August 2004- August 2007) £260,691.

3. University lectures and classes given over past 5 years
I have given several lectures concerning the molecular pathogenesis of myeloid malignancies in the Department of Haematology and in the new Academic Department of Haematology seminar series, John Radcliffe Hospital, Oxford over the past 5 years. The audience is comprised of science and medical graduates, and haematology staff (research and clinical).

4. Graduate Supervision and other Graduate Teaching undertaken over past 5 years
i.I have acted as a supervisor for the following higher degree students: Andrea Pellagatti, Open University (PhD, awarded 2007); Fiona Watkins, Open University (PhD awarded, 2009); Marta Fernandez-Mercado, University of Navarra, Spain, PhD student (April 2010-present); Hannah Smith, St Hilda's College Oxford, DPhil student (October 2010-present).
ii. I have given a lecture on the application of microarray analysis to the study of human malignancy to Oxford DPhil/PhD students as part of the second year DPhil/PhD programme in the NDCLS, Oxford University. I have given these lectures annually from March 2004 to 2007.
iii. I have acted as supervisor of a research project (Erasmus summer practice programme) for Wioleta Dudka, a MSc (Biology) student, University of Warsaw, Poland from August to November, 2010.
iv. I have supervised Isidoro Cobo, a MSc (Biochemistry) student, University of Navarra, Spain, in the summer of 2010.
v. I have supervised research projects undertaken by Esther Recacha and Alba Martin Moreno, undergraduate biology students, University of Navarra, Spain, in the summer of 2010 and 2011, respectively.

5. University Examining undertaken over past 5 years
i. I have acted as an external or internal examiner for 23 DPhil, PhD or MD theses in total, and 5 over the past 5 years:
Year of exam Candidate University
2007 Mr N Fourouclas Anglia Ruskin (Cambridge)
2008 Ms C Marius London
2011 Ms E Payne London
2012 Ms N Roy Oxford
2012 Mr R. Armstrong Belfast

ii. I have acted as an assessor of the transfer to DPhil status reports by Rebecca Fisher (Linacre College, University of Oxford) January in 2006, by Noemi Roy (St John College, University of Oxford) October 2009 and by Chao-Hui Chang (NDCLS) September 2011.
6. University Administration, academic leadership, contribution to the subject outside the University
i. University administration
1. I was a member of the DPhil/PhD programme committee in the NDCLS, Oxford University from June 2003 to 2006. This involved organising a lectures and training programme for each of the three years of higher degree study.
2. I acted as chair of the NDCLS Graduate Studies Open Day, October 2006 at the Medical Sciences Teaching Centre, South Parks Road, Oxford.
3. I was a member of the Merit Awards Review Panel NDCLS, Oxford University, in 2005 and 2008.
4. I was a member of the DPhil/PhD MRC studentships selection committee and interview panel in NDCLS, January 2011.

ii. Selected recent invited lectures
1. Invited speaker at the 11th Congress of the European Haematology Association (EHA) in the MDS Educational Session, June 2006, Amsterdam. Talk entitled 'Molecular pathogenesis of the myelodysplastic syndromes, including the 5q- syndrome.'
2. Invited speaker at the 9th International Symposium on The Myelodysplastic Syndromes, May 2007, Florence, Italy. Talk entitled 'The molecular analysis of the 5q- syndrome'.
3. Invited speaker at the Third European LeukemiaNet meeting on the Genetics of MDS, September 2007, Vienna, Austria. Talk entitled 'Gene expression profiling in MDS'.
4. Invited speaker at the Fourth European LeukemiaNet meeting on the Genetics of MDS, October 2008, Perugia, Italy. Talk entitled 'Recent advances in the molecular pathogenesis of the 5q- syndrome'.
5. Invited speaker at the 10th International Symposium on The Myelodysplastic Syndromes, May 2009, Patras, Greece. Talk entitled 'Gene expression profiling in MDS, including patients with the del(5q)'.
6. Invited speaker at the European Society of Haematology (ESH) conference on the Myelodysplastic syndromes, October 2009, Mandelieu France. Talk entitled ' The Molecular pathogenesis of MDS with the del(5q).'
7.Invited speaker at the 1st Del(5q) Consensus Conference, August 2010, London. Talk entitled 'Molecular mapping of the CDR of the 5q- syndrome.'
8. Invited speaker at the International Conference News in Onco-Hematology, Perugia, Italy, November, 2010. Talk entitled 'Recent advances in the molecular pathogenesis of the 5q- syndrome '.
9. Invited speaker at the 8th meeting of the French Myelodysplasia Group in Strasbourg, France, March 30-1st April 2010. Talk entitled 'Deregulated gene pathways in MDS, including patients with the 5q- syndrome'.
10. Invited speaker in the Educational session at the First Annual Meeting of the Spanish Cooperative Group on Myelodysplastic Syndromes in Madrid, Spain, 11-12th April 2011. Talk entitled 'New insights into molecular pathophysiology of myelodysplastic syndromes'.
11. Invited speaker at the 52nd International symposium on 'Regulation of enzyme activity and synthesis in normal and neoplastic tissues' in Bologna, Italy, 25-27th September 2011. Talk Entitled 'Activation of p53 and up-regulation of the p53 pathway in the myelodysplastic syndromes'.
12. Invited speaker at the First Nordic Conference on the Biology of MDS, 16-18th November 2011. Talk entitled 'Molecular pathogenesis of the 5q- syndrome'.
13. Invited speaker at the "Next Generation Approaches for Evaluation and Treatment of MDS" held as a Friday American Society of Hematology Satellite Symposium, 9th December 2011, San Diego, US. Talk entitled 'Ribosome Function and Molecular Biology of the 5q-Syndrome'.
14. Invited speaker at the third Bone Marrow Failure Disease Scientific Symposium, 22-23rd March 2012, Bethesda, Maryland US. Talk entitled 'Molecular pathogenesis of the 5q-syndrome'.
15. Invited speaker at the 6th COST EuGESMA meeting in Belgrade, Serbia, April 2012. Talk entitled 'Treatment of RPS14-deficient cells with the translation enhancer L-leucine'.
16. Invited speaker at the ESH International Conference on Myelodysplastic Syndromes, Saggart, Dublin, Ireland, 24-27th May, 2012. Talk entitled 'Biology of hematologic manifestations and disease progression in the 5q- syndrome'.
17. Invited speaker at the MDS Forum Education day London, November 19th 2012. Talk entitled ' The biology of the 5q- syndrome disease'.
18. Invited speaker at the 4th International Congress on Leukemia -Lymphoma - Multiple Myeloma in Istanbul, on May 22-25, 2013. Talk entitled 'The molecular biology of MDS'.

iii. Conference organiser/chair in past five years

I have organised or chaired at the following meetings:

1. Member of the International Scientific Committee of the 9th International Symposium on The Myelodysplastic Syndromes, May 2007, Florence, Italy
2. Chair of the MDS simultaneous session at the 12th Congress of the European Haematology Association (EHA), June 2007, Vienna, Austria
3. Chair of the Gene expression profiling session at the Third European LeukemiaNet meeting on the Genetics of MDS, September, 2007, Vienna, Austria
4. Chair of the MDS simultaneous session at the 13th Congress of the European Haematology Association (EHA), June 2008, Copenhagen
5. Chair of the Molecular genetics of MDS session at the Fourth European LeukemiaNet meeting on the Genetics of MDS, October 2008, Perugia, Italy
6. Chair of the Disordered gene expression in hematologic malignancy session at the 50th American Society of Hematology (ASH) Conference, San Francisco, USA, December 2008
7. Member of the International Scientific Committee of the 10th International Symposium on The Myelodysplastic Syndromes and Chair of the Molecular mechanisms and pathophysiology poster session, May 2009, Patras, Greece
8. Chair of the Emerging therapies in myelodysplastic syndromes session at the British Society of Haematology Conference, April 2009, Brighton
9. Coordinating Chair of the Disordered gene expression in hematologic malignancy session at the 51st American Society of Hematology (ASH) Conference, New Orleans, USA, December 2009
10. Faculty member of the 1st Del(5q) Consensus Conference, August 27-29, 2010, London
11. Chair of the Disordered gene expression in hematologic malignancy session at the 50th American Society of Hematology (ASH) Conference, Orlando, USA, December 2010
12. Member of the Organising Committee, Meet the expert on gene expression profiling interactive session and Chair of the Biology of MDS session at the 11th International Symposium on The Myelodysplastic Syndromes May 2011, Edinburgh, UK
13. Faculty member of the First Nordic Conference on the Biology of MDS, 16-18th November, 2011
14. Faculty member of the American Society of Hematology meeting, San Diego, December 2011.

iv. Recent Academic Reviewing

1. I regularly review manuscripts submitted to several journals, including Blood, British Journal of Haematology, Haematologica, Molecular Biotechnology, Leukemia, Genomics, PNAS.
2. I regularly review grant applications for several grant awarding bodies, including Leukaemia and Lymphoma Research, the Association of International Cancer Research, Tenovus, the Research Grants Council (Hong Kong), Cancer Research UK and the BSH UK (Start-up grants).
3. I served on the National Health Institute (NIH)/National Heart, Lung and Blood institute (NHLBI) Special Emphasis Review Panel assessing MDS (MDS: Seeking a cure through discovery on pathogenesis and disease progression) and MPD (Cellular and genetic discovery toward curative therapy in MPD) ZHL1 CRS-I (S2) grant applications in Columbia, Maryland, USA, July, 2005.
4. I acted as an external reviewer for the Quinquennial Review documents of the Cancer Research UK Group at St Bartholomews Hospital, directed by Professor Bryan Young in September 2005.
5. I acted as a member of the Advisory Board of the Cariplo Foundation (Milan, Italy) reviewing research grant applications in Biomedicine (identification of the molecular basis of disease) in November 2009, September 2010 and September 2012.
6. I acted as a reviewer for abstracts submitted to the European Haematology Association (EHA) conference in June 2005 in Stockholm (MDS session) and in June 2011 in London.
7. I acted as a reviewer for abstracts submitted to the 9th International Symposium on the Myelodysplastic Syndromes, May 2007, Florence, Italy and to the 11th International Symposium on The Myelodysplastic Syndromes, Edinburgh, April 2011.
8. I acted as a reviewer for abstracts submitted to the British Society of Haematology conference in April 2009 and April 2011 in Brighton, and in April 2012 in Glasgow .
9. I acted as a reviewer and coordinating reviewer for abstracts submitted to the American Society of Haematology (ASH) Conference in San Francisco, December 2008 and in New Orleans, December 2009 (Disordered gene expression in hematologic malignancy sessions), respectively. I acted as a reviewer for abstracts submitted to the 54th Annual Meeting of the American Society of Hematology (ASH) Atlanta, December, 2012 (session Leukemias - Biology, Cytogenetics and Molecular Markers in Diagnosis and Prognosis)

v. Membership of Scientific/Medical Committees/Societies

Member of the International Myelodysplasic Syndromes Foundation 2004-2009; Member of the Human Genome Organisation (HUGO) 1997-2010; Member of the British Society of Haematology, October 2003 –present; Member of the American Society of Haematology, June 2004-present; Member and Trustee of the UK MDS Forum Steering Group, April 2004 – present; Member of the European LeukemiaNet MDS Work Package, April 2004 – present; Member of the Chronic Myeloid Disorders ICGC Working Group, the Cancer Genome Project, (Sanger Institute) September 2008-present; UK representative of EU EuGESMA COST Action BM0801-microarray analysis of MDS and AML management committee, October 2008-present; member of the International Working Group for Prognosis in MDS (IMG-PM) December 2011-present.

vi. Membership of Oxford Committees

1. Member of the Blood Theme Committee of the Oxford NIHR BioMedical Research Centre (BRC) at the John Radcliff Hospital, Oxford, May 2012-present.

vii. Member of the Editorial Board of Scientific Journals

1. Member of the Editorial Board of the journal Molecular Biotechnology, October1998-present.
2. Associate Editor of the journal Molecular Biotechnology, October 2002 – present.
3. Member of the Editorial Board of the British Journal of Haematology, May 2002-present.
4. Member of the Editorial Board of the Journal of Molecular Signaling, May 2006-present.
5. Member of the Editorial Board of the Journal Haematologica, April 2008-present.
6. Member of the Editorial Board of the Open Leukemia Journal October 2008-present.
7. Member of the Editorial Board of the journal American Journal of Blood Research April 2011-present.

7. Recent Undergraduate Teaching for Colleges

I have acted as a supervisor of research projects (dissertations) for the following pre-clinical students at Oxford University (FHS Physiological Sciences and Medical Sciences): Samantha Warnakulasuriya, (St Hilda's College), June-October 2005; Isla Kennedy McConnell, (Lady Margaret Hall), May-July 2007.

8. College Administration

I was awarded Research Membership of the Common Room of Wolfson College, Oxford in October 2006 to 2012 (currently Ordinary Member of the Common Room).

Recent Prizes

We were awarded the American Society of Hematology (ASH) and National Marrow Donor Program (NMDP) prize of $ 2,500 for outstanding research in haematology and oncology at ASH December 2011, San Diego for our abstract:
Myelodysplastic Syndromes (Abstract No. 3 - Plenary) Malcovati L, Papaemmanuil E, Hellstrom Lindberg E, Boultwood J et al 'Somatic mutation of SF3B1, a gene encoding a core component of RNA splicing machinery, in myelodysplasia with ring sideroblasts'.

The Molecular Pathogenesis of the Myelodysplastic Syndromes

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Abstract

Recent studies have greatly illuminated the molecular landscape of the myelodysplastic syndromes (MDS), and the pace of discovery is accelerating. We now recognise that the most common mutations found in MDS occur in genes that are epigenetic modifiers (TET2, ASXL1, DNMT3A, EZH2, IDH1 and IDH2) or regulators of RNA splicing (SF3B1, SRSF2, U2AF1 and ZRSR2), providing an important link between genetic and epigenetic alterations in this disease. Several regulators of signal transduction (NRAS, JAK2) and a number of transcription factors (RUNX1, p53) are also frequently mutated in MDS. Emerging evidence suggests that specific combinations of these genes cooperate to give the MDS phenotype. The identification of mutations in members of the RNA splicing machinery in MDS represents one of the most important new findings, and implicate abnormalities of mRNA splicing, a pathway not previously known as a target for mutation, in the pathogenesis of this disorder. Splicing factor mutations occur in approximately half of all MDS patients and, unlike most other recurrent gene mutations in MDS, are highly specific for this disorder. The cytogenetic analyses of MDS are characterised by the loss of genetic material and, translocations are rare. The cytogenetic deletion maps of MDS (e.g. 5q-, 7q-, 20q-) provide us with circumstantial evidence for the presence of tumour suppressor genes (TSG). There is growing recognition that the common deletions in MDS contribute to malignancy by haploinsufficiency (a gene dosage effect). The importance of this mechanism is supported by studies concerning MDS patients with the 5q- syndrome, where haploinsufficiency of the ribosomal protein RPS14 plays a critical role in the development of anemia. Similarly, the transcription factor CUX1 has been recently identified as a TSG mapping to 7q, showing haploinsufficiency in MDS and AML with complete or partial loss of chromosome 7. Gene expression profiling studies in MDS have also been fruitful, and have identified key genes and gene pathways deregulated in this disease. Moreover, a new prognostic signature for MDS has recently been identified using this technology. Recent advances in the molecular pathogenesis of MDS are leading to novel clinical, biological and therapeutic insights.

Introduction

The myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell (HSC) malignancies that are characterized by ineffective hematopoiesis resulting in peripheral cytopenias, and typically a hypercellular bone marrow. The MDS are pre-leukemic conditions showing frequent progression (approximately 40% of patients) to acute myeloid leukemia (AML) [1]. Until recent years the genetic aberrations that play an important role in the molecular pathogenesis of MDS were largely unknown. The application of various new high throughput technologies over the past decade, including SNP-array analysis and next generation sequencing, to the study of MDS has resulted in the identification of a host of genes that are recurrently mutated in this disorder [2,3]. In several cases, for example, the identification of submicroscopic deletions or regions of acquired uniparental disomy (UPD) has provided important clues leading to the discovery of such novel gene mutations [4,5]. Gene expression-based microarray analysis, allowing for the simultaneous study of the expression levels of all human genes, has revealed many genes differentally expressed in MDS and highlighted several critical gene networks deregulated in this disorder [6,7]. Technology develoment has been a key driver of recent discoveries in MDS. In this review I discuss the molecular pathogenesis of MDS, with an emphasis on recent advances in the field.

Point mutations in MDS

Recurrent somatic mutations in several genes have been described in MDS (Table 1) and implicated in the development and/or progression of this disorder.

Table 1. Common gene mutations in MDS			
Genes	**Chromosomal Location**	**Frequency in MDS**	**Function of encoded protein**
Signal transduction and transcription factors			
RUNX1	21q22	10%	Core binding transcription factor critical in haematopoiesis
TP53	17p13	5-10%	Tumor suppressor activity regulating cell cycle, apoptosis, senescence, DNA repair and metabolism
NRAS	1p13.2	5%	GTPase that functions as an oncogene when mutated and constitutively active
KRAS	12p12.1	2%	GTPase that functions as an oncogene when mutated and constitutively active
ETV6	12p13.2	2-5%	ETS transcription factor required for hematopoiesis and maintenance of developing vascular network
EVI1	3q26	1-2%	Transcriptional regulator and oncoprotein that may be involved in hematopoiesis, apoptosis, development, differentiation and proliferation
JAK2	9p24.1	5% in MDS 50% in RARS-T	Non-receptor protein tyrosine kinase with roles in cell cycle, genomic instability, apoptosis and mitotic recombination
Methylation of CpG islands			
TET2	4q24	20%	Methylcytosine dioxygenase that converts methylcytosine to 5-hydroxymethylcytosine; required for myelopoiesis
IDH1 IDH2	2q33.3 15q26.1	5%	Isocitrate dehydrogenase converts isocitrate to α-ketoglutarate; regulates TET2 activity
DNMT3A	2p23.3	10%	DNA methyltransferase that functions in de novo methylation and is coordinated with histone methylation to repress transcription
Histone modification			
ASXL1	20q11.2	11-15%	Histone-binding protein that disrupts chromatin in localized areas to enhance or repress transcription
EZH2	7q36.1	5%	Histone methyltransferase involved in gene repression
Spliceosome			
SF3B1	2q33.1	20-28% in MDS >70% in MDS-RS	Spliceosome protein component critical for spliceosome complex assembly
SRSF2	17q25.1	12-15%	Spliceosome protein component critical for spliceosome complex assembly
U2AF1	21q22.3	7-9 %	Spliceosome protein component critical for spliceosome complex assembly
ZRSR2	Xp22.1	3-11%	Spliceosome protein component critical for spliceosome complex assembly
Others			
CBL	11q23.3	2-5%	E3 ubiquitin ligase that participates as a negative regulator of transduction in hematopoietic cells
MDS, myelodysplastic syndromes; RARS-T, refractory anemia with ringed sideroblasts and thrombocytosis; RS, ringed sideroblasts			

Epigenetic Regulator mutations in MDS

The methylation of CpG islands within gene promoters is a major epigenetic transcriptional control mechanism that is frequently dysregulated in human cancers and leukemias [8,9,10] and various histone modifications leading to altered gene expression are also commonly observed [9]. MDS is characterized by frequent epigenetic abnormalities, including the hypermethylation of genes that control proliferation, adhesion, and other characteristic features of this myeloid malignancy [9,11]. It has long been recognised that increased methylation of several tumour suppressor genes, including p15 and E-cadherin, occurs during the progression of MDS, for example [11,12]. Accordingly, several therapies that aim to re-express silenced genes are currently being tested in MDS, including histone deacetylase inhibitors and hypomethylating agents. In particular, the hypomethylating agents 5-azacitidine (AZA) and decitabine (DAC) represent important treatment options for high-risk MDS [11,13].

Several genes involved in the regulation of histone function (EZH2, ASXL1, and UTX) and DNA methylation (DNMT3A, IDH1/IDH2, and TET2) are frequently mutated in MDS, suggesting that epigenetic dysregulation may play a major role in the pathogenesis if this disorder [14,15]. These genes all play important roles in the regulation of gene expression. Somatic deletions and inactivating mutations in TET2 were identified in MPN and MDS based on mapping of loss-of-heterozygosity and microdeletions within a minimal region of chromosome 4q24 [5,16]. TET2 is one of the most commonly mutated genes in MDS (occurring in around 20% of patients) and is also frequently

mutated in a range of other myeloid malignancies including CMML and AML [15,17]. TET2 converts the methylated cytosine to hydroxymethylcytosine, which is then believed to result in the demethylation of the cytosine [18]. TET2 mutations in MDS are thought to result in a loss of catalytic activity. Deletion of Tet2 in the mouse results in increased HSC self-renewal and the development of myeloid skewing in differentiation, and in the eventual development of myeloid malignancies with similarities to MDS [15,19]. The impact of TET2 mutations on MDS patient survival is uncertain, as there have been several conflicting studies [15,17,20]. The activity of TET2 is regulated by αketoglutarate, which is a metabolite generated by IDH1 and IDH2. Mutations of IDH1 and IDH2 have been identified in 5–10% of cases of MDS, and are associated with a poor prognosis [21,22]. The expression of mutant IDH1/2 induces an increase in global 5-methylcytosine levels and interestingly IDH1/2 mutations in AML associate with a specific DNA hypermethylation profile [23]. IDH1/2 mutations inhibit the hydroxylation reaction of methylcytosine by TET2. Either the expression of mutant IDH1/2 or Tet2 depletion impaired hematopoietic differentiation in culture and increased stem/progenitor cell marker expression, suggesting a shared proleukemogenic effect [23].

DNMT3A is a methyltransferase and enzymatically adds a methyl group to cytosine in CpG dinucleotides in DNA. DNMT3A is required for efficient maintenance methylation of active chromosome domains [24]. Ley *et al*, first identified somatic mutation of DNMT3A in AML using whole-genome sequencing [25]. DNMT3A mutations have been reported in around 10% of MDS patients, and have been associated with poor prognosis and more rapid progression to AML [15,26].

Mutations in two polycomb family member genes, additional sexcombslike 1 (ASXL1) and enhancer of zeste homologue 2 (EZH2), have been recently described in MDS [4,27]. The ASXL1 gene encodes a chromatin-binding protein involved in epigenetic regulation in haematopoietic cells, and may play a key role in recruiting the polycomb repressor complex 2 (PRC2) to specific loci. ASXL1 mutations are common in MDS, occurring in around 11-15% of patients, and are associated with a poor prognosis [28]. ASXL1 mutations are common in MDS and CMML cases that later transformed to AML [29,30], suggesting that ASXL1 mutations may play a role in leukaemic transformation. ASXL1 mutations occur in exon 12 of the gene and nonsense and frameshift mutations result in loss of ASXL1 expression. ASXL1 mutations are thought to promote myeloid transformation through loss of PRC2-mediated gene repression [31]. In a mouse model, loss of Asxl1 expression in the haematopoietic cell compartment collaborated with the NRasG12D oncogene to promote a MDS phenotype with myeloproliferative features, including accelerated myeloproliferation, progressive anaemia and impaired survival [31]. We have recently shown that loss of function of ASXL1 results in impaired human myeloid differentiation in culture [32]. EZH2 is a histone H3 and H1 methyltransferase gene that is mutated in 5% of patients with MDS, and it is believed to function as a tumour suppressor [4,33]. EZH2 maps to 7q36, and EZH2 mutations are associated with 7q uniparental disomy or 7q36.1 microdeletion, but not generally with monosomy 7 and del(7q), in malignant myeloid disorders, including MDS [4,33]. Point mutations in EZH2 in MDS are also linked to a poor prognosis [28]. Indeed it has recently been shown that combining the LR-IPSS and EZH2 mutation status identifies 29% of patients with lower-risk MDS with a worse-than-expected prognosis, identifying a patient group that may benefit from earlier initiation of disease-modifying therapy [34].

It has recently been shown that MDS patients with either ASXL1, DNMT3A or TET2 mutations showed a higher overall response rate to hypomethylating therapy (AZA or DAC) when compared with wild type patients [35,36]. Whether patients carrying mutations in other epigenetic regulators respond differently to the epigenetic therapies employed in MDS remains to be assessed.

Rarely MDS is found in association with acquired alpha-thalassaemia (ATMDS), and acquired somatic mutations in the ATRX gene, a chromatin remodeler involved in transcriptional regulation, are the common genetic basis of this disorder [37].

Splicing factor mutations in MDS

The recent discovery of a variety of somatic splicesomal mutations in MDS has revealed a new leukemogenic pathway involving spliceosomal dysfunction. In 2011 Papaemmanuil *et al* used whole-exome sequencing analysis in low-risk MDS and identified frequent mutation of the splicing factor SF3B1 in this patient group [38]. SF3B1 mutations were found in over 70 % of patients whose disease is characterised by ringed sideroblasts [38,39]. The close association between SF3B1 mutation and ring sideroblasts is consistent with a causal relationship, and makes this the first gene to be strongly associated with a specific feature of MDS. SF3B1 is the most commonly mutated gene found in MDS, to date, with approximately 28% of all MDS patients harboring SF3B1 mutations [38,39,40]. At around the same time Yoshida *et al*, also identified

frequent recurrent mutations in SF3B1 and several other genes encoding other members of the RNA splicing machinery, including U2AF35 (U2AF1), ZRSR2 and SRSF2 in MDS using whole-exome sequencing analysis [41]. These splicing pathway mutations were shown to be frequent (occuring in 130 of 228 MDS patients; 57%), and highly specific to MDS. Mutations in SRSF2, U2AF1 and ZRSR2 have been reported in approximately 12-15%, 7-9% and 3-11% of MDS patients, respectively [40,41]. Most of the mutations occurred in a mutually exclusive manner and affected genes involved in the 3'-splice site recognition during pre-mRNA processing [41]. Mutations in the splicing factors PRPF40B, SF1, SF3A1 and U2AF65 are more rarely found in MDS, each occurring in approximately 1-2% of patients.

Most of mutations identified to date are missense and affect rather invariant positions in SF3B1, SRSF2, U2AF1 and other spliceosomal proteins [41]. In U2AF1, the mutations almost exclusively involve highly conserved the two amino acid positions S34 and Q157, almost all SRSF2 mutations are missense changes at P95 [41] and approximately 50 % of SF3B1 mutations involve the amino acid K700E [38,41]. No homozygous mutations have been reported for these three genes. The presence of hot spots and the absence of nonsense or frameshift changes suggests that the vast majority of the splicing factor mutations are gain of function or change of function/neomorphic mutations [38,41,42,43]. However, a recent report described a Sf3b1 heterozygous knockout mouse showing the presence of ring sideroblasts, suggesting that haploinsufficiency of SF3B1 may be the mode of action of SF3B1 mutations in MDS [44]. Notably these mice did not develop MDS, however [44]. In the case of ZRSR2, missense, nonsense and frame shift mutations have been detected and these mutations are considered to be loss of function [41,43]. Since most spliceosomal mutations are considered to result in a gain of function or neomorphic phenotype the application of specific spliceosomal inhibitors may allow for targeting of mutant phenotype [45].

Excision of intronic sequences from pre-mRNAs (pre-mRNA splicing) is an obligatory step for the expression of the majority of higher eukaryotic genes. Splicing of mRNA is carried out by the spliceosome, a complex of five small nuclear ribonucleoproteins (snRNPs) together with other proteins. In MDS the major targets of spliceosome mutations mostly play a role in the initial steps of RNA splicing and are restricted to the components of the E/A splicing complex, including SF3B1, SRSF2, U2AF1 and ZRSR2 [41]. The frequency and specificity of these mutations in this complex, together with the mutually exclusive manner that they were found, suggest that the aberrant function of the E/A splicing complex is major feature of MDS [40,41].

Given the critical functions of the E/A splicing complex on 3′ splice site recognition, the probable consequence of the splicing factor mutations found in MDS would be impaired splicing involving diverse RNA species. Consequent disruption of 3´splice-site recognition could cause altered exon utilization or activation of cryptic 3´splice sites. Moreover, aberrant RNA splicing can generate premature translation termination codons (often present in retained introns). These transcripts are subject to degradation by the nonsense-mediated decay (NMD) pathway [46] and therefore lead to down-regulation of these genes. An increase of inappropriate splicing may ultimately lead to defective expression and thereby indirectly to the loss of function of key downstream target genes, that might include tumor suppressor genes. The specific target mRNAs of the splicing factors mutated in MDS largely remain to be identified, although recent deep sequencing of RNA (RNA seq) from bone marrow samples from a small number of patients with splicing factors mutations do suggest that spliceosomal mutations have effects on specific genes, intruigingly, including several previously shown to play an important role in MDS pathogenesis. For example, a splicing abnormality of RUNX1 has been reported in two cases with SRSF2 mutations [47] and of ASXL1, CBL, EZH1, and RUNX3 in two cases with SF3B1 mutations [44]. Moreover, global gene expression data derived from MDS CD34+ bone marrow cells showed that SF3B1 mutations were associated with down-regulation of key gene networks, including core mitochondrial pathways in MDS [38]. Similarly, the gene expression profiles of MDS patients harboring U2AF1 mutations are characterized by the down-regulation of multiple genes and, in particular, show down-regulation of splicing and RNA recognition motif (RRM) genes [48].

The splicing pathway mutations are highly specific to MDS, and to some extent define distinct clinical phenotypes. For example, SF3B1 mutations are found in most patients with RARS. SRSF2 mutated patients cluster in RAEB-1 and RAEB-2 MDS subtypes and show dysplastic features affecting predominantly granulopoiesis and megakaryopoiesis, and pronounced thrombocytopenias. SRSF2 mutations are also strongly associated with CMML [41]. U2AF1 mutations are most frequently reported in high-risk MDS and MDS patients with U2AF1 mutations show evidence of an increased risk of progression to

AML [40,48]. Interestingly, spliceosome mutations, while mutually exclusive with one another, show a strong but specific tendency to co-occur with one or more genes implicated in aberrant DNA methylation in MDS, suggesting that abnormalities in gene methylation and splicing may cooperate to give the MDS phenotype [43]. SRSF2 and ZRSR2 mutations are common in patients harbouring mutations of the DNA methylation modifier TET2, SF3B1 mutations coexist with mutation of the methyltransferases DNMT3A and U2AF1 mutations have been associated with ASXL1 or TET2 mutations [40].

Several groups have investigated the prognostic impact of spliceosome mutations, with some conflicting results. SF3B1 mutations have been shown to be independent predictors of favourable clinical outcome in MDS by some groups, but not others [39,40,47,49]. Mutation of U2AF1 has been found to have little impact on survival in some studies [40,48], however others have shown that U2AF1 mutations were associated with shorter survival in MDS [47]. SRSF2 mutations have been shown to be predictive of poorer survival with increased transformation to AML [40].

While trends in defining phenotype and prognosis are emerging, detailed functional studies are necessary in order to establish the full clinical relevance of spliceosome gene mutations in MDS evolution. In particular, the question of how spliceosomal protein mutations could lead to a clonal growth advantage in mutant haematopoietic cells needs to be addressed.

Signal transduction and transcription factor mutations

Mutations of genes in the RAS signalling pathway have been found in around 5-10% of MDS patients, with NRAS being the most frequent mutation [50]. RAS mutations have been associated with poor response to treatment and poor prognosis in most, but not all studies of MDS [28,50]. The RAS/MAPK pathway is also frequently deregulated in the childhood MDS juvenile myelomonocytic leukaemia (JMML) [51].

Genes that encode tyrosine kinases are infrequently mutated in MDS. However, around half of patients with refractory anaemia with ringed sideroblasts and thrombocytosis (RARST) possess the point mutation V617F in JAK2, a nonreceptor tyrosine kinase [52]. Internal tandem duplications (ITD) and other constitutively activating mutations of the receptor tyrosine kinase FLT3, frequently found in AML, occur less commonly in MDS and have been reported in approximately 5% of patients [50].

One of the most frequently mutated genes in MDS is RUNX1 (AML1), a transcription factor and critical regulator of definitive haematopoiesis, originally identified as a translocation partner in AML [53]. Point mutations in RUNX1 are found in approximately 10% of patients with MDS [28,53]. Some patients with thrombocytopenia have a congenital haploinsufficiency or mutation of the RUNX1 gene, and show a greater propensity to develop AML [54]. Interestingly, AML1/RUNX1 deficient mice, in addition to splenomegaly and lymphomas, display features of MDS. Point mutations in ETV6, a transcription factor that is also crucial for normal haematopoiesis, have been reported in some patients with MDS. In both MDS and AML, the presence of RUNX1 and ETV6 mutations confers a poor prognosis [28]. Similarly, EVI1, a transcriptional regulator that is essential for haematopoiesis, is mutated in 2% of patients with MDS, and confers a poor prognosis [55]. Mutations in the TP53 tumour suppressor gene are frequently found in MDS (5-10% of patients) and are associated with advanced disease, a complex karyotype and therapy resistance [56]. TP53 mutations in MDS are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis [57]. TP53 mutations are believed to cause an increase in genomic instability.

Cytogenetic (and other submicroscopic genomic) abnormalities

Cytogenetic abnormalities are reported in approximately 50% of cases of *de novo* MDS and 80% of therapy-related MDS (t-MDS). The cytogenetics of MDS is characterized by genetic loss [58,59]. Recent molecular investigations using SNP-array analysis have revealed additional genetic abnormalities in MDS, including micro-deletions and loss of heterozygosity (LOH) due to UPDs [60,61]. The prognostic value of SNP array analysis has been demonstrated in an important recent study of 430 patients with MDS [62]. SNP array analysis of paired bone marrow cells and unaffected blood T cells, combined with cytogenetic karyotyping, detected additional chromosomal lesions in patients with normal and abnormal karyotypes. The newly detected genetic abnormalities contributed to poorer prognosis for patients stratified by current morphologic and clinical risk schemes, perhaps explaining why some patients with IPSS-classified lowrisk karyotypes have poor survival. The presence and number of abnormalities detected by SNP arrays were also found to be independent predictors of survival MDS [62].

Chromosomal deletions – putative tumor suppressor genes

Chromosomal deletions and monosomies are common in MDS and the del(5q) and –7/del(7q) are amongst the most frequently reported karyotypic abnormalities in this disorder. Other recurrent deletions reported in MDS include del(20q), del(11q) and del(17p) [58,59]. It is unknown whether these chromosomal abnormalities are initiating events leading to the development of MDS.

The del(5q), del(7q) and del(20q) in MDS and AML are considered to mark the location for a gene(s) the loss of which may affect important processes such as growth control and normal hematopoiesis. The basis for research on these and other recurrent deletions in MDS and AML is well known. The first step is to characterize the deletions and to identify the commonly deleted region (CDR) i.e. the region of deletion shared by all patients as this localises the gene(s) for further study. The next step typically involves the sequencing of all the candidate genes that map within the CDR in a group of affected patients. The lack of recurrent mutations in any of the genes mapping to the various CDRs identified on 5q and 7q in MDS and AML patients with cytogenetic deletion involving these genomic regions suggests that haploinsufficiency, a dosage effect resulting from the loss of a single allele of a gene [63], may be the molecular mechanism relevant in this group of malignancies. There has been growing recognition that gene haploinsufficiency may play a role in the development or progression of cancer over the last decade, and the importance of this mechanism in the context of myeloid disorders is supported by recent studies concerning MDS patients with the 5q- syndrome [64,65].

The del(5q) and the 5q- syndrome

Interstitial deletion within the long arm of chromosome 5 [del(5q)] is one of the most frequent cytogenetic abnormalities observed in myeloid malignancies, occurring in approximately 10-20% of patients with *de novo* MDS [58] and in a similar proportion of patients with *de novo* AML. The del(5q) occurs as the sole karyotypic abnormality in the 5q- syndrome, the most distinct of the MDS [66]. Importantly, there is a clear genotype-phenotype association in the 5q- syndrome, whereas, for most other chromosomal deletions in MDS and AML there is no such association. Great strides have been made in the elucidation of the molecular basis of the 5q- syndrome [67]. Our group in Oxford identified the CDR of the 5q- syndrome as the approximately 1.5 Mb interval at 5q32 flanked by D5S413 and the GLRA1 gene [68] and demonstrated haploinsufficiency of several candidate genes mapping to this interval in the CD34+ cells of patients, including the ribosomal protein gene RPS14 [69]. In a landmark study Ebert *et al*, demonstrated that haploinsufficiency of RPS14 plays a critical role in the development of the anemia that characterizes this disorder [65]. The genes in the 5q- syndrome CDR were studied by an RNA-mediated interference (RNAi)- based approach and it was shown that haploinsufficiency of RPS14 in normal HSC resulted in a block in erythroid differentiation. Forced expression of an RPS14 cDNA in bone marrow cells from patients with the 5q- syndrome rescued the phenotype, strongly suggesting that that RPS14 is a 5q- syndrome gene [65]. In addition, a block in the processing of pre-ribosomal in RPS14-deficient cells was found, linking the pathogenesis of the 5q- syndrome to Diamond–Blackfan anemia (DBA) [65].

A mouse model of the 5q- syndrome has since been generated by Barlow *et al* using large-scale chromosomal engineering and displays the key features of the human disease, including a macrocytic anemia [64]. The '5q- mouse' shows haploinsufficiency of RPS14 and the bone marrow cells of these mice show an accumulation of p53 protein with increased apoptosis. The '5q- mouse' was crossed with p53 deficient mice and this rescued the progenitor cell defect, restoring HSC bone marrow populations [64]. This illuminating study suggested, for the first time, that a p53-dependent mechanism underlies the pathophysiology of the 5q- syndrome. It is now well recognized that in conditions of 'ribosomal stress' activation of p53 occurs, promoting the transcription of its many target genes and resulting in p53-dependent cell cycle arrest or apoptosis [70]. There is increasing evidence that p53 activation is a common response to reduced levels of ribosomal proteins in a number of human disorders of defective ribosomal biogenesis, most notable of which are the bone marrow failure syndromes such DBA, and now the the 5q- syndrome, and that this mechanism underlies the phenotypes characteristic of these disorders [67,70,71]. Intriguingly, there is evidence to suggest that Lenalidomide acts in part through the promotion of p53 degradation in the 5q- syndrome [72].

Emerging data suggests that mutation of p53, resulting in the inactivation of the p53 protein, may be one of the molecular events necessary for clonal progression of the 5q- syndrome to acute myeloid leukemia [73]. Using sensitive deep-sequencing technology, Jädersten *et al* have demonstrated that small subclones of hematopoietic cells with p53 mutations occur at an early disease stage in around a fifth of patients with MDS with the del(5q), and were associated with an increased risk of leukemic evolution [73].

Several cooperating genetic events appear to be necessary in the development of the 5q- syndrome. Interestingly, it has been suggested that the thrombocytosis observed in some patients with the 5q- syndrome may be the result of deficiency of two microRNA genes; miR-145 and miR-146a, that map within, and adjacent to the CDR, respectively [74]. Starczynowski *et al* [74], have demonstrated that knockdown of miR-145 and miR-146a together in mouse HSCs resulted in thrombocytosis and megakaryocytic dysplasia. MiR145 functions through repression of FLI1, a regulator of megakaryopoiesis and in the 5q- syndrome, where miR145 is reduced, FLI1 is consequently overexpressed, and the production of megakaryocytic cells is increased [75]. Haploinsufficiency for miR-145 and miR-146a in the CD34+ cells of 5q- syndrome patients has been reported in some, but not all studies, however [74,75,76]. We have clearly learnt a great deal about the molecular basis of abnormalities of the erythroid and megakaryocyte lineages in the 5q- syndrome, but he cause of the initial clonal expansion in patients with the 5q- syndrome remains to be determined.

Other types of MDS including secondary MDS with del(5q) or MDS with additional karyotypic abnormalities to del(5q) have a poor prognosis in contrast to the good prognosis of the 5q- syndrome. The 1-1.5-Mb CDR at 5q31 identified in AML and the more advanced forms of MDS by Lai *et al*, is distinct from the CDR of the 5q syndrome. The AML/MDS CDR at 5q31 is flanked by D5S479 and D5S500 and contains the transcription factor EGR1, a candidate gene [77]. Interestingly, Egr1-deficient mice treated with a DNA alkylating agent to induce secondary cooperating mutations develope immature T-cell lymphomas or a myeloproliferative disorder at increased rates and with shorter latencies than that of wild-type mice [78]. Reduced or absent expression of CTNNA1, a putative tumor suppressor gene also mapping to 5q31, has been demonstrated in MDS/AML patients with a del(5q), and it has been suggested that low expression levels of CTNNA1 may play an important role in MDS/AML with the del(5q) [79]. In addition, other genes located on 5q but outside the CDRs have been published as having possible importance in these leukemias; these include NPM1 and APC [67,80]. It is highly likely that the deletion of several genes along chromosome 5q may have various phenotypic effects and contribute to disease pathogenesis.

Monosomy 7 and del(7q)

The –7/del(7q) is found in 5-10% of patients with *de novo* MDS and in approximately 50% of all therapy related cases. The del(7q) is invariably a bad prognostic marker in MDS and AML [81]. It is now recognised that rearrangements and deletions involving chromosome 7 may be very complex and that multiple distinct regions may contribute to the disease phenotype or progression. Over the years several CDRs mapping to 7q have been identified in MDS and AML, including CDRs at 7q22, 7q32-33 and 7q35-36 [82,83]. McNerney and colleagues have recently identify CUX1 as a tumor suppressor gene mapping to the long arm of chromosome 7, showing haploinsufficiency in AML and other myeloid malignancies with -7 or del(7q) [84]. The CUX1 (CUTL1) gene, encoding a transcription factor, maps to the CDR at 7q22. It is thought that CUX1 might act as a TSG in myeloid cells through the regulation of genes involved in the control of the cell cycle [84]. Deletions of chromosome 7q are typically large, and it is thus probable that haploinsufficiency of an additional gene (or genes) mapping to chromosome 7q may contribute to disease pathogenesis in patients thus affected.

Del(20q)

The del(20q) is found in 3-4% of patients with MDS. The AML/MDS CDR of the del(20q) has been narrowed to a 2.6Mb interval mapping to 20q12 and containing the candidate gene L3MBTL [85].

Translocations

In marked contrast to AML, balanced translocations are rare in *de novo* MDS [86]. The leukaemia-associated fusion genes identified include: AML1/MDS1-EVI1 in the t(3;21), TEL-PDGFRB in the t(5;12), PDGFRB-HIP1 in the t(5;7), NPM-MLF1 in the t(3;5), MEL1 in the t(1;3) and MLL-CBP in the t(11;16). The most frequent recurrent translocations in MDS are the t(3;3)(q21;q26) and the inv(3)(q21q26), which lead to the inappropriate activation of the EVI1 gene located at 3q26 [86,87]. Identification of MDS patients with translocations involving the PDGFRB gene [88] has immediate therapeutic implications since such patients are selectively responsive to PDGFR kinase inhibitors such as imatinib.

Gene expression profiling in MDS

The development of gene expression profiling (GEP) analysis using microarray technology around a decade ago has afforded new strategies for investigating the biology and clinical heterogeneity of MDS, and for the identification of new therapeutic targets, predictors of drug response, and prognostic markers in MDS.

With regard to biological insights, an early study analyzing CD34+ MDS cells (n=55) revealed

expression profiles similar to interferon-γ-induced gene expression changes in normal CD34+ cells [89]. Interestingly, distinct gene expression profiles have been associated with some specific FAB and cytogenetic subclasses; CD34+ cells from patients with refractory anemia with ringed sideroblasts were characterized by deregulation of mitochondrial-related genes [89], whilst CD34+ cells from patients with the 5q- syndrome show downregulation of multiple ribosomal genes and genes involved in translation initiation. More recently we performed GEP and pathway analysis on the CD34+ cells of 183 MDS patients [7]. Early MDS showed deregulation of immunodeficiency, apoptosis and chemokine signaling pathways, whereas advanced MDS was characterized by deregulation of DNA damage response and checkpoint pathways. Distinct gene expression profiles and deregulated gene pathways were identified in patients with 5q–, trisomy 8 or –7/del(7q). The deregulated pathways identified in MDS further illuminate the molecular pathogenesis of this disorder, and may provide new targets for therapeutic intervention [7].

Several criteria that form the basis of the MDS classifications and scoring systems most widely used in clinical practice are affected by operator-dependent variation. GEP could enhance current diagnostic and prognostic systems by providing a set of standardized, objective gene signatures. A classification model has been developed to distinguish MDS from both leukaemia and nonleukaemia profiles by an international research consortium using GEP analysis of total bone marrow mononuclear cells from patients with leukemia and MDS [90]. While this model could accurately predict leukaemia in 93% of AML samples, only 50% of the 174 MDS samples were correctly classified, highlighting the marked heterogeneity of MDS, even within defined subsets of this disorder [90]. A prognostic classification model that predicts the time-dependent probability of leukemic transformation in MDS has been generated using GEP analysis of total bone marrow mononuclear cells. The prognostic classification model accurately discriminated patients with a rapid transformation to AML within 18 months from those with more indolent disease [6]. Most recently we have used GEP data on CD34+ cells from a large group of MDS patients to investigate the relationship between gene expression levels and prognosis. A gene expression signature, based on expression data on 20 genes, was identified that outperformed other predictors including one which additionally used clinical information [91]. Moreover, the gene signature based on CD34+ cells significantly identified a separation of MDS patients with a good or bad prognosis in an independent GEP dataset generated from unsorted bone marrow mononuclear cells, enhancing the likely clinical applicability of the prognostic signature in routine practice [91]. GEP-based signatures correlating with survival may contribute to a refined risk classification of MDS.

There is interest in the application of GEP to the identification of drug targets and of markers of drug response in MDS [92]. For example, an erythroid differentiation gene expression signature that predicts response to lenalidomide in MDS has been developed using GEP analysis [93].

Conclusions and future developments

A wealth of new gene mutations have now been identified in MDS, however, further work is necessary to determine which of these represent initiating events in the development of MDS and how they cooperate to give the MDS phenotype. Other impotant goals include the determination of the clinical impact of these mutations on response to therapy and MDS patient survival. Importantly, a recent large study revealed that only mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 are predictors of poor overall survival in patients with MDS, independently of established risk factors (although this study did not include the newly identified splicing factor gene mutations) [28]. Recent advances from sequencing studies suggest that multiple mutations are required for MDS initiation and progression to AML, but further work is needed to fully understand the molecular basis of leukemic transformation in MDS.

It is the opinion of many that to move the field forward, a new classification of MDS based on genetics should be achieved. The acute leukaemias and the lymphomas are all clear evidence of the huge benefit to be gained from this approach. The central problem with MDS is its heterogeneity. Fortunately we now have the technology to achieve a better understanding of the genetic and biochemical basis for this heterogeneity, and this in turn will lead to improved therapies.

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The Demographics and Management of Low-risk Myelodysplastic Syndromes

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Abstract

Low-risk MDS comprise 75% all MDS patients. At diagnosis the majority of patients do not require active therapy. The predominant clinical problem is anemia, and red cell transfusion dependence (or severe anemia) has negative independent prognostic power. Erythropoietin (EPO) remains the mainstay of anemia management in patients with positive predictors for outcome to EPO. Selected subgroups of patients may benefit from lenalidomide (MDS with del(5q)) or immunosuppression (normal karyotype, refractory anemia, younger age, short duration of transfusion). Allogeneic stem cell transplantation may be indicated for selected younger fitter patients with a relatively poorer prognosis, which may include severe thrombocytopenia (platelets <50 x 109/l), heavy red cell transfusion, grade 2/3 fibrosis and disease progression (clonal evolution, or increasing blast cells).

Introduction

The Myelodysplastic Syndromes (MDS) are a very diverse group of diseases with one common feature, namely the presence of morphological dysplasia in bone marrow cells. The definition of 'low-risk' and 'high-risk' disease is constantly being refined. Traditionally in the era of the International Prognostic Scoring System (IPSS) for prognosis (1997-2012) low-risk disease is defined as IPSS categories Low and Intermediate-1.[1] Most of the outcome data and therapeutic decision-making has evolved during this era and for the majority of this summary we will use the IPSS.

Demographics

Low-risk MDS (LR-MDS) comprises 75% of all MDS cases. The median age of presentation is 74 years with a male predominance for most subtypes. Exceptional to this is the strong female predominance of MDS with del(5q) and an equal sex distribution in Refractory Anemia with Ring Sideroblasts (RARS). Databases containing information obtained from several hospitals large and small such as EUMDS or Haematological Malignancies Research Network (www.hmrn.org) create a more representative picture of the demographics of MDS in routine clinical practice compared with data from the specialist single center referral registries (such as Düsseldorf, Pavia and MD Anderson). However the single center registries have the advantage of large numbers, good quality data and a longer duration of follow up.

Low risk disease in the revised IPSS (IPSS-R) era

The IPSS-R[2] introduces several significant changes

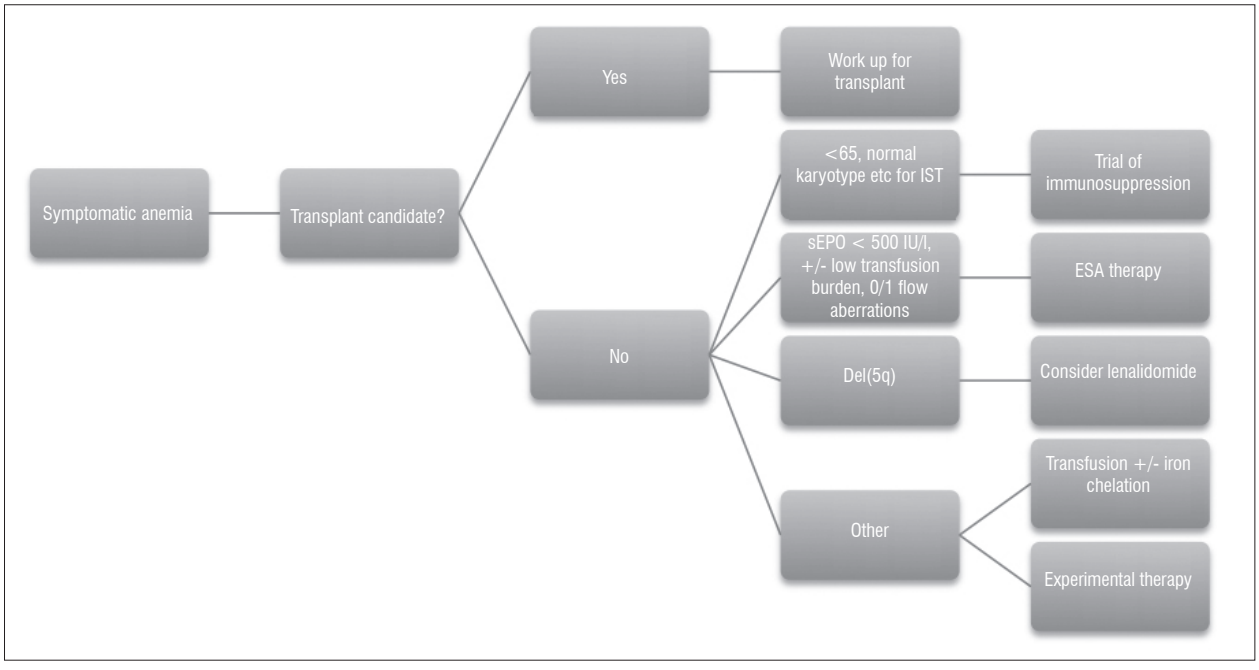

Figure 1. Algorithm: Management of symptomatic anemia in low-risk MDS

to the scoring system, three of which are particularly relevant to low-risk MDS

1. Division of bone marrow blast counts <5% into two categories, namely ≤2% vs. 3or 4%. (>2<5)
2. Subdivision of individual cytopenia values as categorical variables with relative importance now defined as hemoglobin concentration > platelet count > neutrophil count
3. Subdivision of cytogenetic abnormalities into 19 categories and 5 groups.

Low risk disease is now re-defined as IPSS-R Very Low and Low categories with the clinical assignment of the Intermediate group currently unclear with uncertainty as to whether this will segregate better with the definitions of 'low' or 'high' risk. Certainly the IPSS-R subgroups of Very Low and Low better define a good prognostic group of patients than IPSS Low / INT-1 combined.

Management of low-risk MDS

Early data from the EUMDS multicenter registry

This multicountry, multicenter registry programme was established in 2008 and to date has registered >1300 patients with newly diagnosed LR-MDS from 22 countries and >120 centers. At diagnosis, 29% patients have received a red cell transfusion and 15% patients are on treatment with an erythropoetic-stimulating agent (ESA). At 6 months follow up 31% patients are transfusion dependent and 35% patients are receiving an ESA. Thus even at 6 months after diagnosis the majority of LR-MDS patients do not require either red cell transfusion or active treatment.

Clinical significance of red cell transfusion dependence

The Pavia group were the first to recognize the importance of red cell transfusion dependence on outcome and derived the WHO based prognostic scoring system (WPSS) to quantify this.[3] Several independent studies have confirmed this observation and some of the subjective element of transfusion dependence has been replaced by hemoglobin concentration in the latest iteration of WPSS.[4] The mechanism for this effect remains unclear. Possibilities are:

- Transfusion dependence is a surrogate for biological characteristics that confer an adverse outcome
- Transfusion dependent patients have more severe anemia which may contribute to an increased incidence of cardiac death
- Transfusion may be harmful *per se*, either because of iron overload or as yet unidentified factors which could include increased infection risk

Irrespective of this observation, red cell transfusion remains the mainstay of interventional therapy for

anemia in the vast majority of patients, improving quality of life.[5] Despite the availability of active interventions such as those outlined below, the reality is that even in patients responding to these therapies most will lose the response and revert to red cell transfusion.

ESA for symptomatic anemia

Symptomatic anemia is the most common clinical problem in patients with low-risk MDS. Recombinant erythropoietin (EPO) therapy has been successfully applied for a subgroup of such patients for more than 20 years.[6] More recently other erythropoietic stimulating agents (ESAs) such as darbepoietin alfa have also been shown to be efficacious in low-risk MDS patients.[7,8] Factors predictive of response to EPO include a relatively low serum erythropoietin concentration (<500 IU/l) and a low/absent transfusion burden.[9](Figure 1) A lack of aberrant bone marrow myeloid antigen expression by multiparameter flow cytometry may add power to this predictive score.[10] Despite a considerable body of supportive phase 2 study data, no EPO product is licensed for use in MDS, although registration phase 3 studies are now ongoing, specifically in patients with a low/absent transfusion burden. Retrospective cohort comparator studies indicate a potential survival advantage for patients receiving ESA compared with those not receiving ESA.[8]

Lenalidomide for MDS with del(5q)

Following small studies identifying occasional responses to thalidomide[11] in low-risk MDS, a pivotal phase 2 study of the 4-amino-glutarimide analogue lenalidomide has transformed the management of selected patients with MDS with del(5q).[12] The Celgene 004 study has confirmed the superiority of lenalidomide compared with placebo in achieving erythroid response at 16 weeks in transfusion-dependent patients with MDS with del(5q).[13] Previous concerns about increased AML transformation in lenalidomide treated patients are now progressively diminishing although the natural history of MDS with del(5q) is now perhaps established as less indolent than previously thought.[14-16] The presence of a small *TP53* mutated clone confers an adverse prognosis in MDS with del(5q) and probably also a poor response to lenalidomide.[17]

Lenalidomide is also in phase 3 clinical trial for low risk MDS transfusion-dependent patients lacking del(5q) following phase 2 data identifying a minority of responders and a possible gene expression profiling signal that could predict response.[18]

Immunosuppressive therapy

Although immune dysregulation may underlie the hematopoietic defect in a significant proportion of patients with low-risk MDS, patients suitable for immunosuppressive therapy are rare. Factors predictive of response to antithymocyte globulin (ATG) are short duration of transfusion dependence, younger age (<60 yrs), low-risk MDS and normal karyotype.[19] Other putative predictive parameters including bone marrow hypocellularity, presence of a PNH clone and HLA DR15 tissue type are inconsistent between studies. Ciclosporin should be commenced after 2 weeks following ATG administration and continued for 6 months. Median duration of response is 2 years but toxicity is significant and occasionally life threatening. ATG should only be used in centers experienced in its use. Ciclosporin is rarely effective as a single agent in this author's experience.

Hypomethylating agents

Although licensed for use in MDS patients in the US, the trial data for this indication are phase 2 studies only and then in relatively small patient numbers. Superficially, response rates to azacitidine and to decitabine appear similar in low-risk compared with high-risk MDS.[20,21] The development programme for oral azacitidine is likely to focus on low-risk MDS, specifically a poorer risk population of patients with severe thrombocytopenia and red cell transfusion dependence.[22,23]

Allogeneic stem cell transplantation for low-risk MDS

Markov modeling has suggested that for patients with a sibling donor and suitable for myeloablative allogeneic stem cell transplant, delaying transplantation until evidence of disease progression optimizes the gain in life-years for patients with IPSS Low and INT-1 MDS.[24] No such data are available for unrelated donor transplants or for reduced intensity conditioning. It is also unclear what criteria for progression should be adopted in practice as the Markov modeling considered only AML transformation. Other parameters of progression include progressive cytopenias with heavy transfusion requirement, bone marrow blast increase (but insufficient for AML diagnosis i.e. less than 20%), and development of grade 2/3 fibrosis. There are no data to confirm these parameters as clear indications to move to transplant and indeed no data to indicate that transplant will improve the outcome of such patients whose disease progresses.

Management of other cytopenias

The prognostic significance of the degree of thrombocytopenia, first highlighted 25 years ago in the Sanz score,[25] has been re-emphasized in the revised IPSS.[2] Patients with chronic thrombocytopenia and bleeding manifestations are best managed with platelet transfusion. Anabolic steroids are occasionally helpful and thrombopoetin receptor mimetics are now under development in low-risk and high-risk MDS.[26]

Neutropenia may be treated with granulocyte-colony stimulating factor in patients with recurrent infections.

New agents for anemia management

Early phase studies are ongoing with agents whose mechanism of action may be different from those currently available, for example sotatercept and ARRY-614, both potentially targeting the MDS:microenvironment interface in addition to a direct effect on hematopoiesis. Oral azacitidine has been mentioned above.

Summary

Although at presentation most patients with low-risk MDS do not require active therapy, evolution of cytopenias, particularly anemia occurs in the majority during the course of the disease. Management of anemia can be effective with EPO, lenalidomide or immunosuppression but amelioration of anemia is typically transient and red cell transfusion remains the cornerstone of therapy. Novel therapeutic options targeting alternative pathways may prove beneficial for anemia management.

Disclosures

DTB has received honoraria for invited talks and Advisory Board membership from Celgene, AMGEN and Novartis. DTB receives funds from AMGEN and Novartis for global clinical trial work.

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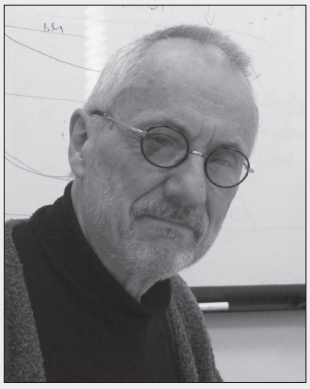

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He earned his medical degree at the University of Bonn, Germany, completed an internship and was Chief Medical Resident at the University of Rochester School of Medicine, Rochester, N.Y. He did his Hematology/Oncology fellowship under E.D.Thomas at the University of Washington, Seattle.

Dr. Deeg then established the Marrow Transplantation Program at Georgetown University in Washington D.C., and served as Director of the Immunology Laboratory at VGH, University of British Columbia,Vancouver before returning to Seattle.

Dr Deeg has worked and published extensively on transplantation biology, GVHD, the pathophysiology and therapy of aplastic anemia and MDS, late complications of cancer therapy and related questions. He has published more than 750 scientific papers. He is the recipient of the Alexander von Humboldt Research Award, he presented the Till and McCullough Lecture at the 11th Biennial CBMTG Conference (2008) in Montreal, and recently was recognized with the "Leadership in Science 2008" award by the Aplastic Anemia and MDS International Foundation. He has served on several NMDP and ASBMT committees, the Committee on Transplantation Biology of ASH, and is a member of the Myelodysplasia Panel of the National Comprehensive Cancer Center Network of the NCI. He has served on numerous editorial boards, including Blood and Biology of Blood and Marrow Transplantation.

"Dr Deeg will present an update on hematopoietic cell transplantation in patients with MDS. He will summarize recent developments of conditioning regimens and analyze the impact of cytogenetics on transplant outcome. He will also discuss the importance of clonal heterogeneity and clonal evolution as a feature of relapse of MDS after transplantation, and options for post-transplant management of relapse."

"Good afternoon. We are presenting now a session on Myelodysplastic Syndromes (MDS), divided into three presentations, one, by Dr Boultwood, on molecular aspects of the pathogenesis of MDS, one by Dr Bowen, on non-transplant management of MDS, and one by Dr Deeg , on the indications for and the results with transplantation for MDS. I hope that at the conclusion of our session you will have an up-to-date overview of many aspects of the rapidly evolving field of basic and clinical research in MDS".

ICLLM 2013

Indolent Lymphomas

Welcome note to Follicular Lymphoma session

The last ten years have seen major advances in the therapy of follicular lymphoma , these have included the incorporation of the monoclonal antibody Rituximab into first line treatment for follicular lymphoma , with recent evidence that bendamustine may be the best partner chemotherapy for this agent published in the Lancet by Rummel and colleagues in February 2013

We have also seen strong evidence that maintenance Rituximab prolongs remissions in patients based on the PRIMA trial led by Salles and also published in the Lancet in 2011

Patients with advanced stage FL can now expect to enjoy first remissions of over 6 years ,with longer remissions in those patients who have a negative PET scan at the end of induction.We have also seen an increasing role for stem cell transplantation in those patients relpaseing early after first line therapy

FL remains , though , an incurable disease in the majority of cases requiring therapy of increasing toxicity to maintain control of symptoms .

Can we do more to prolong remissions in this disease, how will our understanding of the biology of B cell malignancy lead to better and less toxic therapy , and what are we doing now to improve the outlook for this condition

In this session Robert Marcus will review our current therapies for FL with an emphasis on maximising response duration with minimal toxicity .Dan Hodson will discuss the biology of B cell lymphoma and suggest how insights into pathogenesis may lead to improvements in therapy and Nathan Fowler will tell us what agents are being incorporated now into clinical trials that might become standard of care in the near future

We look forward to a stimulating and enjoyable session

Robert Marcus, MD

CURRICULUM VITAE

Robert E. Marcus, MA, FRCP, FRCPath

Consultant Haematologist, Lead Cancer Clinician
Kings College Hospital
Consultant Haematologist
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Robert Marcus, MA, FRCP, FRCPath is consultant haematologist and lead cancer clinician at Kings College Hospital London . Dr Marcus received his medical degree from the University College Hospital Medical School in London and completed specialised haematology training at University College Hospital and a research fellowship in the MRC Leukemia Unit at the Royal Postgraduate Medical School at Hammersmith Hospital in London. Prior to joining King's College Hospital in 2008, Dr Marcus was Consultant Haematologist in Addenbrooke's Hospital in Cambridge for 20 years where he established the regional bone marrow transplant unit and developed a particular interest in Lymphoma

Dr Marcus' research interests include development of novel therapies for lymphoma. He participated in the first clinical studies in monoclonal antibody therapy for lymphoma with the CAMPATH series of antibodies and has been chief investigator in a large number of phase II and III studies on chemotherapy and immunotherapy in lymphoma, and was CI in the definitive R-CVP study that changed clinical practice in Follicular Lymphoma

Dr Marcus is the chairman of the NCRI low-grade lymphoma working party and has chaired numerous review groups and is an examiner for the Royal College of Pathologists. In addition, he is medical advisor to the Lymphoma Association and vice president of the Leukaemia Care Society. Dr Marcus has served on the editorial board of Bone Marrow Transplantation and has authored more than 140 peer-reviewed manuscripts and review articles. He has co-edited three books , including in 2007, a new standard textbook on Lymphoma, now in the process of revision and updating

Conventional Therapy for Low Grade B Cell Lymphoma

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1992 – 1995 University of Cambridge (Gonville and Caius College)

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Schmitz R, Young RM, Ceribelli1 M, Jhavar S, Xiao W, Zhang M, Wright G, Shaffer A, **Hodson DJ**, Buras E, Liu X, Powell J, Yang Y, Xu W, ZhaoH, Kohlhammer H, Rosenwald A, Kluin P, Müller-Hermelink HK, Ott G, Gascoyne RD, Connors JC, Rimsza LM, Campo E, Jaffe E, Delabie J, Smeland EB, Ogwang MD, Reynolds SJ, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, Pittaluga S, Wilson W, Waldmann TA, Rowe M, Mbulaiteye SM, Rickinson AB, and . Staudt LM. *Burkitt Lymphoma Pathogenesis and Therapeutic Targets from Structural and Functional Genomics.* Nature Accepted July 2012.

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The Biology of Indolent Lymphomas and How This May Inform Future Therapy

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The indolent lymphomas comprise a heterogeneous collection of tumours that includes follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma and hairy cell leukaemia. Recent technological advances such as next generation sequencing have greatly increased our understanding of the underlying biology of these tumours. This has implicated new genes and signalling pathways, many of which may be targets for pharmacological manipulation; however it has also revealed new complexities and challenges.

Normal B cell development

Follicular lymphoma (FL) is the commonest of the indolent lymphomas. Its pathogenesis is a multistep process involving both early and late stages of B cell maturation. As such a brief summary of normal B cell development is helpful. The earliest B cells are found in the bone marrow where they negotiate the process of VDJ recombination. Double stranded breaks, introduced by the RAG enzymes allow the immunoglobulin (Ig) genes to be "cut and pasted" leaving each B cell with a unique surface receptor (BCR). Those cells that generate a functional BCR exit the bone marrow as mature, naive B cells. Subsequent encounter with antigen in the context of T cell help then initiates the formation of a germinal centre (GC) within the B cell follicle. The germinal centre reaction is co-ordinated by the transcription factor BCL6 and is associated with intense B cell proliferation, class switch recombination (CSR) to other Ig isotypes and somatic hypermutation (SHM) of the Ig variable region. Higher affinity variants are selected to survive as long-lived memory B cells or plasma cells, whilst those with lower antigen binding ability undergo apoptosis. This default to apoptosis is in part related to the absent expression of BCL2 in normal germinal centre B cells. SHM and CSR in the GC mandate is a further period of deliberately induced DNA damage, this time mediated by the enzyme AID. Whilst the DNA damaging activity of RAG and AID is targeted primarily to the Ig genes, unintended oncogenic lesions are the inevitable cost and contribute to the initiation of B cell malignancy.

Follicular Lymphoma and the t(14:18) translocation

Follicular lymphoma is considered a germinal centre derived tumour[1]. Its immunophenotype and gene expression profile resembles normal GC cells including high expression of the germinal centre genes CD10, BCL6 and AID. However, unlike germinal centre B cells it expresses high levels of the antiapoptotic factor BCL2. This results from the t(14:18) translocation, which is seen in the majority of cases of FL and brings the BCL2 gene under the control of the Ig heavy chain enhancer region. It seems clear that this translocation occurs as an error of RAG mediated VDJ recombination in early stages of bone marrow B cell development but probably has little effect prior to the GC stage as BCL2 expression is a normal feature of immature and naive B cells. Although considered a hallmark feature of follicular lymphoma t(14:18) can not by itself be the cause of FL. BCL2 transgenic mice do not develop FL[2] and in fact a small population of t(14:18) translocated B cells can be detected in a sizable majority of the healthy human population without posing an obvious elevated risk of FL[3]. These t(14:18) cells are not naive B cells but instead resemble post-germinal centre memory B cells, evidenced by high rates of somatic hypermutation and class-switching on the non-productive IgH allele. This excludes the possibility that the act of entering the GC is itself the transforming event for a t(14:18) cell. In fact, the entity of Follicular Lymphoma In Situ (FLIS) may represent the coincidental capture of an innocuous t(14:18) naive B cell on its way through the germinal centre reaction, rather than an early stage of true FL. Therefore it seems clear that in addition to the t(14:18) translocation one or more secondary oncogenic genetic hits are required for the development of FL. The likely perpetrator of these secondary hits is "off-target" somatic mutations introduced by AID during the germinal centre reaction. Whilst BCL2 is itself a logical target for pharmacological manipulation clarifying the identity of these subsequent oncogenic events is clearly a critical step in the development of effective targeted therapy for FL.

Additional Genetic Defects

Recurrent chromosomal aberrations provide clues as to what these subsequent genetic hits might be. A recent systematic analysis of genes in the deleted region of chromosome 6q identified the gene EPHA7 as a negative regulator of oncogenic signalling pathways in follicular lymphoma[4]. Tissue microarray showed its expression to be absent in over 70% of FL whereas it was robustly expressed in normal germinal centres. Importantly an exogenously administered soluble form of EPHA7 suppressed xenograft models of FL suggesting that targeting this pathway is a potential therapeutic strategy in human FL. Also frequently deleted is chromosome 1p36 – deleted in 67% of FL[5-6]. The 12kb minimum deleted region is home to the TNFRSF14 gene, which is further inactivated by point mutation in 44% of FL. TNFRSF14 is reported be involved in fas-mediated apoptosis however its full function in FL currently remains a subject of current research.

Cancer genetics is currently being transformed by the application of next generation sequencing (NGS)[7]. The first human genome took a massive collaborative effort more than a decade to sequence. Current technology, in theory, allows the coding region (exome) to be sequenced in a day for a price similar to that paid for an MRI scan. Although NGS has so far only been applied to small cohorts of FL it has already begun to reveal which aberrations that may be required for the development of follicular lymphoma. Surprisingly the most frequently found class of mutations seem to affect genes involved in histone modification. Inactivating mutations of the histone methyl transferase MLL2 were found in nearly 90% of FL tumours sequenced[8]. This remarkably high frequency is equivalent to that of the "hallmark" t(14:18) translocation suggesting a major role for MLL2 in FL. Another histone methyltransferase, EZH2, showed recurrent activating mutations[9-10]. The same mutations are found in GCB type DLBCL and are consistent with increased EZH2 activity in the normal germinal centre, where it is thought to promote programs of gene expression that favour proliferation and survival. The histone acetyltransferases CREBBP MEF2B and EP300 were also mutated in 41% of FL tumours[8, 11]. In addition to their effects on chromatin they also acetylate BCL6 and p53 and their mutation leads to enhanced BCL6 and suppressed p53 activity[11]. Although there is still much that is not understood about the way these mutations contribute to the pathogenesis of FL it is clear from the mutation frequency alone that pathways regulating histone modification are of vital importance to the development of FL and as such represent important potential opportunities for therapeutic targeting.

It is likely that as larger cohorts of FL tumours are subjected to next generation sequencing in the near future our understanding of FL genetics will continue to expand further. It is pertinent to point out that next generation sequencing has also recently identified unexpected pathways for therapeutic targeting in the other indolent lymphomas. BRAF mutation is found in 100% hairy cell leukaemia[12], MYD88 mutation in 100% Waldenstrom's Macroglobulinaemia[13] and NOTCH or NFKB mutation in over half of splenic marginal zone lymphomas[14-15]. Importantly many of these mutations are in pathways for which targeted therapies are already approved for use in other indications.

The Importance of the Lymph Node Microenvironment

FL cells do not exist in isolation. The tumour is generally localised to lymph node and bone marrow. FL cells fail to grow when put into culture *ex vivo* and there are no cell lines that represent the untransformed stage of the disease. This is because the survival of FL cells is dependent upon signals received from the microenvironment. The histology of FL recapitulates the cellular architecture of normal B cell follicles and germinal centres including the close interaction with follicular dendritic cells (FDCs) and T follicular helper cells (TFH). This interaction is promoted by the receptors CXCR4 and CXCR5 on FL cells with the chemo-attractants CXCL12 and CXCL13 secreted by FDCs and TFHs[16]. Blocking this interaction, for instance with a CXCR4 agonist, might render FL cells more susceptible to therapy by releasing them from their supportive environment

Another crucial signal is delivered through the B cell receptor (BCR). An important feature of normal B cells and many B cell derived tumours is their dependence upon a continued signal through the BCR. The evidence suggests that FL is also dependent upon the continued expression of a functional BCR. Despite ongoing mutation of the BCR there is a strong selective pressure against mutations that render the BCR non-functional[17]. Previous attempts to use anti-idiotype antibodies as therapy induced responses but these were followed by relapse. Importantly these relapses were not associated with down-regulation of the BCR but rather with mutation of the idiotype, supporting the importance of continued BCR signalling to the survival of the FL cell[18]. Interestingly there appears to be a preference for the persistence of the IgM isotype and although switching to IgG is seen on the non-productive allele the majority of FL retains IgM on the expressed allele[19]. Retention of IgM expression seems to be a common feature of many GC derived

lymphomas and transmits a qualitatively different BCR signal from IgG. In some B cell malignancies, such as CLL, the immunoglobulin repertoire is biased toward the use of specific variable gene families suggesting antigen or autoantigen is a source of the BCR signal. Such biased VH gene usage does not appear to be a feature of FL. Although BCR autoreactivity has been detected in some cases of FL[20] it appears that the source of BCR signalling in the majority of cases of FL is probably antigen independent. Fascinatingly, in more than 80% of FL the BCR is modified by the addition of glycans to the Ig variable regions, a feature not seen in normal B cells[17]. This results from the introduction of specific acceptor motifs for glycan addition as a consequence of somatic hypermutation of the Ig V regions. The result of this glycosylation is that it may allow the BCR to interact with mannose-binding lectins on stromal cells, thus generating an antigen independent BCR signal that may promote the survival and proliferation of FL cells. The implication of this finding is that antibodies to lymphoma specific glycans might specifically deprive lymphoma cells of their essential BCR survival signal. An alternative way to block BCR survival signals would be to target one or more of the many downstream kinases such as Syk, BTK, PI3K and mTOR using drugs that are already in clinical use for other indications.

As well as being dependent upon signals from the microenvironment FL seems able to suppress the activity of infiltrating immune cells that might otherwise mount an anti-tumour immune response. FL cells appear capable of biasing the differentiation of CD4 T cells into regulatory T cells (Tregs), which suppress the activity of effector T cells, and total numbers of Treg cells are increased in FL lymph node[21]. Effector cells infiltrating the tumour are dysfunctional in their ability to respond to cytokine stimulation[22]. This appears to be related to high expression of the inhibitory molecule PD1 on FL infiltrating T cells. The implication of these findings is that PD1 neutralising antibodies may be able to restore the anti-tumour immune response as has been shown in a number of other malignancies.

Individual tumours consist of multiple competing subclones

A growing appreciation common to many types of malignancy is that one tumour in a single patient may actually consist of dynamic mix of distinct and competing subclones. Whilst there is often one dominant clone, post-treatment relapses and transformation to high-grade lymphoma (tFL) may not result from the direct evolution of this dominant clone but rather from the expansion of a pre-existing dormant clone or may represent divergent evolution from a common progenitor clone (CPC). A comparison of SHM patterns in paired biopsies before and after high-grade transformation was able to compute genealogical trees reflecting the clonal evolution of tumours[23]. This was able to infer that in two thirds of cases tFL arose through evolution from a common progenitor cell. In only one third of cases did the tFL appear to arise directly from the primary clone. Similarly, analysis of a father / son donor / recipient pair who developed FL and tFL 3 and 10 years respectively after bone marrow transplant showed both shared and unique mutations in each tumour. This suggests that both tumours arose from a common progenitor transferred at the time of BMT that must have existed many years before development of disease[23]. The exact identity of this CPC is unclear although shared Ig variable region somatic mutations suggested a GC experienced cell. However, there is mounting evidence that the earliest steps towards tumour development may occur even before commitment to the B cell lineage. Mice transplanted with haematopoietic stem cells from humans with CLL develop oligoclonal CD5+ B cells[24]. Separate VDJ gene usage confirms that this is not a result of contamination of the graft with CLL cells but rather an intrinsic property of the haematopoietic stem cell compartment. Exome sequencing analysis of a separate donor / recipient pair who both developed FL 7 years after BMT / DLI again showed both shared and unique mutations, suggesting a common progenitor cell[25]. As expected the BCL2 translocation was retrospectively detected in the CD19+ donor lymphocyte infusion but not in CD34+ purified cells. However, fascinatingly, mutation of three genes including EP300, which was identified in both donor and recipient tumours, was also detectable in the CD34+ purified cells. The implication of this finding is that the t(14:18) may not be the first genetic hit in FL but may in fact be a facilitating event in a cell that has already taken the first step to lymphomagenesis. Determining the order of these genetic lesions in FL is not just academic. Mutation targeted treatment will only be effective if it is aimed at pathways that are both key drivers of the tumour and occur in every tumour cell. Otherwise relapse through outgrowth of subclones is inevitable. Current mutation screening usually describes the presence or absence of a mutation and has not until recently attempted to quantify the proportion of cells that possess the mutation as our ability to sequence more deeply continue to improve this will surely become a feature of future sequencing projects. Indeed a recent exome sequencing analysis of FL has attempted to do this and to determine which mutations are key early drivers and which are later subclonal accelerators[26]. One

key finding of this analysis was that the histone acetyltransferase CREBBP was identified as a key early driver. Combined with the high percentage of FL cases that show mutation of CREBBP (or one of its partners MEF2B or EP300)[8] and the previously described presence of EP300 mutation in the stem cell compartment of the BMT transferred FL[25], this suggests that histone acetyltransferase inactivation represents a major component in the pathogenesis of FL and must therefore represent an important pathway for potential target therapy.

Summary

Our understanding of the biology of indolent lymphomas and the rate of discovery has increased dramatically over the last few years. This is largely due to the development of next generation sequencing. Its application to FL and the other indolent lymphomas remains at a relatively early stage but as a greater number of cases are sequenced (and sequenced to a depth to allow subclonal analysis) the key mechanisms of lymphomagenesis will open up even further. Encouragingly, many of the most promising pathways currently established may be amenable to targeting with agents that are already in use or in development for other indications.

Abbreviations used

BCR	B Cell Receptor
FL	Follicular Lymphoma
GC	Germinal Centre
Ig	Immunoglobulin
NGS	Next Generation Sequencing
SHM	Somatic Hypermutation
TFh	T Follicular Helper Cell
tFL	Transformed Follicular Lymphoma
Treg	Regulatory T cell

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Army Achievement Medal, US Army, 1990
Valedictorian. Nuclear, Biological, and Chemical Defense School, US Army, 1990
National Defense Medal, US Army, 1991
Overseas Service Ribbon, US Army, 1991
Dean's List, 1994-1996
Order of Omega Greek Honor Society, 1995-1996
Natural Science and Mathematics Scholar and Fellow, 1996
Georgetown Chief Fellow, 2006-2007

RESEARCH

Grants and Contracts

Funded
N/A

Pending
N/A

Other
N/A

Completed
Principal Investigator, 1%, Developing NK-Cell Therapies to Enhance the Treatment of non-Hodgkin Lymphoma, SPORE, 9/1/2010-7/31/2011, $35,000

Not Funded
N/A

Protocols

Funded

Principal Investigator, A Phase II Study of R-FND, Followed by Zevalin Radioimmunotherapy, and Subsequent Maintenance Rituximab for Advanced Stage Follicular Lymphoma with High-Risk Features, ID03-0287, 2004-2009, $300,000, Genentech

Principal Investigator, Randomized, Open-label, Phase II Trial Comparing Rituximab Plus Sargramostim to Rituximab Monotherapy for the Treatment of Relapsed Follicular B-cell Lymphoma, 2006-0313, 2006-2009, Bayer

Co-Principal Investigator, Phase II Study of Lenalidomide and Rtuximab for Indolent Lymphoma, 2008-0042, PI - Felipe Samaniego, 2006-present

Principal Investigator, Single-arm, Open-label, Phase II Trial of Rituximab Plus Sargramostim for the Treatment of Newly Diagnosed Follicular B-cell Lymphoma in Adults, 2006-0260, 2006-present, $496,647, Berlex Laboratories/NCI/CCOP

Principal Investigator, A Phase I, Multicenter, Open-label, Single-arm, Dose-escalation Study to Evaluate the Safety, Tolerability, Antitumor Activity of Continuous Intravenous Infusion of the Bispecific T-cell Engager Medi-538 in Adults with B-cell Non-Hodgkin's Lymphoma Not Eligible for Curative Therapy, 2007 - 0378, 2007-2008, $277,037, MedImmune

Principal Investigator, Phase II Study of Bendamustine, Mitoxantrone, and Rituximab in Patients with Indolent Non-Hodgkin's Lymphoma, 2008-0204, 2007-2011, $273,351, Cephalon

Co-Principal Investigator, A Phase II, Randomized, Double-Blind, Placebo Controlled Study of the Safety, Pharmacokinetics, and Efficacy of Multiple Doses of Apomab Administered Intravenously in Combination with Rituximab in Patients with Follicular, CD 20-Positive B-Cell Non-Hodgkin's Lymphoma that has Progressed Following Previous Rituximab Therapy, 2008-0149, PI - Michelle Fanale, MD, 2008-2010

Principal Investigator, An Open-Label, Phase 1 Study of MLN8237, a Novel Aurora A Kinase Inhibitor, in Patients with Advanced Hematological Malignancies, 2008-0278, 2008-2010, $359,198, Millennium

Principal Investigator, A Phase 2 Study of Velcade (bortezomib) in Combination with Bendamustine and Rituximab in Subjects with Relapsed or Refractory, Follicular Lymphoma, 2008-0124, PI - Nathan Fowler, MD, 2008-present, $235,435, Millennium

Principal Investigator, An Open-Label, Dose Escalation, Phase 1 Study of MLN4924, A Novel Inhibitor of Nedd8-Activating Enzyme, in Adult Patients with Lymphoma or Multiple Myeloma, 2008-0135, 2008-present, $418,402, Millennium

Principal Investigator, Phase I Dose-escalation Study of Bruton's Tyrosine Kinase (Btk) Inhibitor PCI-32765 in Recurrent B Cell Lymphoma, 2008-0494, 2009-2010, $363,568, Pharmacyclics

Principal Investigator, An Open-label Study to Evaluate the Efficacy and Safety of Treatment with Bendamustine in Combination with Ofatumumab in Previously Untreated Patients with Indolent B-Cell Non-Hodgkin's Lymphoma (NHL), 2009-0980, 2010-2011, $217,900, Cephalon

Principal Investigator, An Open-Label, Multicenter, Randomized, Phase III Study To Investigate The Efficacy And Safety Of Bendamustine Compared With Bendamustine + RO5072759 (GA101) In Patients With Rituximab-Refractory, Indolent Non-Hodgkin's Lymphoma, 2010-0197, 2010-present, $496,060, Genentech

Principal Investigator, A long-term Study of Bruton's Tyrosine Kinase (Btk) Inhibitor PCI-32765 in B Cell Lymphoma and Chronic Lymphocytic Leukemia, 2010-0467, 2011-present, $109,595, Pharmacyclics

Principal Investigator, A Multicenter, Open-label, Phase 2, Safety and Efficacy Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Refractory De Novo Diffuse Large B-Cell Lymphoma, 2011-0134, 2011-present, $348,927, Pharmacyclics

Principal Investigator, A Phase 3 Open-label Randomized Study to compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy followed by Rituximab in Subjects with Previously Untreated Follicular Lymphoma, 2011-0805, 2011-present, Celgene

Principal Investigator, A Phase I Study to Investigate the Safety and Clinical Activity of CAL-101 in Combination with Chemotherapeutic Agents and CD20 mAb in Patients with Relapsed or Refractory Indolent B-cell Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia, 2010-0811, 2011-present, $216,313, Calistoga Pharmaceuticals

Principal Investigator, An Open-label, Single-Arm, Phase I Study of AEB071 (a Protein Kinase C Inhibitor) in Patients with CD79-Mutant Diffuse Large B-cell Lymphoma, 2011-0681, 2011-present, Novartis

Principal Investigator, Fludarabine, Mitoxantrone, and Dexamethasone (FND) Plus Chimeric Anti-CD20 Monoclonal Antibody (rituximab) for Stage IV Indolent Lymphoma, DM97-261, 2011-present, $381,408, Genentech

Unfunded

Principal Investigator, A Retrospective Review of Bone marrow Biopsy and Flow Cytometry Results from Patients with Follicular Lymphoma, DR08-0818, 2009-present

Principal Investigator, A Retrospective Review of Patients with Primary Intraocular Lymphoma, DR09-0356, 2009-present

Principal Investigator, A Phase I Trial of Lenalidomide and Rituximab Plus Expanded Autologous NK Cells in Patients with Relapsed Indolent and Mantle Cell Lymphoma, 2010-0199, 2010-present

Patents and Technology Licenses

Patents
N/A

Technology Licenses
N/A

Grant Reviewer/Service on Study Sections

Cancer Research UK, Clinical Trials Awards and Advisory Committee (CTA, Member, 2012-present

CLL Global Research Foundation, Not for profit Research Funding, Grant Reviewer, 2012-present

Lymphoma Research Foundation, Scientific Advisory Board, Member, 2012-present

PUBLICATIONS

1. Peer-Reviewed Original Research Articles
2. Fowler N, Spell D. Case report. Parotid gland metastasis as the initial manifestation of a non-small cell lung cancer. Southern Medical J. Vol 95:S:25, 2002.
3. Fowler N, Asatiani E, Cheson B. Needle tract seeding after bone marrow biopsy in non-Hodgkin lymphoma. Leuk Lymphoma 49(1):156-8, 1/2008.
4. Fowler N, Younes A. There will be blood: targeting tumor vasculature. Blood 113(10):2121-2122, 3/2009.
5. Goldman L, Ezzat S, Mokhtar N, Abdel-Hamid A, Fowler N, Gouda I, Eissa S, Abdel-Hamid M, Loffredo C. Viral and non-viral risk factors for non-Hodgkin's Lymphoma in Egypt: heterogeneity by histological and immunological subtypes. Cancer Causes Control 20(6):981-7, 8/2009. e-Pub 3/2009.
6. Mazloom A, Fowler N, McLaughlin P, Iyengar P, Cabinillas F, Fayad L, Pro B, Medeiros J, Rodriguez A, Reed V, Urbauer D, Gonzalez G, Dabaja B. Outcome of patients with diffuse large B-cell lymphoma of the testis by era of treatment: the M. D. Anderson Cancer Center experience. Leuk Lymphoma 51(7):1217-1224, 7/2010.
7. Phan J, Mazloom A, Medeiros J, Shihadeh F, Rodriguez A, Fayad L, Fowler N, Reed V, Horace P and Dabaja B. The benefit of consolidative radiation therapy in patients with diffuse large b-cell lymphoma treated with R-CHOP chemotherapy. Journal of Clinical Oncology 28(27)(4):4105-7, 9/2010.
8. Mazloom A, Rodriguez A, Ha CS, Medeiros LJ, Wogan C, Shihadeh F, Allen P, Fowler N, Dabaja B. Incidence of gastric involvement in patients with nongastrointestinal extranodal marginal zone lymphoma. Cancer. e-Pub 12/2010.
9. Shahani S, Ahmad A, Barakat FH, Chuang HH, Fowler NH, Myers JN, Stava C, Habra MA. F-18 FDG PET/CT detecting thyroid plasmacytoma after the successful treatment of gastric large B-cell lymphoma. Clin Nucl Med 36(4):317-9, 4/2011.
10. Fowler N, Kahl BS, Lee P, Matous JV, Cashen AF, Jacobs SA, Letzer J, Amin B, Williams ME, Smith S, Saleh A, Rosen P, Shi H, Parasuraman S, Cheson BD. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: The phase II VERTICAL study. J Clin Oncol 29(25):3389-95, 9/2011. e-Pub 8/2011.
11. Fowler N. Role of Maintenance Rituximab (Rituxan) Therapy in the Treatment of Follicular Lymphoma. Pharmacy and Therapeutics 36(9):590-598, 9/2011.
12. Vadhan-Raj S, Fayad LE, Fanale MA, Pro B, Rodriguez A, Hagemeister FB, Bueso-Ramos CE, Zhou X, McLaughlin PW, Fowler N, Shah J, Orlowski RZ, Samaniego F, Wang M, Cortes JE, Younes A, Kwak LW, Sarlis NJ, Romaguera JE. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. Ann Oncol 23(6):1640-5, 6/2012. e-Pub 10/2011.
13. Khouri IF, Saliba RM, Erwin WD, Samuels BI, Korbling M, Medeiros LJ, Valverde R, Alousi AM, Anderlini P, Bashir Q, Ciurea S, Gulbis AM, de Lima M, Hosing C, Kebriaei P, Popat UR, Fowler N, Neelapu SS, Samaniego F, Champlin RE, Macapinlac HA. Nonmyeloablative allogeneic transplantation with or without 90yttrium ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. Blood 119(26):6373-8, 6/2012. e-Pub 5/2012.
14. Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, Neelapu SS, Samaniego F, McLaughlin P, Fanale M, Younes A, Cabanillas F, Fowler N, Newberry KJ, Sun L, Young KH, Champlin R, Kwak L, Feng L, Badillo M, Bejarano M, Hartig K, Chen W, Chen Y, Byrne C, Bell N, Zeldis J, Romaguera J. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol 13(7):716-23, 7/2012. e-Pub 6/2012.
15. Westin JR, Thompson MA, Cataldo VD, Fayad LE, Fowler N, Fanale MA, Neelapu S, Samaniego F, Romaguera J, Shah J, McLaughlin P, Pro B, Kwak LW, Sanjorjo P, Murphy WA, Jimenez C, Toth B, Dong W, Hagemeister FB. Zoledronic Acid for Prevention of Bone Loss in Patients Receiving Primary Therapy for Lymphomas: A Prospective, Randomized Controlled Phase III Trial. Clin Lymphoma Myeloma Leuk. e-Pub 12/2012.
16. Advani RH, Buggy JJ, Sharman JP, Smith SM, Boyd TE, Grant B, Kolibaba KS, Furman RR, Rodriguez S, Chang BY, Sukbuntherng J, Izumi R, Hamdy A, Hedrick E, Fowler NH. Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies. J Clin Oncol 31(1):88-94, 1/2013. e-Pub 10/2012.

Invited Articles
N/A

Editorials
N/A

Other Articles
N/A

Abstracts

1. S.A. Siddique, N. Fowler, E. Asatiani, B. Mavromatis, P. Cohen, C.M. Kessler and B.D. Cheson. Infectious complications associated with alemtuzumab treatment. ASCO Meeting

Abstracts 25(18S) (#13504), 6/2007.
2. Cataldo V, Thompson M, Toth B, Sanjoro P, Bekele N, Jimenez C, Murphy W, Huen A, Arbuckle R, Fanale M, Fayad L, Fowler N, Kwak L, McLaughlin P, Neelapu S, Pro B, Rodriguez A, Shah J, and Hagemeister F. Bone loss in patients with previously untreated lymphoma: The effect of periodontal disease on the use of zoledronic acid. Blood (ASH Annual Meeting Abstracts) 112:5297, 11/2008.
3. McLaughlin P, Neelapu S, Fanale M, Rodriguez M, Ayala A, Pro B, Hagemeister F, Younes A, Neel S, Fowler N, Hess M, and Kwak L. R-FND followed by radioimmunotherapy for high-risk follicular lymphoma. Blood (ASH Annual Meeting Abstracts) 112:3056, 11/2008.
4. Fowler N, McLaughlin P, Kwak L, Fanale M, Hagemeister F, Fayad L, Pro B, and Samaniego F. Lenolidomide and rituxan for untreated indolent b cell non-Hodgkin's lymphoma. ASCO Meeting Abstracts 27(15s) (#8558), 5/2009.
5. Matous J, Letzer J, Rosen P, Noga S, Fowler N, Smith S, Amin B, Shi H, Parasuraman S, and Cheson B. Bortezomib, bendamustine, and rituximab in patients (pts) with relapsed (rel) or refractory (ref) follicular lymphoma (FL): Dose finding results of the VERTICAL study. ASCO Meeting Abstracts 27(Suppl 15s) (#8550), 6/2009.
6. Fowler N, Khan S, and Gilliam M. Non-Hodgkin's lymphoma and hepitatis C prevalence of co-infection and outcomes following anti-viral theapy: A Review of the literature. 2009 Pan Pacific Lymphoma Conference, http://www.unmc.edu/cce/panpacific/index.htm, 6/2009.
7. Fowler N, Khan S, and Gilliam M. Non-Hodgkin's lymphoma and hepatitis c: prevalence of co-infection and outcomes following anti-viral therapy: a review of the literature. 2009 Pan Pacific Lymphoma Conference, 8/2009.
8. Fowler N, McLaughlin P, Hagemeister F, Kwak L, Fanale M, Neelapu S, Fayad L, Pro B, Sergent C, White S, and Samaniego F. A biologic combination of lenalidomide and rituximab for front-Line therapy of indolent b-cell non-Hodgkin's lymphoma. Blood (ASH Annual Meeting Abstracts) 114(22):683, 11/2009.
9. Pollyea D, Smith S, Fowler N, Boyd T, Smith A, Sirisawad M, Honigberg L, Hamdy A, and Advani R. A phase I dose escalation study of the Btk inhibitor PCI-32765 in relapsed and refractory b cell non-Hodgkin lymphoma and use of a novel flourescent probe pharmacodynamic assay. Blood (ASH Annual Meeting Abstracts) 114(22):1430, 11/2009.
10. Westin J, Thompson M, Cataldo V, Toth B, Sanjorjo P, Bourgeois S, Jimenez C, Murphy W, Fanale M, Fayad L, Fowler N, Kwak L, McLaughlin P, Neelapu S, Pro B, Rodriguez A, Shah J, and Hagemeister F. Bone loss in lymphoma patients receiving frontline therapy: Urine NTx and bone specific alkaline phosphatase provide early evidence of zoledronic acid response. Blood (ASH Annual Meeting Abstracts) 114(22):1508, 11/2009.
11. Fowler N, Kahl B, Rosen P, Matous J, Cashen A, Jacobs S, Letzer J, Amin B, Williams M, Ross M, Smith S, Saleh A, Shi H, Parasuraman S, and Cheson B. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL study. Blood (ASH Annual Meeting Abstracts) 114(22):384, 11/2009.
12. Mazloom A, Fowler N, Iyengar P, and Dabaja B. Primary testicular diffuse large b-cell lymphoma, M.D. Anderson Cancer Center experience. Blood (ASH Annual Meeting Abstracts) 114(22):1055, 11/2009.
13. Vadhan-Raj S, Fayad L, Fanale M, Pro B, Rodriguez A, Hagemeister F, Ames K, Buesno-Ramos C, Zhou X, McLaughlin P, Fowler N, Shah J, Samaniego F, Younes A, Kwak L, and Romaugera J. Randomized clinical trial of rasburicase administered as a standard fixed five days dosing vs a single dose followed by as needed dosing in adult patients with hematologic malignancies at risk for developing tumor lysis syndrome. Blood (ASH Annual Meeting Abstracts) 114(22):48, 11/2009.
14. Khouri I, Harrell R, Valverde R, Korbling M, Manshouri T, Samuels B, Maadani F, Okoroji G, Bassett R, Amin A, Anderlini P, De Lima M, Giralt S, Hosing C, Kebriaei P, Popat U, Qazilbash M, Ueno N, Stachowiak A, Erwin B, Fayad L, Pro B, Fowler N, McLaughlin P, Neelapu S, Younes A, Champlin R, and Podoloff D. Stem cell transplantation with 90yttrium ibritumomab tiuxetan (90YIT) in non-Hodgkin's lymphoma (NHL): Observations from PET pre-treatment imaging and responses in allografted refractory follicular histologies. Blood (ASH Annual Meeting Abstracts) 114(22):357, 11/2009.
15. Fowler NH, McLaughlin P, Hagemeister FB, Kwak LW, Fanale M, Neelapu SS, Fayad LE, Orlowski RZ, Wang M, Samaniego F. Complete response rates with lenalidomide plus rituximab for untreated indolent B-cell non-Hodgkin's lymphoma. ASCO Meeting Abstracts 28(15s (Suppl)) (#8036), 5/2010.
16. Perini GF, Romaguera JE, Rodriguez MA, Pro B, Younes A, Fowler NH, Hagemeister F, Samaniego F, Kwak LW, Fayad L. Diffuse large B-cell lymphoma (DLBCL) with bone marrow (BM) involvement, clinica presentation, central nervous system (CNS) relapses, and outcomes of 121 patients treated at M.D. Anderson Cancer Center. ASCO Meeting Abstracts 28(15s (Suppl)) (#8072), 5/2010.
17. Advani R, Sharman JP, Smith SM, Pollyea DA, Boyd TE, Grant BW, Kolibaba KS, Buggy JJ, Hamdy A, Fowler NH. Effect of Btk inhibitor PCI-32765 monotherapy on responses in patients with relapsed aggressive NHL: Evidence of antitumor activity from a phase I study. ASCO Meeting Abstracts 28(15s (Suppl)) (#8012), 5/2010.
18. Fowler N, Sharman JS, Smith SS, Pollyea DP, Boyd TB, Grant BG, Kolibaba KK, Buggy JB, Hamdy AH, Advani, RA. A Phase I Trial of Btk inhibitor PCI-32765 in patients with relapsed non-Hodgkin's lymphoma: Evidence of antitumor activity. Haematologica 95(371(Suppl 2)) (#0893), 6/2010.
19. Batty N, Ghonimi E, Feng L, Younes A, Rodriguez A, Wager E, Martinez F, Wang M, McLaughlin P, Fowler N, and Hagemeister F. Blood transfusion and erythropoiesis stimulating agents (ESAs) use in patients with diffuse large B-cell lymphoma (DLBCL). Blood (ASH Annual Meeting Abstracts) 116(21) (#3357), 11/2010.
20. Okoroji G, Silva L, Saliba R, Korbling M, McLaughlin P, Hosing C, Anderlini P, Alousi A, de Lima M, Kebriaei P, Popat U, Qazilbash M, Fayad L, Samaniego F, Fowler N, Champlin R, Hagemeister F, and Khouri I. Outcome in follicular lymphoma (FL) patients (pts) relapsing after autologous stem cell transplantation (ASCT): Allografting vs conventional therapy. Blood (ASH Annual Meeting Abstracts) 116(21) (#3510), 11/2010.
21. Padmanabhan S, Shea T, Vose J, Reeder C, Berdeja J, McDonagh K, Goy A, Kelly K, Zhou X, Liu H, Fingert H, and Fowler N. Phase I study of an investigational aurora A kinase inhibitor MLN8237 in patients with advanced hematologic malignancies. Blood (ASH Annual Meeting Abstracts) 116(21) (#2799), 11/2010.
22. Fowler N, Sharman J, Smith S, Boyd T, Grant B, Kolibaba K, Furman R, Buggy J, Loury D, Hamdy A, and Advani R. The Btk inhibitor, PCI-32765, induces durable responses with minimal toxicity in patients with relapsed/refractory B-cell malignancies: Results from a phase I study. Blood (ASH Annual Meeting Abstracts) 116(21) (#964), 11/2010.
23. Burger J, O'Brien S, Fowler N, Advani R, Sharman J, Furman R, Izumi R, Buggy J, Loury D, Hamdy A, Byrd J, and Blum K. Thr Bruton's tyrosine kinase inhibitor, PCI-32765, is well tolerated and demostrates promising clinical activity in chronic lymphomcytic leukemia (CLL) and small lymphocytic lymphoma (SLL): An update on ongoing phase I studies. Blood (ASH Annual Meeting Abstracts) 116(21) (#57), 11/2010.
24. R. Advani, J. P. Sharman, S. M. Smith, D. A. Pollyea, T. E. Boyd, B. W. Grant, K. S. Kolibaba, J. J. Buggy, A. Hamdy, N. H. Fowler. Btk inhibitor PCI-32765 monotherapy induces objective responses in patients with relapsed aggressive NHL: Evidence of antitumor activity from a phase 1 study. Journal of Clinical Oncology 29(15) (#54096), 5/2011.
25. Fowler N, Hagemeister F, McLaughlin P, Kwak L, Romaguera J, Fanale M, Neelapu S, Fayad L, Orlowski R, Wang W, Pro B, Lacerte L, Samaniego f. High Response Rates with Lenalidomide Plus Rituximab for Untreated Indolent B cell non-Hodgkins Lymphom. Ann Oncol 22(Suppl 4), 6/2011.
26. Fowler N, Mclaughlin P, Fisch M, Dakhil S, Bury M, Fayad L, Shah J, Neelapu S, Romaguera J, Rodriguez D, Ayala A, Kwak L. Rituximab plus sargramostim for the treatment of newly diagnosed follicular lymphoma: Final Results of a Phase II study. Ann Oncol 22(Suppl 4), 6/2011.
27. de Vos S, Schreeder M, Flinn I, Coutre S, Leonard J, Wagner-Johnston N, Fowler N, Boccia R, Barrientos J, Boyd T, Sharman J, Holes L, Lannutti B, Johnson D, Jahn T, and Miller L. A phase 1 study of the selective phosphatidylinositol 3-kinase-delta (PI3Ko) inhibitor, Cal-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with previously treated, indolent non-Hodgkin's lymphoma (iNHL). Blood (ASH Annual Meeting Abstracts) 118(21) (#2699), 11/2011.
28. Sharman J, de Vos S, Leonard J, Furman R, Coutre S, Flinn I, Schreeda M, Barrientos J, Wagnor-Johnston N, Boyd T, Fowler N, Holes L, Lannutti B, Johnson D, Jahn T, and Langdon M. A phase 1 study of the selective phosphatidylinositol 3-kinase-delta (PI3Ko) inhibitor, CAL-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Blood (ASH Annual Meeting Abstracts) 118(21) (#1787), 11/2011.
29. Vadhan-Raj S, Spasojevic I, Zhou X, Romaguera J, Fanale M, Fayad L, Fowler N, Huen A, Hagemeister F, Rodriguez M, Neelapu S, Samaniego F, Younes A, and Kwak L. Effects of aprepitant on drug metabolism in lymphoma patients receiving multi-day chemotherapy regimen of cyclophosphamide, doxorubicon, vincristine, prednisone, + rituxan (R/CHOP): Randomized, cross-over study. Blood (ASH Annual Meeting Abstracts) 118(21) (#1613), 11/2011.
30. Khouri I, Saliba R, Valverde R, Samuels B, Korblin M, Alousi A, Anderlini P, Bashir Q, de Lima M, Hosing C, Kebriaei P, Nieto Y, Popat U, Qazilbash M, Neelapu S, Fowler N, Samaniego F, Wang L, Champlin R, and Macainlac H. Nonmyeloablative allogenic stem cell transplantation with/without 90yttrium ibritumomab tiexetan (90YIT) is curative for relapsed follicular lymphoma: Median 9 year follow-up results. Blood (ASH Annual Meeting Abstracts) 118(21) (#662), 11/2011.
31. Fowler N, Neelapu S, Fanale M, Rodriguez M, Pro B, Hagemeister F, Younes A, Shah J, Kwak L, Rodriguez D, and McLaughlin P. Phase II study with R-FND followed by 90-Y Ibritumomab tiuxetan radioimmuntherapy and rituximab maintenance for untreated high-risk follicular lymphoma. Blood (ASH Annual Meeting Abstracts) 118(21) (#99), 11/2011.
32. Fowler N, Munteanu M, Davis G, Brown P, Czuczman M. Results of a Phase II Study with Bendamustine and Ofatumumab in Untreated Indolent B-Cell Non-Hodgkin's Lymphoma. Blood (ASH Annual Meeting Abstracts) 118(21), 11/2011.
33. Fowler N, Kahanic S, Ferero A, Murteanu M, Davis G, Brown P, Van Den Neste E, Offner F, Bron D, and Czuczman M. Results of a phase II study with bendamustine and ofatumumab in untreated indolents B-cell non-Hodgkin's lymphoma. Blood (ASH Annual Meeting Abstracts) 118(21) (#778), 11/2011.
34. Nelson K, Samaniego F, Hagemeister F, Lacerte L, Kwak L Neelapu S, Fayad L, LeBlanc D, and Fowler N. Dermatologic side effects of lenalidomide and rituximab in indolent lymphoma. 2012 Pan Pacific Lymphoma Conference, http://www.unmc.edu/cce/panpacific/index.cfm?L1_ID=21&CONREF=21, 7/2012.
35. Gardner K, Dabaja B, Reed V, Kim M, Gambos D, Sorenson E, and Fowler N. Priamry intraocular diffuse large B-cell lymphoma: Outcomes following combined modality treatment. 2012 Pan Pacific Lymphoma Conference, http://www.unmc.edu/cce/panpacific/index.cfm?L1_ID=21&CONREF=21, 7/2012.
36. Rawal S, Fowler N, Zhang M, Wang Z, Muzzafar T, Harun N, Baladadayuthapani V, Sharma R, Delgado D, Wallace M, Heise C, Lacerte L, Samaniego F, Davis E, and Neelapu S. Activation of T and NK cells following lenalidomide therapy in patients with follicular lymphoma. Blood (ASH Annual Meeting Abstracts) 120(21) (#2766), 11/2012.
37. Fowler N, de Vos S, Schreeder M, Leonard J, Flinn I, Coutre S, Wagner-Johnston N, Sharman J, Boccia R, Barrientos J, Boyd T, Holes L, Lannutti B, Johnson D, Jahn T, Miller L, and Godfrey W. Combinations of the phosphatidylinositol 3-kinase-delta (PI3Ko) inhibitor Gs-1101 (Cal-101) with rituximab and/or bendamustine are tolerable and highly active in previously treated, indolent non-Hodgkin lymphoma: Results from a phase I study. Blood (ASH Annual Meeting Abstracts) 120(21) (#3645), 11/2012.
38. Coutre S, Leonard J, Furman R, Barrientos J, de Vos S, Flinn I, Schreeder M, Wagner-Johnston N, Sharman J, boyd T, Fowler N, Holes L, Lannutti B, Johson D, Miller L, and Jahn T. Combinations of the slective phosphatidylinositol 3-kinase-delta (PI3Kdelta) inhibitor GS-1101 (Cal-101) with rituximab and/or bendamustine are tolerable and highly active in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): Results from a phase I study. Blood (ASH Annual Meeting Abstracts) 120(21) (#191), 11/2012.
39. Fowler N, Neelapu S, Hagemeister F, McLaughlin P, Kwak L, Roamguera J, Fnaale M, Fayad L, Orlowski R, Wang M, Turturro F, Oki Y, Lacerte L, and Samaniego F. Lenalidomide and rituximab for untreated indolent lymphoma: Final results of a phase II study. Blood (ASH Annual Meeting Abstracts) 120(21) (#901), 11/2012.
40. Westin J, Chu F, Fayad L, Kwak L, Fowler N, Romaguera J, Hagemeister FB, Fanale M, Samaniego F, Allen R, Feng L, Baladandayuthapani V, Rotem-Yehudar R, and Neelapu S. Phase II safety and efficacy study of CT-011, a humanized anti-PD-1 monoclonal antibody, in

combination with rituximab in patients with relapsed follicular lymphoma. Blood (ASH Annual Meeting Abstracts) 120(21) (#793), 11/2012.

41. Fanale M, Lai C, Rimes S, Ramirez M, Hagemeister F, Fowler N, Younes A, Fayad L, Rodriguez MA, Turturro F, Samaniego F, Romaguera J, Levin V, Horowitz S, Woolery J, and Milbourne A. Positive maternal-fetal outcomes with treatment of lymphoma during pregnancy: UT MD Anderson Cancer Center prospective experience. Blood (ASH Annual Meeting Abstracts) 120(21) (#3670), 11/2012.
42. Oki Y, Westin J, Fowler N, Neelapu S, Hagemeister FB, McLaughlin P, Kwak L, Romaguera J, Fanale M, Younes A, Rodrigues MA, Orlowski R, Wang M, Ouzounian S, Samaniego F, and Fayad L. R-HCVAD alternating with R-methotrexate cytrabine in younger patients (pts) with IH and high-risk age adjusted-IPI DLBCL. Blood (ASH Annual Meeting Abstracts) 120(21) (#3707), 11/2012.
43. Oki Y, Chuang H, Chasen B, Pan T, Fanale M, Dabaja B, Fowler N, Romaguera J, Fayad L, Hagemeister FB, Rodriguez A, Neelapu S, Samaniego F, Kwak L, and Younes A. The prognostic value of interim PET scan in patients with classical Hodgkin lymphoma. Blood (ASH Annual Meeting Abstracts) 120(21) (#1529), 11/2012.

Book Chapters

1. McLaughlin P, Fowler N, Liu N, Medeiros J. The Indolent Lymphomas. In: The MD Anderson Manual of Medical Oncology, 2nd Edition. McGraw-Hill, 2010.
2. Fowler N, Horowitz S, McLaughlin P. Therapy of B-cell lymphoproliferative disorders. In: Experimental and Clinical Hematopathology. Ed(s) D Jones. Springer/Humana, 2010.
3. Fowler N, McLaughlin P. Non-Hodgkin's Lymphoma. In: Advances in Malignant Hematology. Ed(s) Saba, HI and Mufti, GJ. Wiley-Blackwell: Oxford, UK, 2011.

Books (edited and written)
N/A
Letters to the Editor
N/A
Manuals, Teaching Aids, Other Teaching Publications
N/A
Other Publications
N/A

EDITORIAL AND REVIEW ACTIVITIES
Editor/Service on Editorial Board(s)
N/A
Member of Editorial Review Board
N/A
Journal Reviewer
Reviewer, Cancer, 2009-present
Reviewer, Clinical Hematology/Oncology, 2009-present
Reviewer, Leukemia & Lymphoma, 2009-present
Reviewer, Leukemia Journal, 2009-present
Reviewer, Thompson Reuters Drug Profiles, 2009-present
, Journal of Clinical Oncology, American Society of Clinical Oncology, 2010-present
Reviewer, Annals of Hematology, 2012-present
Other Editorial and Review Activities
N/A

TEACHING
Teaching Within Current Institution -
Formal Teaching
Courses Taught
N/A
Training Programs
N/A
Other Formal Teaching
Lecturer, Hematology Lecture Series
9/2008-present

Supervisory Teaching
Committees
Advisory Committees
N/A
Supervisory Committees
N/A
Examining Committees
N/A
Direct Supervision
Undergraduate and Allied Health Students
N/A
Medical Students
Clinical Mentor, MS2 Preceptorship Program, Jeff Farnum, MD, 9/2010-8/2011
Clinical Mentor, MS2 Preceptorship Program, Scott Ellsworth, MD, 9/2010-8/2011
Clinical Mentor, MS2 Preeptorship Program, Yusra Siddique, MD, 9/2010-8/2011
Graduate Students
N/A
Postdoctoral Research Fellows
N/A
Clinical Residents and Fellows
Clinical Mentor, DoCM Hematology/Oncology Fellowship Program, Fellows on the Lymphoma/Myeloma Rotation, 8/2007-present
Other Supervisory Teaching
Clinical Mentor, Hematology Fellowship Program, Fellows on the Lymphoma/Myeloma Rotation, Clinical Residents and Fellows, 8/2007-present
Clinical Mentor, Observership Program, Observers on the Lymphoma/Myeloma Service, Observers, 8/2007-present

Teaching Outside Current Institution
Formal Teaching
Courses Taught
N/A
Training Programs
N/A
Other Formal Teaching
Lecturer, CNS Lymphoma, Baylor College of Medicine
6/2009

Supervisory Teaching
Committees
Advisory Committees
N/A
Supervisory Committees
N/A
Examining Committees
N/A
Direct Supervision
Undergraduate and Allied Health Students
N/A
Medical Students
N/A
Graduate Students
N/A
Postdoctoral Research Fellows
N/A
Clinical Residents and Fellows
N/A
Other Supervisory Teaching
N/A

CONFERENCES AND SYMPOSIA
Organization of Conferences/Symposia (Include chairing session)
N/A

Presentations at National or International Conferences
Invited

Fowler N, McLaughlin P, Kwak L, Fanale M, Hagemeister F, Fayad L, Pro B, and Samaniego F. Lenolidomide and Rituxan for Untreated Indolent B cell non-Hodgkin's lymphoma, American Society of Clinical Oncology, Orlando, FL, 5/30/2009

Fowler N, Kahl B, Rosen P, Matous J, Cashen A, Jacobs S, Letzer J, Amin B, Williams M, Ross M, Smith S, Saleh A, Shi H, Parasuraman S, Cheson B. Bortezomib, Bendamustine and Rituximab in Patients with Relapsed or Refractory Follicular Lymphoma: Encouraging Activity in the Phase 2 VERTICAL Study, American Society of Hematology, New Orleans, LA, 12/7/2009

Advani R, Sharman JP, Smith SM, Pollyea DA, Boyd TE, Grant BW, Kolibaba KS, Buggy JJ, Hamdy A, Fowler NH. Effect of Btk inhibitor PCI-32765 monotherapy on responses in patients with relapsed aggressive NHL: Evidence of antitumor activity from a phase I study, American Society of Clinical Oncology, Chicago, IL, 6/5/2010

Fowler N, Sharman J, Smith S, Boyd T, Grant B, Kolibaba K, Furman R, Buggy J, Loury D, Hamdy A, Advani R. The Btk Inhibitor, PCI-32765, Induces Durable Responses with Minimal Toxicity in Patients with Relapsed/Refractory B-cell Malignancies: Results from a Phase I Study, American Society of Hematology, Orlando, FL, 12/7/2010

Fowler N, Mclaughlin P, Fisch M, Dakhil S, Bury M, Fayad L, Shah J , Neelapu S, Romaguera J , Rodriguez D, Ayala A, Kwak L. Lenalidomide plus rituximab is a highly effective and well-tolerated biologiv therapy in untreated indolent B cell non-Hodgkin's lymphoma, 11th International Conference on Malignant Lymphomas, Lugano, Switzerland, 6/17/2011

Fowler N. Frontline therapy for indolent lymphoma, MDACC and The University Hospital Center Zagreb, Leukemia and Lymphoma Conference - East and West Are Together, Dubrovnik, Croatia, 9/21/2011

Fowler N, Neelapu S, Fanale M, Rodriguez M, Pro B, Hagemeister F, Younes A, Shah J, Kwak L, Rodriguez D, McLaguhlin P. Phase II Study with R-FND Followed by 90-Y Ibritumomab Tiuxetan Radioimmunotherapy and Rituximab Maintenance for Untreated High-Risk Follicular Lymphoma, American Society of Hematology, San Diego, CA, 12/11/2011

Fowler N, Munteanu M, Davis G, Brown P, Czuczman M. Results of a Phase II Study with Bendamustine and Ofatumumab in Untreated Indolent B-Cell Non-Hodgkin's Lymphoma, American Society of Hematology, San Diego, CA, 12/12/2011

Fowler N. Combination therapy with bendamustine in non-Hodgkin's lymphoma, SymBio Pharmaceuticals, Treakisym International Symposium, Tokyo, Japan, 6/2/2012

Fowler N. Targeting the B-cell Receptor Pathway for NHL, University of Medical Nebraska, 2012 Pan Pacific Lymphoma Conference, Maui, HI, 7/20/2012

Fowler N. Should we change front line therapy of symptomatic indolent non-Hodgkin's

lymphoma, 2012 Toronto Lymphoproliferative Conference, Toronto, Canada, 9/28/2012

Fowler N. Follicular Lymphoma – Who, When, and How to Treat?, American Society of Hematology, 2012 ASH State of the Art Symposium, Chicago, IL, 9/29/2012

Fowler N. Follicular Lymphoma – Who, When, and How to Treat?, American Society of Hematology, 2012 ASH State of the Art Symposium, Los Angeles, CA, 10/13/2012

Fowler N, Advani R, Sharman J, Smith S, McGreivy J, Kunkel L, Troung V, Zhou C and Boyd T. The Bruton's Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) is Active and Tolerated in Relapsed Follicular Lymphoma, 54th American Society of Hematology Annual Meeting, Atlanta, GA, 12/9/2012

Fowler N, Neelapu S, Hagemeister FB, McLaughlin P, Kwak L, Romaguera J, Fanale M, Fayad L, Orlowski R, Wang M, Turturro F, Oki Y, Lacerte L, and Samaniego F. Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study, 54th American Society of Hematology Annual Meeting, Atlanta, GA, 12/11/2012

Other, Including Scientific Exhibitions

N/A

Seminar Invitations from Other Institutions

The Road to Discovery: Emerging Therapies in Blood Cancers, Leukemia & Lymphoma Society, The Woodlands, TX, 3/26/2009

Rituxan therapy for the front-line treatment of low-grade or Follicular, CD20+, B-cell Non-hodgkin's Lymphoma, Genentech/BiogenIdec, Physician's World-Rituxan Heme Speakers Bureau, Chevy Chase, MD, 5/5/2009

Rituxan for the treatment of patients with non-Hodgkin's lymphoma, BiogenIdec and Genentech, Physicians World, Dallas, TX, 5/12/2009

Do we need chemotherapy to treat indolent lymphoma?, 11th Post-ICML Symposium, Munich, Germany, 9/17/2011

How I manage follicular lymphoma, Physician's Education Resources, 16th Annual International Congress on Hematologic Malignancies, Snowbird, UT, 2/23/2012

Treatment of Non-Hodgkin's Lymphoma, Leukemia & Lymphoma Society, Rocky Mountain Blood Cancer Conference, University of Colorado Hospital, Denver, CO, 4/13/2012

A Chemo-free future? The evolution of treatment for indolent lymphoma, Grand Rounds-Memorial-Sloan Kettering Hospital, New York City, NY, 6/12/2012

Hematologic malignancies: Lymphoma/Myeloma, MDACC Faculty Speakers Bureau, Grand Round Series: Christus St. John's Hospital, Houston, TX, 6/20/2012

Emerging treatment approaches for indolent non-Hodgkin's lymphoma, Institute of Continuing Healthcare Education, Grand Rounds: Baylor College of Medicine, Houston, TX, 9/21/2012

Emerging treatment approaches for indolent non-Hodgkin's lymphoma, Princess Margaret Hospital, Grand Rounds: Hematology/Oncology, Toronto, Canada, 9/27/2012

Grand Rounds: Follicular Lymphoma, Institute for Continuing Healthcare Education, St Mary's Hospital, Long Beach, CA, 10/12/2012

Lectureships and Visiting Professorships

N/A

Other Presentations at State and Local Conferences

Fowler N. Novel therapies for aggressive & indolent lymphoma, 2012 Hematologic Malignancies Conference, UT MD Anderson Cancer Center, Houston, TX, 10/10/2012

PROFESSIONAL MEMBERSHIPS/ACTIVITIES

Professional Society Activities, with Offices Held

National and International

American Medical Association
Member, 1/2007-present

American Society of Clinical Oncology
Member, 1/2008-present

American Society of Hematology
Member, 1/2008-present

Local/State

Texas Medical Association
Member, 1/2007-present

UNIQUE ACTIVITIES

1. **International Experience**

1. Externship: National University of Ireland, Galway, Ireland (2000) Completed 3 months WHO organized internal medicine externship
2. Medical Mission: Mulukuku, Nicaragua (1997) Part of multidisciplinary medical relief team providing medical assistance to refugee population

2. **Volunteer Experience**

3. President and Founder, Halo House Foundation
4. Senior Mentor, University of Texas Medical Branch (2000) Worked with undergraduate pre-medical students as part of Medical School Familiarization Program
5. Gross Anatomy Tutor, University of Texas Medical Branch (Fall 1997) Tutored freshman students weekly
6. Ripley House Volunteer, Houston, TX (1995) Taught Houston Police Officers basic Spanish

3. **Community and University Involvement**

7. Medical Team Captain, Avon Breast Cancer Walk (2005) Organized and led group of health professionals in support of event
8. Cancer Support Group, Texas Department of Criminal Justice (2001 - 2002) Founded and developed, in conjunction with the American Cancer Society, a cancer support group for Texas inmates
9. Recruiting Committee, Internal Medicine Residency Program, University of Texas, Organized and led committee for internal medicine resident recruiting.

DATE OF LAST CV UPDATE

2/13/2013

A Non "Genotoxic " Future for the Therapy of Low Grade B Cell Lymphoma.

Nathan Fowler MD

Lead, Indolent Lymphoma Research Group, Department of Lymphoma/Myeloma, MD Anderson Cancer Center

Introduction

Indolent non-Hodgkins Lymphoma (NHL) represent a heterogeneous group of diseases with varying clinical characteristics and outcomes following therapy. Multimodality treatment and the adoption of maintenance approaches following induction chemotherapy have resulted in prolonged remission times in some patients, but the majority still relapse and many die of their disease. Several traditional chemotherapeutic regimens are effective but are associated with considerable acute and long term toxicities. Recently, improved understanding of some of the biologic processes which drive lymphomagenesis have led to the development of several new "non-chemotherapuetic" agents. Drugs targeting key elements of signaling pathways such as the B-cell receptor pathway, the phosphoinositide 3-kinase (PI3K)/AKT/MTOR pathway, the ubiquitin/-proteasome pathway, apoptosis pathways and components of the immune microenvironment are rapidly entering clinical studies. Although many of these agents are still in early development, preliminary results suggest that several new drugs, alone or in combination with traditional therapy, have the potential to substantially improve the outcomes of patients with this chronic illness. This review will discuss some of the novel non-genotoxic agents in clinical trials with a focus on agents with significant activity in indolent NHL.

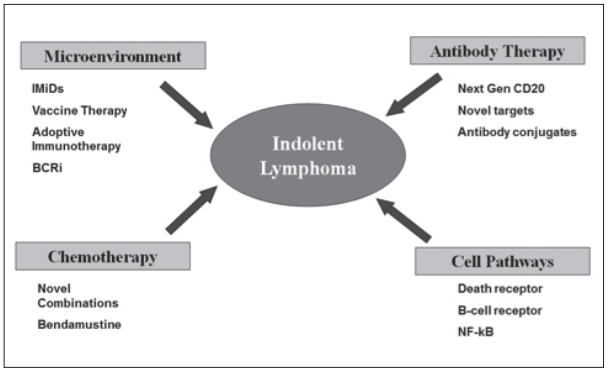

Figure 1: Emerging Therapy Approaches to Indolent Lymphoma.

Antibody-Based Therapy

The impact of the one of the first targeted biologic treatments, rituximab, on the treatment of indolent NHL cannot be overstated. As a single agent, rituximab has a response rate of around 70% in untreated patients and the majority of combination trials have confirmed that the addition of rituximab to chemotherapy results in improved response rates, progression free survival (PFS), and in some cases overall survival.[1-3] Hoping to improve on these results, several next-generation monoclonal antibodies targeting CD20 have been developed. GA101, a type II fully humanized and glycoengineered anti-CD20 antibody has inferior complement-dependant cytotoxicity *in vitro* compared to rituximab, but binds strongly to Fc RIII and may be better at inducing antibody dependant cellular cytotoxicity (ADCC).[4] In a recent phase II study, GA101 had activity similar to rituximab in patients with relapsed follicular lymphoma.[5] Ofatumumab, another fully humanized anti-CD20 antibody (type I) binds to a different epitope of CD20 than rituximab and induces marked compliment-dependant cytotoxicity *in vitro*.[6] As a single agent, ofatumumab induced a 42% overall response rate (ORR) in patients with relapsed follicular lymphoma, with a toxicity profile similar to rituximab.[7] Studies exploring these agents in combination with chemotherapy regimens such as CHOP and bendamustine are underway and will be reported soon.

Several other antibodies are in development targeting other B-lineage antigens such as CD19, CD80 and CD22 and appear active. Conjugating these antibodies with a toxin or radionucleotide is another potential approach to induce cell death. Insotuzumab ozogamicin (CMC-544) is an anti-CD22 antibody linked to the DNA damaging agent calicheamicin. In an early phase study, 63% of patients with indolent lymphoma responded to the drug at the recommended dose level.[8]

The B-Cell Receptor Pathway

The B-cell receptor (BCR) pathway is critical in

the selection and development of normal B-cells. Signaling through this pathway from functional mutations or through antigen binding results in increased transcription of NFkB target genes and is thought to drive malignant B-cell development.[9] Several agents targeting critical components of this pathway are in development and have shown promise in indolent NHL.

Bruton's tyrosine kinase (BTK) is a proximal element of the BCR pathway that can amplify downsteam signaling. Ibrutinib, a selective irreversible inhibitor of BTK, induces cell death *in vitro* and inhibits BCR pathway signaling in animal models.[10] In a recently published phase I study, responses were observed in multiple histologies, including 38% in patients with relapsed follicular lymphoma.[11] In patients at the recommended phase II dose, the response rate was 55%. Toxicity was mild, and there did not appear to be evidence of cumulative toxicity with increased exposure.[12] Phase II studies are underway exploring irbutinib alone and in combination with chemotherapy in patients with relapsed indolent NHL.

Activation of PI3K is frequently associated with constitutive activation of the BCR. GS1101 is an oral inhibitor of the delta isoform of PI3K (which is primarily expressed in lymphocyctes). In a recent phase I study, 17 of 28 patients with indolent NHL, and 14 of 54 patients with chronic lymphocytic lymphoma experienced a response.[13] Myelosuppression was mild and transient transamanitis was observed in a minority of patients. Combination studies of GS1101 with rituximab and/or bendamustine in indolent NHL were reported at ASH 2012 and demonstrated safety of the combination(s).[14]

Immunomodulatory Drugs (IMiDs)

The microenvironment is increasing recognized as a critical component in the pathogenesis of multiple subtypes of NHL and represents an exciting target for emerging therapeutics. Immunomodulatory drugs (IMiDs) are a developing class of agents that have demonstrated the ability to alter the immune environment within the malignant node and bone marrow. Although the exact mechanism is still poorly understood, emerging evidence suggests that IMIDs may affect cell-cell signaling, cytokine secretion, and immune cell recognition of tumor.

Lenalidomide, a potent analog of thalidomide, has demonstrated significant activity in CLL, indolent NHL, diffuse large cell lymphoma, and mantle cell lymphoma. Elegant studies by Gribbon and colleagues showed lenalidomide's potential to improve immune cell recognition of tumor through the repair of dysfunctional immune synapses.[15] An early pilot study with single-agent oral lenalidomide at 25 mg/day given on days 1-21 of each 28-day cycle for up to 52 weeks was examined in indolent NHL in the phase II NHL-001 study. Patients (N=43) with relapsed follicular lymphoma, small lymphocytic leukemia (SLL), or marginal B-cell lymphoma were enrolled. Lenalidomide treatment led to an overall response rate (ORR) of 23% (7% complete response), with responses observed in FL (27% ORR) and SLL (22% ORR) subtypes. Median duration of response (DOR) had not yet been reached at >16.5 months.[16]

Although lenalidomide has activity as monotherapy, some of the most promising results have emerged from combination studies. Preclinical studies at our institution showed combining lenalidomide with anti-CD20 therapy could be synergistic, with the potential to increase ADCC.[17] In patients with relapsed/refractory indolent NHL (FL, SLL, or marginal zone lymphoma), the combination of lenalidomide with rituximab (R2) showed ten of 12 evaluable patients (83%) responded to R2, including 4 of 6 rituximab-refractory patients and 5 of 9 patients with follicular lymphoma (88% ORR, 55% CR).[18] The potential for the combination was further emphasized by a randomized CALGB study comparing lenalidomide versus lenalidomide plus rituximab. Superior activity was reported in the combination are (ORR 75% vs 49%) with no significant increase in adverse events.[19]

In untreated patients with indolent NHL, investigators at MD Anderson conducted a large phase II study (N=110) with lenalidomide and rituximab. Objective responses were observed in 85% of patients including 98% of patients with follicular lymphoma. Most patients remain in remission with a projected 3 year PFS of 81% in the follicular lymphoma subset.[20] Phase III studies comparing this combination versus chemotherapy in indolent lymphoma are underway.

Conclusion

The future is bright for the treatment of follicular lymphoma. Improved understanding of the key role of the immune microenvironment coupled with identification of critical targetable pathways in indolent NHL have led to the development of several novel and active non-genotoxic agents. However, despite several early successes, most new agents do not result in complete response and cure remains elusive in most patients. Further studies, focusing

on clarifying mechanisms of cell death, biomarkers of response and resistance pathways are needed. In the future we will see the integration of these and other new agents into therapy, with the potential to not only decrease the toxicity associated with treatment, but potentially dramatically improve outcomes in patients with indolent lymphoma.

References

1. Witzig TE, Vukov AM, Habermann T,et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma:phase II trial in the North Central Cancer Treatment Group. JCO 2005;23:1103-8.
2. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. JCO 2003;21:1746-51.
3. Gregory S A, et. al. Management of Follicular Lymphoma in the Up-Front and Relapsed Settings Oncology 2010;24:1-10.
4. Mössner E, Brünker P, Moser S, et al.(2010) Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 115:4393–4402.
5. Sehn L, Goy A, Offner, FC, et al: Randomized phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: Preliminary analysis of the GAUSS study. ASH. Abstract 269. Presented December 12, 2011
6. Cheson, B. Leonard J. Monoclonal antibody therapy for B-cell non-Hodgkins Lymphoma. NEJM. 359; 2008: 613-626.
7. Hagenbeek, A et al. First clinical use of ofatumumab, a fully human anti CD-20 monoclonal antibody in relapsed or refractory follicular lymphoma. Blood. 111; 2008: 5486-5495.
8. Dang NH, Smith MR, Offner F, et al.(2009) Anti-CD22 immunoconjugate inotuzumab ozogamicin (CMC-544) + rituximab: clinical activity including survival in patients with recurrent/refractory follicular or 'aggressive' lymphoma [abstract 584] Blood, 114.
9. Davis RE, Ngo VN, Lenz G, et al: Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature 463:88-92, 2010.
10. Honigberg LA, Smith AM, Sirisawad M, et al:The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in modelsof autoimmune disease and B-cell malignancy. ProcNatl Acad Sci US A 107:13075-13080, 2010.
11. Advani RH, Buggy JJ, Fowler N, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/ refractory B-cell malignancies. J Clin Oncol. 2013;31:88-94.
12. Fowler NH, Advani RH, Sharman J, et al. The Bruton's Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Is Active and Tolerated in Relapsed Follicular Lymphoma. ASH Annual Meeting Abstracts. 2012;120:156.
13. Kahl B, Byrd JC, Flinn IW, et al. Clinical Safety and Activity In a Phase 1 Study of CAL-101, An Isoform-Selective Inhibitor of Phosphatidylinositol 3-Kinase P110{delta}, In Patients with Relapsed or Refractory Non- Hodgkin Lymphoma. ASH Abstracts. 2010;116:1777
14. Fowler NH, de Vos S, Schreeder MT, et al. Combinations of the Phosphatidylinositol 3-Kinase-Delta (PI3K{delta}) Inhibitor Gs-1101 (CAL- 101) with Rituximab and/or Bendamustine Are Tolerable and Highly Active in Previously Treated, Indolent Non-Hodgkin Lymphoma: Results From a Phase I Study. ASH Abstracts. 2012;120: 3465.
15. Ramsay AG, Gribben JG. Immune dysfunction in chronic lymphocytic leukemia T cells and lenalidomide as an immunomodulatory drug. Haematologica. 2009;94:1198-1202.
16. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol. 2009;27(32):5404-5409.
17. Zhang L, Qian Z, Cai Z, et al. Synergistic antitumor effects of lenalidomideand rituximab on mantle cell lymphoma in vitro and in vivo. Am J Hematol. 2009;84:553-559.
18. Dutia M, DeRoock I, Chee K, et al. R2: Preliminary Results of a Phase II Study of Lenalidomide and Rituximab in Relapsed / Refractory Indolent Non-Hodgkin's Lymphoma (NHL). ASH Abstracts. 2009;114:1679.
19. Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma. ASCO Abstracts. 2012; abstr 8000.
20. Fowler NH, Neelapu SS, Hagemeister FB, et al. Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study. ASH Abstracts. 2012;120:901.

ICLLM 2013

Chronic Myeloid Leukemia

I would like to welcome you as participants in the session on Chronic Myelogenous Leukemia (CML) and personally thank the organizers for invitating me to participate in the 4th International Congress on Leukemia – Lymphoma – Myeloma here in Istanbul. We will conclude this morning's session with three presentations. The diagnosis and treatment of CML has undergone a revolutionary metamorphesis, with a 5 year overall survival before and after Gleevec of 30% and 90%. In 2010 we celebrated the 50th anniversary of the discovery of the Philadelphia chromosome, first identified by Nowell and Hungerford in 1960, and reported as a translocation between chromosomes 22 and 9 by Janet Rowley in 1973. I will begin this session with a historical perspective on CML by talking about where our studies followed on those of Janet Rowely, in which we identified BCR and ABL as the genes at the breakpoints of the Philadelphia translocation. Dr Ibrahim Haznedaroglu of the Hacettepe University in Ankara will then discuss the current management of CML with tyrosine kinase inhibitors. Dr Nelson Chao of Duke University Medical Center will conclude the session by focusing on the topic of hematopoietic stem cell transplantation for CML in the era of tyrosine kinase inhibitors.

Elenora Heisterkamp

CURRICULUM VITAE

A. Personal Information

Name in Full	Nora C. Heisterkamp, Ph.D.
Business Address	Division of Hematology/Oncology, MS # 54 Childrens Hospital of LosAngeles 4650 Sunset Blvd., Los Angeles, CA 90027
Business Phone	(323) 669-4595
E-mail address	heisterk@hsc.usc.edu.

B. Education

High School	Gymnasium-ß (high school), Alexander Hegius, Deventer, The Netherlands, 1973.
College or University	"Propaedeuse" in Biology, University of Groningen, Groningen, The Netherlands, 1974 "Kandidaats B1" (Bachelor Equivalent), Cum Laude in Biochemistry, University of Groningen, Groningen, The Netherlands, 1977. Ph.D. (Genetics), University of Groningen, Groningen, The Netherlands, 1981
Fellowships	Full time research on RNA populations during differentiation of the fungus Schizophyllum commune; binding interaction of RNA polymerase of E. coli with promoters of an rRNA cistron, and resistance of 5-hydroxymethyluracil-containing DNA of several phages of Bacillus subtilis to restriction enzyme cleavage, University of Groningen, The Netherlands, 1977-1981. Teaching Assistant, University of Groningen, The Netherlands,1978-1980. Guest Worker, Carcinogenesis Mechanisms and Control Section, Laboratory of Viral Carcinogenesis, NCI, NIH, Frederick, MD, 1981. Visiting Fellow, Carcinogenesis Mechanisms and Control Section, Laboratory of Viral Carcinogenesis, NCI, NIH, Frederick, MD, 1981-1984.
Honors and Awards	Honorary Doctorate in Medicine, Erasmus University, Rotterdam, The Netherlands, 1984 Inventor's Award of The United States Department of Commerce for the invention of "Deoxyribonucleic Acid Molecules Useful as Probes for Detecting Deleterious Genes incorporated into Chromosomal DNA", 1986.

C. Professional Background

Academic appointments

Visiting Associate Professor of Pediatrics and Microbiology, University of Southern California, 1987-1989.
Associate Professor of Pathology and Microbiology, University of Southern California, 1989-1994.
Professor of Research Pediatrics and Pathology, University of Southern California, 1994-

Specific teaching responsibilities (courses taught)

Hem/Onc Fellows lectures November 2001
Hem/Onc Fellows lectures November 2002, 2003
Hem/Onc Fellows lectures September 2004, 2005
Hem/Onc Fellows lecture January 2007
Member USC Path Graduate Committee 2006-2008
USC Path #570 Spring/Fall semester 2003
USC Path #570 Fall semester 2005
USC Path #570 Fall semester 2007
USC Path #570 Fall semester 2009
USC Path #570 Fall semester 2011

Specific administrative responsibilities (school or university committees)

CHLA patent committee, 1991-1997
Member CHLA Research Council, 1995-1998
Program leader CHLA RI Developmental Biology Program, 1995-1998
Chair, Bridging Fund, 1995-2010
K12 Internal Advisory Board committee member 2010-
CHLA Committee on Faculty Appointments, Promotions and Tenure member 2010-
USC Keck School of Medicine Faculty Research Council 2012-

Other employment or activity

Senior Scientist, Laboratory of Molecular Genetics, Oncogene Science, Inc., Mineola, NY. During this time developed the first FDA approved DNA diagnostic test for human cancer (test for BCR/ABL in Leukemia). Supervised with Dr. Groffen, 4 technicians, 3 graduate students and 4 junior PhD scientists, 1984-1987.
Senior Scientist, Section of Molecular Genetics, Division of Medical Genetics, Children's Hospital of Los Angeles. 1987-1989
Senior Scientist, Section of Molecular Diagnosis, Department of Pathology, Childrens Hospital of Los Angeles. 1989-1994.
Senior Scientist, Section of Molecular Carcinogenesis, Department of Pathology, Children's Hospital of Los Angeles. 1994-1999
Senior Scientist, Section of Molecular Carcinogenesis, Division of Hematology/Oncology, Children's Hospital of Los Angeles. 2000-
Member, Scientific Advisory Board, Oncogene Science Inc., 1984-1987
Member, Advisory Committee Pfizer Inc., 1986-1987
P01 Site Visit Reviewer, NIH, 1988
P01 Site Visit Reviewer, NIH, 1989
P01 Site Visit Reviewer (Philadelphia), NIH, 1990
P01 Site Visit Reviewer (Chicago), NIH, 1990
Ad hoc reviewer Mammalian Genetics Study Section NIH, 1993
Ad hoc reviewer Mammalian Genetics Study Section NIH, 1994
NIH PO1 Reviewer (Memphis), 1997
NIH PO1 Reviewer (New York), 2001
Grant reviewer for the Dutch Cancer Society and US -Israel Binational Science Foundation, 1998-2001
NIH Ad hoc reviewer Cancer Genetics Study Section, 2004
NIH NCI PO1 Review, Cluster Review Hematology Oncology 1 Oct 10-12 2004
NIH-NCI PO1 Molecular Oncology Special Emphasis Panel June 4/5 2007
NIH-NCI PO1 Molecular Oncology Special Emphasis Panel June 4/5 2008
Member Spinoza Prize selection committee NWO the Netherlands 2007-2011
NIH-NCI PO1 Molecular Mechanism and Target Therapies Special Emphasis Panel May 23-25 2011
NIH-NCI Program Project Review Panel Meeting II. June 13-June 14 2012

D. Society Memberships

AAAS

ASM

E. Consultantships

F. Research Activities

Major areas of research interest

Drug resistance mechanisms in leukemia

Role of the microenvironment in protection of cancer cells

Signal transduction

Regulation of macrophage polarization

Involvement of Bcr and Abr as negative regulators of the small GTPase Rac in sepsis, asthma and pulmonary hypertension

Research in Progress

Study of leukemia-stromal adhesion mechanisms

Role of the BAFF-R in survival of ALL cells

Molecular mechanisms of environmentally-mediated drug resistance

Glycomics as a tool for diagnosis and treatment of acute lymphoblastic leukemia

Patents and Inventions

Groffen, J., Heisterkamp, N., and Stephenson, J.R. Probes and Methods Useful for Detecting Chromosomal Translocations. U.S. Serial No. 671,296, filed November 14, 1984. Issued

Stephenson, J.R., Groffen, J., and Heisterkamp, N. Deoxyribonucleic Acid Molecules Useful as Probes for Detecting Deleterious Genes Incorporated into Chromosomal DNA. U.S. Serial No. 749,178, filed June 26, 1985. Issued

Groffen, J., Heisterkamp, N., and Pattengale, P.K. BCR/ABL Transgenic Animals as Models for Philadelphia Chromosome Positive Chronic Myelogenous and Acute Lymphoblastic Leukemia. U.S. Serial No. 5,491,283 filed November 22, 1989. Issued

Groffen, J., and Heisterkamp, N. Hypervariable Restriction fragment Length Polymorphisms within the ABR Gene. U.S. Serial No. 5,273,878, filed August 30, 1990. Issued 12/28/1993.

Groffen, J, Heisterkamp, N., ten Hoeve, J. Diagnostics and Treatments for Cancers Expressing Tyrosine Phosphorylated CRKL Protein. U.S. Patent Serial No. 5,667,981. Filed May 13, 1994, issued September 16, 1997.

Groffen, J., Heisterkamp, N. BCR/ABL Transgenic Animals as Models for Philadelphia Chromosome Positive Chronic Myelogenous and Acute Lymphoblastic Leukemia. U.S. Patent Serial No. 5,849,996. Issued, December 15, 1998.

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INVITED LECTURES

*CML: Biology and Therapy April 4-7 1992, Martha's Vineyard, Cape Cod MA. "Cytogenetic evolution in transgenic mice with P190"
*USC Cancer Center Grand Rounds October 14 1997
*Pasadena, Developmental Biology Symposium, October 10 2001
*CHLARI Seminar Series, March 5 2002
*CHLA Medical Fellows presentation November 2001, 2002, 2003 (1 hour)
*USC Signal Transduction Meeting October 13 2002 (1 hour)
*UCLA Lecture "Bcr/Abl-caused leukemogenesis" February 11, 2003
CALTECH Pre-med students September 24 2003 (15 min)
*Brussels, Belgium. Invited lecure "Bcr in leukemia and sepsis" April 14 2004
*CHLA Medical Fellows September 1 2004 "Mouse models in biomedical research"
*Heidelberg, Germany. XXII. Symposium of the International Association for Comparative Research on Leukemia and Related Disorders-IACRLRD. Invited lecture "From BCR to BCR/ABL in the mouse". July 2-5, 2005.
*CHLA Medical Fellows September 1 2005 "Mouse models in biomedical research"
*Grand Rounds USC Norris Cancer Center Sept 20 2005 "From Bcr/Abl to Bcr in the mouse"
*Grand Rounds CHLA Hematology/Oncology Jan 11 2006 "Mouse models for Ph-positive ALL in the study of drug treatment"
*CHLA Medical Fellows January 31 2007 "Mouse models in biomedical research"
*CHLA Research Seminar series Nov 2007 "Record keeping for dummies- a lowtech approach"
*PHILADELPHIA CHROMOSOME SYMPOSIUM: PAST, PRESENT AND FUTURE
The 50th Anniversary of the Discovery of the Philadelphia Chromosome symposium September 28, 2010 Philadelphia. "Philadelphia chromosomal breakpoints- two linear breaks with complex consequences"
*Tokyo, Japan. The XXV Symposium of the International Association for Comparative Research on Leukemia and Related Disorders-IACRLRD. Invited lecture "Approaches to overcome environmentally-mediated drug resistance in ALL" September 15-17, 2011.
*Mannheim, Germany. The 9th Annual Symposium of the European LeukemiaNet/13th Annual Symposium of the German Competence Network "Acute and Chronic leukemias". Keynote lecture "Review of the evidence that BCR-ABL causes leukemia". January 31 –February 1 2012.
*CHLA Grand Rounds Hematology/Oncology March 7 2012 "The BAFF-R: a new target for treatment of acute lymphoblastic leukemia"
*USC Grand Rounds Hematology August 24 2012 "The BAFF-R: a new target for treatment of acute lymphoblastic leukemia"
*Boston. Symposium Sept 17-19 2012. Galectins and Galectin Therapeutics". September 18 2012 "Galectin-3 as communicator between acute lymphoblastic leukemia cells and their microenvironmental support cells"

BCR-ABL: Past, Present and Future

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Clinicians who currently treat leukemia have an expanding toolkit of tests and assays that provide critical information about the differential diagnosis, prognosis, and therapy for their patients. This has not always been the case- 30 years ago, CML was treated mainly with busulfan and splenectomy. Our papers entitled "Translocation of c-*abl* oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukemia" and "Localization of the c-abl oncogene adjacent to a translocation breakpoint in chronic myelocytic leukemia" that appeared in Nature in 1983 marked the beginning of the molecular era for leukemias. With the development of basic science techniques for cloning, it had became possible for the first time to analyze human DNA. We molecularly cloned parts of the human *ABL* gene and subsequently collaborated with a group in Rotterdam including Gerard Grosveld, Annelies de Klein, Claus Bartram and others to localize *ABL* on the Ph-chromosome in CML. We then cloned translocation breakpoints from the DNA of CML patients who had undergone splenectomy and through this identified and named the Breakpoint Cluster Region (*BCR*) gene. Methods utilized in that period were time-consuming and imprecise but ultimately led to the subsequent development of Imatinib as a highly effective drug for the treatment of chronic myeloid leukemia. Currently it is possible to determine the DNA sequence of the entire genome, as well as the transcriptome, of individual CML patients. Moreover, the cellular processes disturbed by Bcr/Abl, including its signal transduction pathways, and the characteristics of CML stem cells are being understood in unprecedented detail, allowing for the identification of targets for therapy other than Bcr/Abl. Based on this expanding information a cure for CML should ultimately be possible.

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CURRICULUM VITAE

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Prof. Dr. Ibrahim C Haznedaroğlu, MD is Clinical Professor of Medicine & Haematology at the Hacettepe University Medical School in Ankara, Turkey, an institution he has worked at since graduating from the University of Ankara, School of Medicine in 1988.

Prof. Dr. Haznedaroğlu has authored over 300 publications in indexed scientific journals; these papers have been cited about 3000 times in journals and textbooks. He is the Associate Editor of Turkish Journal of Hematology and UHOD-International Journal of Hematology and Oncology. He has served as a reviewer in Blood, Stem Cells, Nature CV, Thrombosis Research, Thrombosis and Hemostasis, Clinical and Applied Thrombosis/Hemostasis, Expert Opinion in Pharmacotherapy, and many other international journals. In 2002, he received the Scientific Promotion Award, from the Scientific and Technical Research Council of Turkey and in the following year the Ibn-i Sina Medical Science Award from TUSAV. His main clinical and research interests are hematological neoplasms, chronic myeloid leukemia, and hemostasis. He is a member of European Leukemia Net WP4 (CML) since its establishment.

Current Management of Chronic Myeloid Leukemia (CML) With Tyrosine Kinase Inhibitors (TKI)

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Current initial frontline therapy for chronic myeloid leukemia (CML) is chronic oral administration of tyrosine kinase inhibitor (TKI).[1,2] During the last decade, the introduction of TKI to the treatment regimen of CML has significantly affected the survival of the patients. Imatinib mesylate is the first TKI in the clinic. The survival benefit of imatinib to the CML is excellent[3]. Then next generation TKIs namely dasatinib[4,5], nilotinib[6], bosutinib[7] and ponatinib[8] have been developed for the management of the CML patients. The life expectations and outcomes of the TKI-treated patients with CML could be as perfect as the age- and sex-matched chronic drug-receiving patients with such as diabetes and hypertension. The proper clinical and laboratory monitorization of CML patients are absolutely necessary to reach those successful outcomes.[9-11] Complete hematological response (CHR), early complete cytogenetic response (CCyR), faster major molecular response (MMR), and the deeper, durable molecular responses (MR4, MR4.5, MR5) are the ultimate goals of the TKI-receiving patients with CML[12]. The surrogate markers of the CML outcome (rate, depth, and time to cytogenetic and molecular response) are vital in the clinical management of the disease.[1,13-17]

Critical evaluations of the CML patients to hit those targets shall be made at the baseline, and at the 3rd month, 6th month, 12th month, 18th month, and 24th month after the TKI administration. The treatment milestones are checked during the time-lines of evaluation.[12] Increased expectations regarding CML have currently evolved to cure the disease reached on the MR4 or MR4.5 with the discontinuation of the drug TKI.[18] On the other hand, disease progression (accelerated phase (AP) CML or blastic crisis (BC)) under TKI is a great disaster.[19-21] The survival after the progression into AP/BC is still significantly shorter even in the TKI era. However, the risk of progression has been decreased with the introduction of more powerful TKIs.[22-24] The major attention shall be paid for the prevention of disease progression particularly for the treatment-naïve CML or TKI refractory diseases. Clinical response, the depth of response, and the impact of TKI used on the disease outcome should always be focused during the long-term management of CML.[12]

Investigational efforts tried to improve the results of CML first-line therapy of imatinib obtained from the IRIS trial. Those attempts include imatinib dose increase particularly in high-Sokal risk[25], imatinib-based combinations[26], and setting the second-generation TKIs as first line therapy[24,27]. Dose optimization studies of TKI such as German CMLIV[28] and TIDEL[29] have been taken into account for the increments in the safety, efficacy, tolerability, adherence, and acceptable manageable drug toxicity. The aim of this review is to outline critical steps of TKI administration practices during the long-term clinical course of CML based on the

data obtained from the randomised clinical trials (RCT) and international recommendations. The efficacy of TKI treatment, TKI side effects, off-target complications, long-term morbidities due to the both the disease and drug are common arguments of the management of CML. Standardized definitions of molecular response in CML under TKI have been performed by Europen LeukemiaNet (ELN). MR4 can be achieved by a BCR-ABL expression < 0.01%, MR4.5 by <0.0032% BCR-ABL^{IS}, and MR5 by <0.001% BCR-ABL^{IS}.[28]

Baseline evaluation and management of the patient with CML

Standard baseline evaluation of the de novo CML patient includes exact medical diagnosis of CML, basic laboratory evaluation covering complete blood count (CBC)[30] and peripheral blood smear (PBS), bone marrow histopathology, conventional cytogenetics and/or FISH analyses for Ph* chromosome, and quantitative molecular analyses for the BCR-ABL1. Tumor load and disease phase should be defined.[12] Newly diagnosed chronic phase CML patients should be stratified based on the Sokal[31], Euro/Hasford[32] and EUTOS[33] CML prognostic scoring systems. Novel recent investigations for the de novo CML patients have searched the validity of gene expression profiling, genetic polymorphisms, next generation genomics, multi-drug resistance genes (MDR, OCT1), fusion transcripts and pre-existing BCR-ABL kinase domain mutations.[34-43]

Current initial TKI treatment for chronic phase CML is imatinib 400 mg po.[12] Second generation TKIs, namely dasatinib[27] 100 mg po and nilotinib[24] 600 mg po have also been registered for the first-line therapy of CML. There is a tendency for the prescription of more powerful TKIs in high-Sokal risk CML patients and high-risk patients with complex caryotypic abnormalities at the beginning of the disease for the prevention of disease progression. Likewise young and low prognostic risk CML patients are candidates of 2nd generation TKIs for the sake of drug discontinuation in the future. However, heterogenous presentation and course of CML, individual characteristics, compliance and preferences of the patients, comorbidities, different toxicity profile of the drug and the physician-clinical center experience shall all be considered during the initial decision making for 1st line TKI of the newly diagnosed chronic phase CML.[12,24,27]

Evaluation and management at the 3rd month after the initiation of TKI in the patient with CML

Standard disease assessments at the 3rd month following the TKI treatment of the chronic phase CML patient include critical clinical evaluation and CBC/PBS to reveal complete hematological response (CHR), cytogenetic analyses to search the cytogenetic response, and quantitative molecular BCR-ABL analyses to identify molecular response at the 3rd month of oral TKI administration.[12] Optimal response at the 3rd month of imatinib is CHR and minor cytogenetic response. However particularly after the introduction of the powerful second generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher. Recent RCT studies[24,27,44-50] indicated that the critical BCR-ABL transcript level (10% cut-off value) the 3rd month following the TKI treatment may have a prognostic significance in patients with CML. This scientific observation has been made with imatinib in GIMEMA[44], German CML IV[26], Hammersmith[51], DASISION[52], ENESTnd[22]; with dasatinib in DASISION[49], and with nilotinib in ENESTnd[22] trials. The challenges for the widespread routine use of the 10% BCR-ABL transcript cut-off at the 3rd month of TKI are present. First, the estimated ratio of BCR-ABL/ABL is highly technique dependant. Many laboratories in the World still not qualified for the international harmonization of scale (IS). High ratio values on IS scale, house keeping control gene problem, variations in the samples, delays in the exact molecular assessment time after TKI and early unexpected variation kinetics of response in individual CML patients complicate the universal decision of the 10% BCR-ABL transcript cut-off at the 3rd month of TKI. Furthermore, the tumor burden at diagnosis, prognostic scoring, gene profile, cytoreduction with TKI dosage, treatment adherence, and numerous confounding effects may obscure the real-life decision at the 3rd month of TKI outside the clinical trials. Nevertheless, any CML patient that does have a BCR-ABL over 10% after the 3 months of TKI presents a strong warning requiring a more careful and more frequent monitoring based on the clear RCT data. If the CML patient exhibits no CHR and/or no minor cytogenetic response, the failure of the 1st line TKI is evident. If the initial failed TKI treatment for CML was imatinib, nilotinib or dasatinib shall be given. If one of the two 2nd generation TKIs (nilotinib or dasatinib) was used as the 1st line therapy and failed, the other one (dasatinib or nilotinib) could be administered. Increasing the dose of imatinib has been tried in the literature but seems to be a dying art in the era of stronger TKIs. Drug tolerability and adherence to the treatment should always be sought. Effective management of the treatment-related adverse effects is a vital part of the CML care.[12]

Evaluation and management at the 6th month after the initiation of TKI in the patient with CML

Standard disease assessments at the 6th month following the TKI treatment of the chronic phase CML patient include critical clinical evaluation to establish CHR, cytogenetic analyses to search the cytogenetic response, and quantitative molecular BCR-ABL analyses to identify molecular response at the 6th month of oral TKI administration. Optimal response at the 6th month of imatinib is at least partial cytogenetic response (Ph* chromosome lower than 35%).[12] However particularly after the introduction of the powerful second generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher. CCyR at 6 months and/or BCR-ABL below 1% following 6 months of 2nd generation TKIs are considered as optimal. Any CML patient that does have a BCR-ABL over 10% and/or Ph* chromosome over 35% after the 6 months of TKI (particularly nilotinib and dasatinib) may be accepted as failure and the tratment strategy may be changed. Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and switch to 2nd generation TKIs may be performed. Cumulative incidence of MMR is higher with both nilotinib and dasatinib. Early switch from imatinib to 2nd generation TKI is rational since the RCTs indicated the higher probability to obtain better responses as well as the progression-free survival (PFS) and overall survival (OS).[24,27] Prevention of disease progression seems to be better achieved with more powerful 2nd generation TKIs. Specific long-term drug adverse effects (such as pleuropulmonary syndrome for dasatinib and metabolic syndrome for nilotinib) as well as the increased treatment costs shall be considered. Drug tolerability and adherence to the treatment should always be sought.[12]

Evaluation and management at the 12th month after the initiation of TKI in the patient with CML

Standard disease assessments at the 12th month following the TKI treatment of the chronic phase CML patient include critical clinical evaluation to establish CHR, cytogenetic analyses to search the cytogenetic response, and quantitative molecular BCR-ABL analyses to identify molecular response at the 12th month of oral TKI administration.[12] Optimal response at the 12th month of imatinib is at least CCyR. However particularly after the introduction of the powerful second generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher.[1,6,8,15,16,22,28,44,45,48,50,51,53-63] CCyR at 12 months and BCR-ABL below 0.1% following 6 months of 2nd generation TKIs are considered as optimal. Any CML patient that does have a BCR-ABL over 1% and/or Ph* chromosome over 1% after the 12 months of TKI (particularly nilotinib and dasatinib) may be accepted as failure and the tratment strategy may be changed. Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and switch to 2nd generation TKIs may be performed. Drug tolerability and adherence to the treatment should always be sought.[12]

Evaluation and management at the 18th month after the initiation of TKI in the patient with CML

Standard disease assessments at the 18th month following the TKI treatment of the chronic phase CML patient include critical clinical evaluation to establish CHR, CCyR, and quantitative molecular BCR-ABL analyses to identify molecular response at the 18th month of oral TKI administration.[12] Optimal response at the 18th month of imatinib is at least MMR. However particularly after the introduction of the powerful second generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher.[1,4,6,10,11,17,23,38,39,42,44,45,47-57] CCyR at 18 months and BCR-ABL below 0.1% following 18 months of 2nd generation TKIs are considered as optimal. Any CML patient that does have a BCR-ABL over 1% and/or Ph* chromosome over 1% after the 18 months of TKI (particularly nilotinib and dasatinib) may be accepted as failure and the tratment strategy may be changed.[15] Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and switch to 2nd generation TKIs may be performed. Drug tolerability and adherence to the treatment should always be sought.[12]

Evaluation and management at the 24th month and thereafter following the initiation of TKI in the patient with CML

Standard disease assessments at the 24th month following the TKI treatment of the chronic phase CML patient include critical clinical evaluation to establish CHR, CCyR, and quantitative molecular BCR-ABL analyses to identify molecular response at the 18th month of oral TKI administration.[12] Optimal response at the 24th month of imatinib is at least the continuation of MMR. However particularly after the introduction of the powerful second generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher. CCyR at 24 months and BCR-ABL below 0.1% following 24 months of 2nd generation TKIs are considered as optimal. Any CML patient that does have a BCR-ABL over 1% and/or Ph* chromosome over 1% after the 24 months of TKI (particularly nilotinib and dasatinib)

may be accepted as failure and the tratment strategy may be changed.[15] Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and switch to 2nd generation TKIs may be performed. Drug tolerability and adherence to the treatment should always be sought. Quality of life is especially a matter of concern in CML patients receiving long-term maybe lifetime TKI drugs.[12]

In case of the intolerance to any TKI and/or multi-TKI resistant CML cases with or without mutations, 3rd line treatment includes bosutinib, ponatinib, allogeneic stem cell transplantation, and experimental therapies.[64-66] Mutations detected during the TKI therapy may be resulted in drug alterations and entire treatment strategy based on the nature of the mutation. T315I is a unique mutation making the CML patient irresponsive to many TKIs and let allografting be an option in the case.[15] Combination treatments such as TKI plus interferon[67] are still a matter of research and rarely used outside clinical trials.

Evaluation for the discontinuation of TKI in the superior-TKI responder patient with CML shall be performed in long-term for instance after 2 years. The deeper molecular responses (MR4, MR4.5, MR5) are candidates for the TKI discontinuation.[68] MR4 can be achieved by a BCR-ABL expression < 0.01%, MR4.5 by <0.0032% BCR-ABL^{IS}, and MR5 by <0.001% BCR-ABL^{IS}.[28,46] Treatment-free remissions and re-induction of the remission with the same TKI seem to be possible based on the data from the STIM trial.[68] Pregnancy represents a way of TKI discontinuation because of the negative impact of any TKI to the organogenesis.

Patients with AP/BC CML would be treated with the most powerful TKI available and multi-agent chemoterapy before allografting.[19-21,65,69-71] Since those patients with advanced phase CML still do have a worse prognosis, prevention of disease progression is the most significant aspect of CML disease management.

Future perspectives of CML

The future of CML and TKI treatment will reveal better understanding the disease pathobiology, leukemic stem cells, signal transduction and their translation to the patient care.[34-43] Cure of CML and the eradication of minimal residual disease (MRD) via the multi-hit drugs with distinct biological actions would be possible. The cessation of the therapy with the aim of cure, stem cell depletion, stem cell exhaustion, immunological control of the disease may be the future strategies in the management of CML.

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41. Schemionek M, Steidl U, Schwab A, et al. Metastasis Suppressor 1 Is Downregulated in CML Stem Cells and Overexpression Impairs Early Leukemic Cell Propagation. ASH Annual Meeting Abstracts 2012;120:2776-.
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44. Castagnetti F, Gugliotta G, Breccia M, et al. The BCR-ABL Transcript Levels At 3 and 6 Months Predict the Long-Term Outcome of Chronic Myeloid Leukemia Patients Treated Frontline with Imatinib Mesylate: A Gimema CML WP Analysis. ASH Annual Meeting Abstracts 2012;120:1678-.
45. Gugliotta G, Castagnetti F, Palandri F, et al. Cytogenetic and Molecular Responses At 3 Months Are Associated with A Better Outcome in Early Chronic Phase (ECP) Chronic Myeloid Leukemia (CML) Patients Treated with Nilotinib. ASH Annual Meeting Abstracts 2012;120:2797-.

46. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010;116:3758-65.
47. Jain P, Kantarjian HM, Nazha A, et al. Early Molecular and Cytogenetic Responses Predicts for Significantly Longer Event Free Survival (EFS) and Overall Survival (OS) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia (CML) in Chronic Phase (CP) - an Analysis of 4 Tyrosine Kinase Inhibitor (TKI) Modalities (standard dose imatinib, high dose imatinib, dasatinib and nilotinib). ASH Annual Meeting Abstracts 2012;120:70-.
48. Kim DDH, Lee HG, Kamel-Reid S, Lipton JH. BCR/ABL Transcript At 3 Months Predicts Long-Term Outcomes Following Second Generation Tyrosine Kinase Inhibitor Therapy in the Patients with CML in Chronic Phase Who Failed Imatinib. ASH Annual Meeting Abstracts 2012;120:2777-.
49. Saglio G, Kantarjian HM, Shah N, et al. Early Response (Molecular and Cytogenetic) and Long-Term Outcomes in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Exploratory Analysis of DASISION 3-Year Data. ASH Annual Meeting Abstracts 2012;120:1675-.
50. White DL, Saunders VA, Yeung DT, Grigg A, Hughes TP. Early Molecular Response to Imatinib in CP-CML Patients: The Significance of Early Dose Intensity and OCT-1 Activity in Responders and Efficacy of Dose Escalation and Switch to Nilotinib in Non-Responders. ASH Annual Meeting Abstracts 2012;120:693-.
51. Marin D, Hedgley C, Clark RE, et al. Predictive value of early molecular response in patients with chronic myeloid leukemia treated with first-line dasatinib. Blood 2012;120:291-4.
52. Kantarjian H, O'Brien S, Jabbour E, et al. Impact of treatment end point definitions on perceived differences in long-term outcome with tyrosine kinase inhibitor therapy in chronic myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:3173-8.
53. Choi S-Y, Lee S-E, Kim S-H, et al. Nilotinib Versus High-Dose Imatinib in Early Chronic Phase CML Patients Who Have Suboptimal Molecular Responses to Standard-Dose Imatinib: Updated Data From RE-Nice Study. ASH Annual Meeting Abstracts 2012;120:3775-.
54. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood 2012;120:1390-7.
55. Cortes JE, Brummendorf TH, Khoury HJ, et al. Assessment of Early Cytogenetic Response As a Predictor of Long-Term Clinical Outcomes in a Phase 1/2 Study of Bosutinib in Chronic Phase CML. ASH Annual Meeting Abstracts 2012;120:2798-.
56. Cortes JE, Pasquini R, Kantarjian HM, et al. First-Line Treatment and Management of Chronic Myeloid Leukemia (CML) in Clinical Practice: Update of > 1800 Patients (Pts) in the WORLD CML Registry. ASH Annual Meeting Abstracts 2012;120:3750-.
57. Falchi L, Kantarjian HM, Quintas-Cardama A, et al. Clinical Significance of Deeper Molecular Responses with Four Modalities of Tyrosine Kinase Inhibitors As Frontline Therapy for Chronic Myeloid Leukemia. ASH Annual Meeting Abstracts 2012;120:164-.
58. Hughes TP, Lipton JH, Spector N, et al. Switching to Nilotinib Is Associated with Continued Deeper Molecular Responses in CML-CP Patients with Minimal Residual Disease After >= 2 Years On Imatinib: Enestcmr 2-Year Follow-up Results. ASH Annual Meeting Abstracts 2012;120:694-.
59. Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK 2012;26:2197-203.
60. Rosti G, Castagnetti F, Gugliotta G, Palandri F, Baccarani M. Second-generation BCR-ABL inhibitors for frontline treatment of chronic myeloid leukemia in chronic phase. Critical reviews in oncology/hematology 2012;82:159-70.
61. Rosti G, Gugliotta G, Castagnetti F, et al. Five-Year Results of Nilotinib 400 Mg BID in Early Chronic Phase Chronic Myeloid Leukemia (CML): High Rate of Deep Molecular Response - Update of the Gimema CML WP Trial CML0307. ASH Annual Meeting Abstracts 2012;120:3784-.
62. Sail KR, Chen L, Jackson J, et al. Treatment Patterns Among Patients with Philadelphia Chromosome Positive Chronic Myeloid Leukemia (Ph+ CML) Treated with Imatinib in a Community Setting. ASH Annual Meeting Abstracts 2012;120:3179-.
63. Wu B, Zhong H, Saglio G, Chen F. Different Strategies for First-Line Treatment of Chronic Myeloid Leukaemia: An Economic Analysis. ASH Annual Meeting Abstracts 2012;120:4696-.
64. Quintas-Cardama A, Kantarjian H, Cortes J. Bosutinib for the treatment of chronic myeloid leukemia in chronic phase. Drugs of today 2012;48:177-88.
65. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-up of the PACE Trial. ASH Annual Meeting Abstracts 2012;120:163-.
66. Ahmed S, Saliba RM, De Lima M, et al. Sequential Treatment After Allogeneic Stem Cell Transplantation for Chronic Myelogenous Leukemia. ASH Annual Meeting Abstracts 2012;120:3129-.
67. Nicolini FE, Etienne G, Dubruille V, et al. Pegylated Interferon-{alpha} 2a in Combination to Nilotinib As First Line Therapy in Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia Provides High Rates of MR4.5. Preliminary Results of a Phase II Study. ASH Annual Meeting Abstracts 2012;120:166-.
68. Mahon F-X, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. The lancet oncology 2010;11:1029-35.
69. Chae YK, Kantarjian HM, Romo CG, et al. Prognostic Factors in the Blastic and Accelerated Phase of Patients with Chronic Myeloid Leukemia (CML) in the Tyrosine Kinase Inhibitor (TKI) Era. ASH Annual Meeting Abstracts 2012;120:3786-.
70. Ghanem H, Kantarjian HM, Jabbour EJ, Cortes JE, Quintas-Cardama A. Rare Blast Phase (BP) Phenotypes of Chronic Myeloid Leukemia (CML). ASH Annual Meeting Abstracts 2012;120:4434-.
71. Strati P, Kantarjian HM, Thomas DA, et al. Hypercvad Plus Imatinib or Dasatinib for Patients with Lymphoid Blastic Phase of Chronic Myeloid Leukemia. ASH Annual Meeting Abstracts 2012;120:3766-.

CURRICULUM VITAE

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PERSONAL INFORMATION

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Chapel Hill, NC 27514
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Nationality: U.S.A.

EDUCATION

1973	High School, Sao Paulo, Brazil
1977	B.A. cum laude, Harvard University, Cambridge, Massachusetts
	M.D. with honors, Yale University, New Haven, Connecticut
	M.B.A., Duke University, Durham, North Carolina

POSTGRADUATE MEDICAL TRAINING

1981-1984	Resident in Medicine, Stanford University Medical Center, Stanford, CA
1984	Internist, Menlo Medical Clinic, Menlo Park, CA
1985	Visiting Lecturer, University of Hong Kong-Queen Mary Hospital
1986	American Cancer Society Fellow, Stanford University, Stanford, CA
1985-1988	Fellow in Oncology, Stanford University Medical Center, Stanford, CA

POSITIONS

1989-1990	Physician Specialist, Bone Marrow Transplantation Program, Stanford University Medical Center, Stanford, CA
1989-1996	Assistant Director, Director, Outpatient Clinic Bone Marrow Transplantation Program Stanford University Medical Center, Stanford, CA
1991 - 1996	Assistant Professor of Medicine, Bone Marrow Transplantation Program Stanford University Medical Center, Stanford, CA
1996 - present	Director, Bone Marrow Transplantation Program, Duke University, Durham, NC
1996 - 2000	Associate Professor of Medicine, Duke University, Durham, NC
1998	Acting Chief, Medical Oncology, Duke University, Durham, NC
2000 - present	Co-founder, Aldagen, Research Triangle Park, NC
2001 - present	Co-Director, Stem Cell Laboratory, Duke University, Durham, NC
2001 - present	Professor of Medicine (tenure) & Immunology, Duke University, Durham, NC
2004 - present	Chief, Division of Cellular Therapy/BMT, Duke University, Durham, NC
2008 - present	Senior Leadership Council, Duke Comprehensive Cancer Center
2010 - present	Donald D. and Elizabeth G. Cooke Distinguished Professor
2012 - present	Co-founder C2Regenerate, Triangle Park, NC

AWARDS/HONORS

1975	Dreyfus Fellow, Harvard University
1977	Harvard University B.A. cum laude
1978	Yale Fellow
1981	Yale University M.D. with honors
1981	Alpha Omega Alpha
1986	Timothy Becket Jr. Award for Excellence in Clinical Teaching (Voted by the Stanford University Hospital Housestaff)
1994	Nycomed Prize, International Society of Pediatric Oncology Meeting (Best Scientific Presentation)
1998	Robert and Alma Mortensen Lectureship-Texas A&M University
1999	R. Wayne Rundles Award for Excellence in Cancer Research Duke Comprehensive Cancer Center
2000	Best Abstract, American Society for Blood & Marrow Transplantation, 2000 Annual Meeting
2002	Mortimer M. Bortin Award for Best Clinical Research Abstract, 2002 Tandem BMT Meeting
2006	Elected to the Association of American Physicians (AAP)
2011	American Society of Hematology (ASH) BLOOD Journal Top Reviewer
2012	National Biodefense Science Board Member

MEMBERSHIP

1981	Alpha Omega Alpha (Yale University)
1986	American Association for the Advancement of Science (Member).
1987	American College of Physicians (Member).
1990	American Society of Clinical Oncology (Member).
1991	American Society of Hematology (Member)
1994	American Society of Blood and Bone Marrow Transplantation (Member)
2000	American Association of Immunologists (Member)
2006	Association of American Physicians (Member)

LICENSURE

1982	California G47663 (inactive)
1996	North Carolina #96-01574

BOARD CERTIFICATION

1984	American Board of Internal Medicine; Specialty: Internal Medicine (#100635)
1987	American Board of Internal Medicine; Sub-Specialty: Oncology (#100635)

NATIONAL COMMITTEES

1993 - 1996	Diagnostic and Therapeutic Technology Assessment (DATA) panel of the American Medical Association
1994 -present	American Society of Hematology, Abstract Reviewer
1994 - 1998	American Society of Hematology, Session Chairperson
1995 - present	NCI site visit team (ad hoc member)
1995, 1996	NIH Study Section - Experimental Therapeutics - 2, ad hoc member
1995 -1998	National Marrow Donor Program - Membership and Process Improvement
1995	American Society of Blood & Bone Marrow Transplantation-Program Committee
1995	Keystone Symposia, Workshop leader
1997 – 2002	Cancer and Acute Leukemia Group B
2000 – 2001	Leukemia/Lymphoma/Myeloma Progress Review Group, NCI
2000 - 2006	Leukemia/Lymphoma Society of America Grant Review Committee
2000 – present	Gateway for Cancer Research, Grant Review Committee
2001 - 2005	Board of Scientific Councilors, NHLBI (full member), NCI (ad hoc)
2002	Program Chair, ASBMT Annual Meeting
2003 - 2005	Vice-President elect, VP and President, American Society of Blood and Marrow Transplantation
2003-2006	Lymphoma Committee, CALGB
2004 - present	Steering Committee, Clinical Trial Network (BMT CTN)
2005 - present	Chair, Radiation Injury Treatment Network (RITN)
2006	Principal Investigator, Centers for Medical Countermeasures against Radiation (CMCR)
2006 - 2010	Steering Committee, Immune Tolerance Network (ITN)
2007	American Society of Oncology, Scientific Review Committee
2007 - present	NIH Study Section – Clinical Oncology – full member
2008	American Society of Oncology, Scientific Review Committee – Track Leader
2006 - present	Director, ASBMT Clinical Scholars Training Course
2008 - present	Chair, Board of Scientific Councilors, Gateway for Cancer Research
2009	Board Member – National Marrow Donor Program
2009	Council Member – National Institutes of Allergy and Infectious Diseases
2012	National Biodefense Science Board – Voting Member

LOCAL COMMITTEES (Current)

Hematology Oncology Fellows Committee
Duke Comprehensive Cancer Center Executive & Advisory Committee
Duke Cancer Institute Senior Leader
Clinical Oncology Executive Committee
Resource Utilization Council
Cell Therapy Steering Committee
Department of Medicine Executive Board
Stem Cell Research Oversight
Chancellor's Science Council
Multiple search committees

PUBLIC SERVICE

1990 - 1996	Arbor Free Clinic, Attending Physician
1999 - 2001	Chapel Hill Soup Kitchen
2007 – present	Durham Project Access – Member, Board of Directors

MAJOR RESEARCH INTERESTS:

Graft versus host disease
Bone marrow transplantation
Stem cell biology
Immune reconstitution
Hematopoiesis
Mitigation of radiation effects
Global Health (Oncology)

EDITORIAL BOARD (current)

Biology of Blood and Marrow Transplantation (Associate Editor)
Blood
Journal of Immunology (Associate Editor)
Oncology Today (Associate Editor)

REVIEWER

New England Journal of Medicine Blood
Journal of Immunology Experimental Hematology
Bone Marrow Transplantation Science
Journal of Clinical Investigation Leukemia
Journal of the National Cancer Institute Journal of Clinical Oncology
Journal of Experimental Medicine Biol Blood Marrow Transplantation
Nature Medicine Science Translational Medicine

PEER-REVIEWED PUBLICATIONS

P-1. Yamaguchi H., Chao N. and Gershon R. Molecular composition of an antigen specific Ly-1 T suppressor inducer factor. Journal of Experimental Medicine. 155: 655-665, 1982.

P-2. Chao N., Levine J. and Horning S. Retroperitoneal fibrosis following treatment for Hodgkin's Disease. Journal of Clinical Oncology 5:231-232, 1987.

P-3. Todd J.A., Acha-Orbea H., Bell J.I., Chao N., Fronek Z., Jacob C.O., McDermott M., Sinha A., Timmerman L., Steinman L. and McDevitt H.O. A molecular basis for MHC class II - associated autoimmunity. Science 240:1003-1009, 1988.

P-4. Chao N., Jacob C., Timmerman, L. and McDevitt, H.O. Molecular characterization of class II (B1 domain) antigen in the BB diabetes prone and resistant rat. Immunogenetics 29:231-234, 1989.

P-5. Schmidt-Wolf I, Aihara M, Negrin R, Blume KG and Chao NJ. Restoration of lymphokine activated killer cell activity after cryopreservation. Journal of Immunological Methods 125:185-189, 1989.

P-6. Chao NJ and Blume KG. Allogeneic bone marrow transplantation: Part I. Western Journal of Medicine 151:638-663, 1989.

P-7. Chao NJ and Blume KG. Autologous bone marrow transplantation: Part II. Western Journal of Medicine 152:46-51, 1990.

P-8. Aihara M, Blume KG and Chao NJ. Assessment of purging with multidrug-resistance (MDR) modulators and etoposide (VP-16): Results of long-term marrow cultures. Experimental Hematology 18:940-944, 1990.

P-9. Chao NJ, Aihara M, Sikic BI and Blume KG. Modulation of etoposide (VP-16) cytotoxicity by verapamil or cyclosporine in multiply drug-resistant human leukemic cell lines and normal bone marrow. Experimental Hematology 18:1193, 1990.

P-10. Chao NJ, Rosenberg S and Horning S. CEPP(B): Well-tolerated and effective treatment for patients with Hodgkin's lymphoma. Blood 76:1293-1298, 1990.

P-11. Blume KG, Schmidt GM, Chao NJ and Forman SJ. Bone marrow transplantation from histocompatible sibling donors for patients with acute lymphoblastic leukemia. Hematology and Blood Transfusion 33:636-637, 1990.

P-12. Chao NJ, Duncan SR, Long GD, Horning SJ, Blume KG. Corticosteroid therapy for diffuse alveolar hemorrhage in autologous bone marrow transplantation. Annals of Internal Medicine 114:145-146, 1991.

P-13. Aihara M, Aihara Y, Schmidt-Wolf G, Schmidt-Wolf I, Sikic BI, Blume KG and Chao NJ. A combined approach for purging multidrug resistant leukemia cell lines in bone marrow, using a monoclonal antibody and chemotherapy. Blood 77:2079-2084, 1991.

P-14. Forman SJ, Schmidt GM, Nademanee AP, Amylon MD, Chao NJ, Fahey JL, Konrad PN, Margolin KA, Niland JC, O'Donnell MR, Parker PM, Smith EP, Snyder DS, Somlo G, Stein AS, and Blume KG. Allogeneic bone marrow transplantation as therapy for primary induction failure for patients with acute leukemia. Journal of Clinical Oncology, 9:1570-1574, 1991.

P-15. Chao NJ, Nademanee AP, Long GD, Schmidt GM, Donlon TA, Parker P, Slovak ML, Nagasawa LS, Blume KG, and Forman SJ. Importance of bone marrow cytogenetic evaluation prior to autologous bone marrow transplantation for Hodgkin's disease. Journal of Clinical Oncology, 9:1575-1579, 1991.

P-16. Chao NJ, Forman SJ, Schmidt GM, Snyder DS, Amylon MD, Konrad PN, Nademanee AP, O'Donnell MR, Parker PM, Stein AS, Smith E, Wong RM, Hoppe RT, and Blume KG. Allogeneic bone marrow transplantation for high risk acute lymphoblastic leukemia during first complete remission. Blood, 78:1923-1927, 1991.

P-17. Horning SJ, Chao NJ, Negrin RS, Hoppe RT, Kwak LW, Long GD, Stallbaum B, O'Connor P, Blume KG. The Stanford experience with high-dose etoposide cytoreductive regimens and autologous bone marrow transplantation in Hodgkin's disease and non-Hodgkin's lymphoma: preliminary data. Annals of Oncology, Suppl 1:47-50, 1991.

P-18. Advani R, Chao NJ, Horning SJ, Blume KG, Ahn DK, Lamborn KR, Fleming NC, Bonnem EM, and Greenberg PL. Granulocyte-macrophage colony stimulating factor (GM-CSF) as an adjunt to autologous hemopoietic stem cell transplantation for lymphoma. Annals of Internal Medicine, 116:183-189, 1992.

P-19. Schmidt-Wolf IGH, Aihara M, Negrin RS, Blume KG, and Chao NJ. In vitro and in vivo activity of murine lymphokine-activated killer cells after cryopreservation. Transfusion, 32:42-45, 1992.

P-20. Marie J-P, Brophy NA, Ehsan MN, Aihara Y, Mohamed NA, Cornbleet J, Chao NJ, and Sikic BI. Expression of Multidrug Resistance Gene mdr1 mRNA in a Subset of Normal Bone Marrow Cells. British Journal of Hematology, 81:145-152, 1992.

P-21. Chao NJ, Tierney DK, Bloom JR, Long GD, Barr TA, Stallbaum B, Wong RM, Negrin RS, Horning SJ, and Blume KG. Dynamic assessment of quality of life following autologous bone marrow transplantation. Blood, 80:825-830, 1992.

P-22. Kuhl S-J, Sikic BI, Blume KG, and Chao NJ. Use of etoposide in combination with cyclosporine for purging multidrug resistant leukemic cells from bone marrow in a mouse model. Experimental Hematology, 20:1048-1054, 1992.

P-23. Chao NJ, Stein AS, Long GD, Negrin RS, Amylon MD, Wong RM, Forman SJ; Blume KG. Busulfan/etoposide - Initial experience with a new preparatory regimen for autologous bone marrow transplantation in patients with acute non-lymphoblastic leukemia. Blood, 82:319-323, 1993.

P-24. Chao NJ, Schriber JR, Grimes K, Long GD, Negrin RS, Raimondi CM, Horning SJ, Brown SL, Miller L, and Blume KG. G-CSF "mobilized" peripheral blood progenitor cells accelerate granulocyte and platelet recovery following high dose chemotherapy. Blood 81:2031-2035, 1993.

P-25. Schlegel PG, Schmidt-Wolf G, Schmidt-Wolf IGH, Kwak L, Blume KG, and Chao NJ. LAK activity against autologous lymphoma cells following bone marrow transplantation. Cancer Research, Therapy and Control, 3:145-152, 1993.

P-26. Schmidt GM, Niland JC, Forman SJ, Fonbuena PP, Dagis AC, Grant,MM, Ferrell BR, Barr TA, Stallbaum BA, Chao NJ, and Blume KG. Extended follow-up in 212 long-term allogeneic bone marrow transplant survivors. Transplantation, 55:551-557, 1993.

P-27. Chao NJ, Advani RA, Berry GJ, Horning SJ, Weiss LM and Blume KG. Acute lymphoproliferative malignancy following autologous bone marrow transplantation for non-Hodgkin's lymphoma. Transplantation, 55: 1425-1428, 1993.

P-28. Chao NJ, Schmidt GM, Niland JC, Amylon MD, Long GD, Nademanee AP, Negrin RS, O'Donnell MR, Parker PM, Smith EP, Snyder DS, Stein AS, Wong RM, Blume KG, and Forman SJ. Cyclosporine, methotrexate, and prednisone compared with cyclosporine and prednisone for prophylaxis of acute graft-versus-host disease. New England Journal of Medicine, 327:1225-1230, 1993.

P-29. Snyder DS, Taguchi J, Chao NJ, Amylon MD, Long GD, Negrin RS, Nademanee AP, O'Donnell MR, Schmidt GM, Stein AS, Parker PM, Smith EP, Konrad P, Stepan DE, Molina A, Lipsett JA, Hoppe RT, Niland JC, Dagis AC, Wong RM, Forman SJ, and Blume KG. Fractionated total body irradiation and high-dose etoposide as a preparatory regimen for

bone marrow transplantation for 99 patients with acute leukemia in first complete remission. Blood, 82:2920-2928, 1993.
P-30. Schriber JR, Negrin RS, Chao NJ, Long GD, Horning SJ, and Blume KG. The efficacy of granulocyte-colony stimulating factor following autologous bone marrow transplantation for non-Hodgkin's lymphoma with monoclonal antibody purged bone marrow. Leukemia, 7:1491-1495, 1993.
P-31. Kuhl, J-S Duran GE, Chao NJ, and Sikic BI.Effects of the methoxymorphilino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow. Cancer Chemotherapy and Pharmacology, 33:10-16, 1993.
P-32. Chao NJ, Schriber J, Long GD, Negrin RS, Catolico M, Brown BW, Miller LL, and Blume KG. A randomized study of erythropoietin and G-CSF versus placebo and G-CSF for patients with Hodgkin's and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation.Blood, 83:2823-2828, 1994.
P-33. Snyder DS, Negrin RS, O'Donnell MR, Chao NJ, Amylon MD, Long GD, Nademanee AP, Stein AS, Parker PM, Smith EP, Somlo G, Margolin K, Lipsett JA, Hoppe RT, Slovak ML, Niland JC, Dagis AC, Wong RM, Forman SJ, and Blume KG. Fractionated total body irradiation and high-dose etoposide as a preparatory regimen for bone marrow transplantation for 94 patients with chronic myelogenous leukemia in chronic phase. Blood, 84:1672-1679, 1994.
P-34. Schriber JR, Chao NJ, Long GD, Negrin RS, Tierney DK, Kusnierz-Glaz C, Lucas KS, and Blume KG. Granulocyte colony stimulating factor (G-CSF) following allogeneic bone marrow transplantation. Blood, 84:1680-1684, 1994.
P-35. Schlegel PG,Schlegel PG; Aharoni R; Smilek DE; Fernandez LP; McDevitt HO; Tran N; Vaysburd M; Chao NJ. Prevention of graft-versus-host disease by synthetic peptides with high binding affinity for class II MHC molecules.Blood, 84:2802-2810, 1994.
P-36. Chao NJ, Kastrissios H, Long GD, Negrin RS, Horning SJ, Wong RW, Blashke T; Blume KG. A new preparatory regimen for autologous bone marrow transplantation for patients with Hodgkin's and Non-Hodgkin's lymphoma. Cancer, 75:1354-9, 1995.
P-37. Horning SJ, Negrin RS, Chao NJ, Long GD, Hoppe RT, and Blume KG. Fractionated total body irradiation, etoposide and cyclophosphamide and autografting in Hodgkin's disease and non-Hodgkin's lymphoma. J. Clin Oncol, 12:2552-2558, 1995.
P-38. Negrin RS, Kusnierz-Glas CR, Still BJ, Schriber JR, Chao NJ, Long GD, Hoyle C, Hu WW, Horning SJ, Brown BW, Blume KG, and Strober S. Transplantation of enriched and purged peripheral blood progenitor cells from a single apheresis product in patients with non-Hodgkin's lymphoma. Blood, 85:3334-3341, 1995.
P-39. Fernandez LP, and Chao NJ. Lack of effect of thalidomide on IL-2 response and production. Experimental Hematology, 23:978-85, 1995.
P-40. Long GD, Negrin RS, Hoyle CF, Kusnierz-Glaz KR, Schriber JR, Blume KG, and Chao NJ. Multiple cycles of high dose chemotherapy supported by hematopoietic progenitor cells as treatment for patients with advanced malignancies. Cancer, 76:860-8, 1995.
P-41. Parker PM, Chao NJ, Snyder DS, Nademanee A, O'Donnell MR, Schmidt GM, Stein AS, Smith EP, Molina A, Stepan DE, Kashyap A, Planas I, Somlo G, Margolin K, Niland JC, Zwingenberger K, Wilsman K, Blume KG, and Forman SJ. Thalidomide therapy for chronic graft-versus-host disease. Blood, 86:3604-3609, 1995.
P-42. O'Donnell MR, Long GD, Parker PM, Niland J, Nademanee A, Amylon M, Chao NJ, Negrin RS, Schmidt GM, Slovak ML, Smith EP, Snyder DS,, Stein AS, Traweek T, Blume KG, Forman SJ. Busulfan/cyclophosphamide as conditioning regimen for allogeneic bone marrow transplantation for myelodysplasia. Journal of Clinical Oncology, 13(12):2973-2979, 1995.
P-43. Zaia JA, Schmidt GM, Chao NJ Snyder DS, Nademanee A, O'Donnell MR, Stein AS, Smith EP, Molina A, Stepan DE, Kashyap A, Planas I, Somlo G, Margolin K, Niland JC, Blume KG, and Forman SJ. Pre-emptive ganciclivir based solely on asymptomatic pulmonary cytomegalovirus infection in allogeneic bone marrow transplant recipients: Long-term follow-up. Biology of Blood and Marrow Transplantation, 1(2):88-93, 1995.
P-44. Schlegel PG, Vaysburd M, Chen Y, Butcher E, Chao NJ. Selective inhibition of T cell costimulation mediated by VCAM-1 prevents murine graft-versus-host disease. Journal of Immunology, 155: 3856-3865, 1995.
P-45. Pattarelli P, Jeffrey RB, Chao N. Gallbladder wall thickening is neither sensitive nor specific for hepatic venoocclusive disease following bone marrow transplantation. Ultrasound International 1:163-4, 1995
P-46. Schlegel PG, Chao NJ. Immunomodulatory peptides with high binding affinity for class II MHC molecules for the prevention of graft-versus-host disease. Leukemia and Lymphoma 18:179-184, 1996.
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Research Support

NIH – 1U19 AI067798-01 (Chao, Nelson J., PI) 08/31/2010 – 07/30/2014
Centers for Medical Countermeasures Against Radiation

The broad and long term objectives of this research application focuses on rapid biodosimetry and mitigation of radiation injury as well as advancing education in this area.

R21/33-AI080525 (Chao, Nelson J.) 07/01/2008 - 06/30/2013
NIH

The objective of this project will be to establish the model and the biological monitoring of the impact of combined radiation and dermal wound injuries. The R33 followed on studies will optimize therapeutic responses and extend the combined injury model to include burns.

P01 CA47741 (Chao, Nelson) 09/30/2009 – 06/30/2014
NIH/NCI
Novel Approaches for Stem Cell Transplantation
The long-term objective of this project is to improve the outcome following high dose chemotherapy for hematological diseases. The project related to this grant studies the outcome following allogeneic stem cell transplantation for leukemias and lymphomas.

5-P30-CA14236-28 (Lyerly, Kim, PI) 01/01/2010 - 12/31/2014
NIH/NCI
Comprehensive Cancer Center Core Grant (Bone Marrow Transplantation Program, Program Leader)
The major goals of this project are to integrate program coordinators with specific research nurse/data management support under the administrative direction of the clinical trials office as one shared resource.

Hematopoietic Stem Cell Transplantation for CML in the TKI Era

Nelson Chao, MD
Duke University

The treatment for chronic myeloid leukemia has evolved dramatically and continues to evolve. The introduction of Bcr-Abl tyrosine kinase inhibitors has clearly resulted in a dramatic improvement in responses, disease free survival and overall survival. Moreover, newer generation of TKIs continue to be developed. In this backdrop, the mainstay for cures for CML, allogeneic hematopoietic cell transplantation (HCT), has appropriately decreased. There is no doubt that allogeneic HCT can cure patients with CML. CML is one of the diseases that is sensitive to the graft-vs.-leukemia effect. So under what circumstances and when should one consider allogeneic HCT?

The easiest scenario is that of patients with blast crisis CML. Patients who present with blast crisis or progress to blast crisis while on therapy have a poor prognosis. In this setting, the treatment of choice would be to start with a new TKI to induce a first or second chronic phase. Once the patient achieves a chronic phase, they should move quickly to an allogeneic HCT. In the setting of chronic phase, it is a bit more difficult to be sure of the appropriate time. Clearly patients who are responding well should be left alone. However, there are several subcategories where HCT should be considered. There is a group of patients that are truly intolerant of TKIs and these patients should be considered for allogeneic HCT. Another group are patients that are not compliant with their medication. This group presents a particularly difficult decision as to when the optimal time is since we would like to proceed to an allogeneic HCT before the induction of resistance. Other patients in chronic phase would include those with mutations that allow for resistance to known TKIs. These patients do not do well in the long run. Other patients would include those that have high Sokal scores, or who fail several TKIs.

It is important to note that allogeneic HCT has changed significantly over the TKI era as well. Outcomes from ablative HCT have improved decade by decade based on improvements in supportive care especially with new antibiotics, antivirals and antifungals. Moreover, novel regimens such as non myeloablative and reduced intensity regimens allow for patients to undergo allogeneic HCT with a significantly lower treatment associated morbidity and mortality. While there has not been any head to head comparison of ablative vs. non ablative conditioning regimens, the sensitivity of CML cells to the graft-vs.-leukemia effect suggest that these lower intensity approaches should result in excellent outcomes. Moreover, the use of donor lymphocyte infusions to consolidate the responses are also effective in this disease.

Lastly, cost is always an issue in many countries. The cost of TKIs to be taken forever (at least for the time being) can be quite high. While allogeneic HCT is not cheap, in general, it is a one time high cost procedure but if the patient is cured without sequelae, the patient returns to an excellent state of health without the need for continued chronic medication. Thus, allogeneic HCT continues to have a role, albeit a smaller one, in patients with CML. As both drug therapy and HCT continue to evolve, this area will continue to be a focus of intense research.

ICLLM 2013

Chronic Lymphocytic Leukemia

For decades, chronic lymphocytic leukemia (CLL) has been considered a somehow boring indolent disease of the elderly without much need for therapeutic intervention and without effective treatment options. Since the late nineties, however, understanding of the genetic and biologic background of the disease has dramatically increased and provided a rationale basis for the plethora of effective treatment modalities for this malignant disease already available or under development. This session will give an overview about the current state of the art of treating CLL and its future perspectives.

Professor Emili Montserrat will describe treatment goals and their implications for designing effective trials for the management of patients with CLL.

Professor Eva Kimby will discuss the perspectives opened by new drugs and treatment strategies for poor-risk CLL which are currently under investigation.

Professor Peter Dreger will review the definition and treatment options for patients with high-risk CLL

Peter Dreger, M.D.

Emili Montserrat

Emili Montserrat is Professor of Medicine at the Institute of Hematology and Oncology, Hospital Clínic, University of Barcelona and Chairman of the *European Research Initiative for CLL* (ERIC). His main areas of interest are chronic lymphoproliferative disorders and lymphomas in which he and his group have made seminal contributions. Emili Montserrat is one of the founding members of the *International Workshop on CLL (IWCLL)* and the *European Hematology Association (EHA)* of which he is Past-President.

Emili Montserrat is on the board of the most important journals in hematology and oncology and is a regularly invited key-speaker at the most important meetings in hemato-oncology. He has received many awards, including the *Lilly Award in Biomedicine*, *National Award in Oncology (Fundación Echevarne, Spain), Severo Ochoa Award, Rai-Binet (IWCLL) Medal, and is Distinguished Senior Investigator of the University of Barcelona* and Corresponding Member of the *Royal Academy of Medicine*, Barcelona. He received the life-time achievement awards from the *European Society of Medical Oncology* and the *European Hematology Association*. Emili Montserrat is also honorary member of many universities and scientific organizations, among them the *Royal College of Pathology* (London). Emili Montserrat is also Doctor Honoris Causa by the University of Athens, Greece, and honorary member of many haematological and oncological societies from over the world.

Chronic Lymphocytic Leukemia Treatment: Goals and Endpoints

Emili Montserrat

University of Barcelona

In the last few years, important progress has been made in the management of patients with chronic lymphocytic leukemia (CLL). Regarding indications for therapy, treatment is only justified in the presence of signs or symptoms of disease activity such as B-symptoms, lymphadenopathy or splenomegaly increasing in size or causing compressive problems, decreasing Hb levels or platelet counts due to bone marrow infiltration, autoimmune hemolytic anemia not responsive to standard therapy, rapid lymphocyte doubling time (i.e., less than 6 months) and hypogammaglobulinemia with infections. Of note, an increased WBC count by itself or hypogammaglobulinemia with no infections are not by themselves indications for therapy. Likewise, treatment is not justified on the sole basis of poor prognosis biomarkers such as unmutated *IGVH* genes, high expression of ZAP-70 in neoplasic lymphocytes or poor cytogenetics (e.g., 17p-). The same applies to newly described mutations (e.g., NOTCH-1, SF3B1, MYD88, BIRC-3) whose clinical meaning has not been fully validated and for which standardized detection methods are not yet available.

In spite of the plethora of new prognostic factors, prognostication should continue to be based on traditional factors. Clinical stages (Rai, Binet), lymphocyte doubling time, and serum beta-2 microglobulin leves are more than enough to predict the course of the disease.

The physician advising therapy to a given patient with CLL should keep in mind that the goal of therapy is to prolong survival and to improve quality of life. Once therapy is needed it is highly recommended to perform a FISH chromosome analyses since patients with 17p- do not respond to conventional therapy. Alemtuzumab is useful in 17p- or TP53 mutated cases without a high tumor burden. There is also some indication that lenalidomide could be effective across all genetic groups. In patients without these abnormalities, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is the best therapy. However, FCR can be only safely applied to patients with good performance status, normal renal function, and not actively replicating HBV. Moreover, patients older than 70 poorly tolerate FCR, leaving the majority of patients without a satisfactory treatment. The CR rate with FCR is 40%-70%. Based on shortly expected results from clinical trials, the combination of rituximab and bendamustine is likely to replace FCR in frail and elderly patients. There is also some indication that the third generation anti-CD20 monoclonal antibody GA101 might replace in the future rituximab. Ofatumumab is another anti-CD20 monoclonal antibody approved for fludarabine-refractory patients.

With all these therapies there is a strong correlation between the degree of response and patients'

outcome. According to the IWCLL, within clinical trials CRs can be subclassified into (1) minimal-residual-disease (MRD) negative, and (2) MRD-positive. Cases with MRD-negative CR have a better PFS and overall survival. This observation has important derivates such as the potential benefits of "consolidation" or "maintenance" therapy in patients MRD-positive at the end therapy or using MRD-negativity as a surrogate endpoint in clinical trials. Importantly, because of their experimental nature, MRD status should not be used to guide therapy outside clinical trials.

Although the relationship between MRD-negativity and improved overall survival can be considered as a new paradigm in CLL treatment, paradigms are created to be challenged. In this regard, a number of biological agents targeting BCR (e.g., Ibrutinib, GS1101) are proving to be highly effective in CLL therapy. These agents, which seem to be effective in all genetic groups, cause a rapid and dramatic improvement in the patient's general status and the reduction in the size of lymph nodes; this however is accompanied by a transient increase in blood lymphocyte counts, reflecting lymphocytes shifting among different compartments (bone marrow, lymph nodes, blood). Moreover, in most cases the bone marrow is not completely cleaned up from the disease, so the proportion of CR as defined by current criteria is relatively small (around 10%). Paradoxically, however, the PFS and overall survival seem to be remarkably prolonged. Although the caveat is the relative short median follow up of patients treated with these novel agents, this observation (long PFS and overall survival in patients not in CR) indicates that the same goal (prolonging survival) might be achieved through different strategies and that treatment endpoints should be most likely treatment-specific.

An extremely challenging situation is the treatment of patients who are refractory to- or have a short response duration (e.g., less than 1 year) with FCR since their prognosis is very poor (median survival inferior to 2-3 years). Due to this fact, the possibility of performing a non-myeloablative allogeneic stem cell transplant should be considered in good candidates. Novel forms of T-cell therapy (e.g. CAR-T cells) are being actively investigated. In addition to cases refractory to therapy, the management of elderly patients or those with comorbidities require new and more effective forms of therapy. For patients not participating in trials, chlorambucil continues being a reasonable approach. In that setting, there is some proof that the combination of chlorambucil with an anti-CD20 monoclonal antibody results in a higher response rate and longer PFS. Finally, due to its increasing complexity patients with CLL should be managed in referral institutions where new treatment approaches and the inclusion of patients in trials are possible.

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Eva Kimby, M.D, Ph.D., Professor

Dr Eva Kimby is Professor of Haematology at the Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.

Dr Kimby studied medicine at Karolinska Institutet in Stockholm, where she obtained her M.D., Ph.D. and Professor degrees. Dr Kimby is lecturer for students at the Karolinska Institute and in international meetings on CLL and lymphomas. Her main research interests are indolent lymphoma, CLL and the applications of immunotherapy. She is actively involved as a key investigator in several haematology trial groups and the principal investigator for two large Nordic rituximab +/- interferon trials. Dr Kimby was elected chairman of the group for indolent lymphomas within the Swedish and Nordic Lymphoma Group in 1997 (ongoing) and was the first chairman of the Swedish CLLL group. Dr Kimby is also a member of several international scientific societies and vice president in ERIC (European Research Initiative on CLL), working member of the EBMT CLL/lymphoma subcommittees and of the International Workshop on Waldenströms macroglobulinemia and has an Advisory role on the Board of European Network Mantle cell lymphoma. She has published more than 130 papers and several reviews in peer-reviewed international journals and is supervisor for Ph.D. students and Opponent at the defense of Ph.D.-theses.

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Swedish PI Several CLL, FL and Waldenstrom trials.
Collaborator and coinvestigator in International trials in Waldenströms macroglobulinemia.
Coinvestigator in the Stockholm alemtuzumab trials and in several international trials in CLL and lymphoma.

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Stockholm 2013-01-28

New therapies in Chronic lymphocytic leukemia (CLL)

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There are today many effective therapies for patients with CLL, as the fludarabine –cyclophosphamide (FC) +rituximab (R) and bendamustine + R regimens, but these are not tolerable for aged patients with comorbidities, and most patients will get multiple relapses and will require several therapies during their life-time. Accumulation of negative prognostic features, clonal evolution and resistance to chemotherapy evolve over time, and there is a great need for new therapies. CLL is a malignancy of mature B-cells, which are dependant on host factors in the tissue microenvironment. Abnormalities in the T-cells in CLL patients are seen, as a suppressed F-actin polarization at the contact site between the T-cells with APCs (immunesynapse). Many signalling pathways are activated in CLL, including the B-cell receptor (BCR) and the NF-kB. Several kinases are essential for the BCR signal transduction as the bruton tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3K)-delta, both critical for activation, proliferation and survival of B cells for their homing and retention in lymphoid tissues. BTK and PI3Kδ signaling has been shown to be hyperactive in B-cell malignancies as CLL and small-molecule inhibitors of these kinases are under development for therapy in CLL.

Ibrutinib and idelalisib are oral inhibitors of BTK and PI3Kδ, respectively, with potency to reduce proliferation, enhance apoptosis, and inhibit homing and retention of malignant B cells in lymphoid tissues. Phase 1and 2 trials have demonstrated that these drugs are highly active in pts with heavily pretreated CLL with reductions in disease-associated chemokines, profound reductions in lymphadenopathy, and clinical benefit. With both drugs there is a lymphocyte redistribution to blood, which may persist over months, but without clinical symtoms. The safety profile has been acceptable with some problems with loose stool, with idelalisib mostly reversible AST/ALT increase in 5% of patients. Lenalidomide, an immune-modulating drug, approved for myeloma, with down-modulatiion of cytokines like TNF-alfa and IL-6 and inhibition of VEGF and with immune system activation effects, especially on NK-cells. In CLL, treatment with lenalidomide in-vitro and in-vivo in patients, has shown an enhancement of the immune synapse formation and clinical efficacy in several CLL trials. In summary, the background, mode of action and efficacy of some new CLL drugs will be reviewed in this talk.

Peter Dreger

Peter Dreger started his scientific career in 1985. After 3 years of basic research in experimental bone marrow transplantation he joined the Second Department of Medicine at the University of Kiel in 1988. Together with Norbert Schmitz he established a scientific program of experimental and clinical blood stem cell transplantation. Significant contributions were made in the fields of allogeneic peripheral blood stem cell transplantation and allogeneic and autologous transplantation for lymphoma and CLL.

In 2005 he accepted the position of a Professor and Head of the Division of Stem Cell Transplantation at the University of Heidelberg. Peter Dreger is founding member of the German CLL Study Group (Responsibility: Transplant studies). He has worked with the EBMT for many years and served as chairman of the CLL subcommittee of the EBMT Chronic Leukemia WP from 2005-2010. Since March 2010, he is chairman of the EBMT Lymphoma Working Party.

High-risk chronic lymphocytic leukemia: definition and treatment options

Peter Dreger

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On behalf of the European Group for Blood and Marrow Transplantation (EBMT)

Key points

Chronic lymphocytic leukemia is considered high-risk if one or more of the following criteria is present: (i) presence of symptomatic disease with del 17p or TP53 mutations, (ii) fludarabine resistance, (iii) early relapse (within 2 years) after intensive treatment

Additional high-risk factors (SF3B1, NOTCH1 mutations) are emerging but still need prognostic validation

Although kinase inhibitors targeting the B cell receptor signalling pathway, such as inbrutinib, may open new avenues of disease control in CLL, the only modality with documented long-term efficacy in CLL is allogeneic stem cell transplantation (alloSCT)

Novel forms of (reduced intensity) conditioning (RIC) have resulted in dramatic reduction of early morbidity and mortality of alloSCT, making this procedure now suitable for comorbid and elderly patients

This "new" alloSCT is working particularly well in chronic lymphocytic leukemia (CLL) based on strong graft-versus-leukemia (GVL) efficacy.

New alloSCT is effective also in poor-risk CLL and can provide long-term disease-free survival.

Preliminary evidence suggests that alloSCT indeed can change the natural history of poor-risk CLL, and novel CLL-targeting drugs may have the potential to further improve transplant outcome.

High-risk CLL

In 2006, the EBMT worked out definitions for high-risk CLL justifying alloSCT. Criteria for "poor-risk CLL" according to this "EBMT Transplant Consensus" are purine analogue refractoriness, relapse within two years after purine analogue combination therapy, and CLL with TP53 lesion requiring treatment [1]. More recently, these definitions were confirmed by the iwCLL guideline seminar paper [2]

Since then, however, a huge body of novel treatment modalities has been studied in these indications. These comprise rituximab-purine analogue or bendamustin combination regimens, alemtuzumab-containing regimens, and new drugs, such as flavoperidole, lenalidomide, and ibrutinib. Therefore, it needs to be addressed if high-risk CLL is still high-risk with the 2013 treatment arsenal.

del 17p and TP53 mutations: Although fludarabine-cyclophosphamide-rituximab (FCR) has been shown to improve overall survival in CLL when administered as first-line therapy, even this highly effective combination does not seem to be capable to improve the dismal natural course of patients with del 17p-deleted CLL [3;4]. Similarly, FC-ofatumumab [5], bendamustin-rituximab [6], alemtuzumab (even in combination with fludarabine or high-dose steroids) [7] flavopiridol [8], and lenalidomide [9] do not provide sustained disease control in patients with 17p-. Recently, promising results were reported for the Bruton's tyrosine kinase inhibitor ibrutinib, alone [10] or in combination with bendamustin and rituximab. The ibrutinib-bendamustin-rituximab regimen yielded a 71%-response rate in seven relapsed or refractory patients with 17p- CLL. However, the observation time was too short to conclude on long-term efficacy [11].

Purine-analogue refractoriness: Similarly, these new agents and drug combinations do no provide significant disease control when administered to patients with fludarabine-refractory disease [12].

Early relapse after intensive pretreatment: There are no detailed studies showing the effect of individual salvage regimens in this risk group. However, the overall outlook of patients early after FCR or FC is poor: In a post-hoc analysis of patients relapsing within the CLL8 trial, the overall survival after start of salvage treatment of those patients whose disease recurred within the second year after end of study treatment was about 2 years, and thereby comparable to that of truly refractory patients [13]. Similarly, time to FCR failure was a significantly adverse factor for survival after frist salvage treatment in 114 patients relapsing after FCR in a study from the MD Anderson Cancer Center [14].

In addition, novel potential clinical and biological risk factors indicating a poor outcome with conventional immunochemotherapy have emerged recently, such as MRD response [15;16] and mutations of the driver genes SF3B1, NOTCH1, and BIRC3 [17-21]. However, further prospective validation of these markers is needed before definite conclusions on their prognostic value can be drawn.

Role of allogeneic transplantation in the treatment of high-risk CLL

After it had been recognized that in CLL the antileukemic effect of alloSCT is largely – if not entirely – due to the graft-versus-leukemia activity (GVL) conferred with the hematopoietic stem cell graft [22-25], and that engraftment and GVL can be achieved without preceding myeloablative treatment [26-28], the avenues for a completely new form of allogeneic transplantation were opened. This "new" alloSCT is fundamentally different from the traditional myeloablative transplantation, is applicable to a large proportion of the CLL target population, and represents the most effective and only curative treatment of CLL available today. Its clinical effectiveness relies on the initiation of cellular immune therapy permanently active in the patient, thereby providing a treatment modality which is in a biological sense completely different to any other cytotoxic or immunological therapy. Accordingly, the numbers of (non-myeloablative) allotransplants for CLL are steadily increasing, making CLL now the most frequent indication for alloSCT among all lymphomas in the European Group for Blood and Marrow Transplantation (EBMT) registry. In contrast, autoSCT is rapidly declining.

The purpose of this overview is to summarize the knowledge characterizing the efficacy and tolerability of modern alloSCT strategies in CLL, and to describe the resulting role of alloSCT in the current therapeutic arsenal for CLL.

Evidence for efficacy of "new" alloSCT in CLL

The basis of "new" (non-myeloablative or reduced-intensity conditioning; RIC) alloSCT in CLL is that GVL effects are active. Evidence for GVL efficacy in CLL derives from the observation that – in contrast to autologous SCT or other intensive therapies – the relapse incidence seems to decrease over time after RIC alloSCT. Accordingly, all larger studies on RIC alloSCT in CLL show a *plateau* at 40-50% in the disease-free survival curve [29-32].

The most convincing proof of the GVL principle in CLL comes from studies analyzing the kinetics of minimal residual disease (MRD) after RIC alloSCT. MRD denotes a disease burden remaining after specific therapy which is only detectable at a subclinical level. For CLL, this is defined as a contamination of five CLL cells or less per nl of peripheral blood in the absence of clinical signs or symptoms of the disease. Patients showing less than one CLL cell in 10,000 benign leukocytes in peripheral blood or bone marrow are considered as being MRD negative [2].

Altogether, MRD kinetics studies consistently indicate that permanent MRD negativity after alloSCT for CLL can be reached in the context of immunomodulating intervention [29;33;34]. Both the durability of MRD remission and its sensitivity to immunomodulation strongly suggest that GVL is effective in CLL. Unfortunately, GVL in CLL seems to be closely correlated to chronic GVHD, implying that

it is essentially dependent on allogeneic effects with broader specificity rather than on a CLL-specific reactivity of donor GVL effector cells.

Risks and tolerability of "new" alloSCT in CLL

The core feature of modern alloSCT strategies is that their tolerability has dramatically increased in comparison to traditional conditioning based on standard-dose total body irradiation (TBI) or myeloablative doses of oral busulfan. Together with a tremendous improvement of supportive treatment (e.g. antiemetics, antibiotics, CMV monitoring etc.) during the last decade, this makes a huge difference for the patients especially during the early transplant phase (i.e. conditioning, transplantation, and aplasia): Higher-grade nausea and mucositis will affect only a small minority of patients undergoing RIC, and although grade 3-4 infections still occur in up to 60% of the patients, only few result in life-theatening complications 29-32. Accordingly, the "early death rate" (i.e. death within the first 100 days after alloSCT) has dramatically decreased from up to 40% in the old days of traditional conditioning down to less than 3% with RIC. This has to be taken into account when considering the risk of dying with and without transplant. Despite the remarkable improvements in terms of early fatalities, non-relapse mortality (NRM) after RIC alloSCT for CLL still mount up to 15%-25% during the first two post-transplant years. This seems to be largely due to complications of acute and chronic GVHD.

Apart from its impact on NRM, chronic GVHD is the major determinant of long-term morbidity affecting quality of life (QOL) after alloSCT. At least 25% of survivors will experience impaired life satisfaction during the first post-transplant years with chronic GVHD being a robust predictor of reduced QOL 35. However, in many affected patients clinical symptoms of chronic GVHD decrease over time: In their series of 82 patients, Sorror et al observed a 5-year cumulative incidence of extensive chronic GVHD of 49% for related and 53% for unrelated recipients. Overall, in an increasing proportion of patients chronic GVHD resolved during follow-up, allowing discontinuation of therapeutic immunosuppression after a median of 25 months 30.

In conclusion, transplant-related long-term morbidity after alloSCT for CLL can be significant but is mainly restricted to those patients who have ongoing active chronic GVHD. The morbidity caused by alloSCT for patients with poor-risk CLL must be weighed against the morbidity due to uncontrolled disease and palliative treatment associated with non-transplant salvage strategies.

Can alloSCT improve the outcome of poor-risk CLL?

del 17p and TP53 mutations: Data from randomized trials or prospective trials focussing on patients with TP53 lesions are not available. However, subset data from prospective phase-II studies as well as a larger registry analysis [36] strongly suggest that long-term disease control can be achieved in 30-45% of patients with 17p- referred to alloSCT. A post-hoc analysis of from the GCLLSG CLL3X trial indicates that this is also true for patients with TP53 mutation in the absence of 17p- [29].

Purine-analogue refractoriness: Similarly, the published phase-II evidence indicates that alloSCT can overcome the poor prognostic impact of purine-analogue refractoriness if the patient can be put into a state of sensitive disease by other measures prior to transplant [29-32].

Early relapse after intensive pretreatment: There is no structured data available on the specific effect of alloSCT in this subset. However, since the prognosis of these patients with conventional salvage treatment is not worse than that of fludarabine-refractory patients, and there is no fundamental biological difference between patients with early relapse and those wiho are truly fludarabine-refractory, it can be anticipated that alloSCT is at least as effective as in true purine-analogue refractoriness. A preliminary single center analysis confirms this assumption [37].

Can alloSCT change the natural course of poor-risk CLL?

Although there is no doubt from the published CLL transplant studies that alloSCT can largely improve the prognosis of individual poor-risk patients, it is unclear to what extent alloSCT indeed can impact the natural history of the patient population with aggressive CLL, and what its overall clinical value for the treatment armory of CLL might be. This question can be properly addressed only by prospective trials comparing alloSCT with non-transplant strategies in defined clinical risk situations by intention-to-treat. It is crucial for such comparisons that patients are followed from the time of reaching transplant indication as triggered by need for treatment rather than from the time of alloSCT. A trial planned by the GCLLSG to address this question could not be launched because of the extremely complex regulatory requirements for clinical trials involving unrelated donors which are currently effective in Germany.

A retrospective study from Heidelberg comparing patients with poor-risk CLL with transplant indication according to the EBMT criteria in a donor-versus-no-donor landmark analysis suggested a survival advantage for those patients for whom a donor could be found [37]. However, this single retrospective analysis from a single center has to be regarded as very preliminary. A survival advantage of alloSCT over non-transplant strategy in patients with relapsed CLL was also concluded from a systematic meta-analysis using a Markov decision model [38]. Due to its artificial design, however, this study has also serious limitations.

Nevertheless, these results are encouraging, confirm the current important role of alloSCT in the treatment of poor-risk CLL, and warrant further studies in this field. The new drugs that are about to enter the therapeutic arena in CLL will hopefully help to improve the results of alloSCT by reducing the tumor load before transplant and/or eradicating MRD post transplant.

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ICLLM 2013

Aggressive Lymphomas

It is a great pleasure for us to welcome all of you to this session dedicated to Aggressive Lymphomas. We already have a session dedicated to diffuse large B cell lymphoma in this meeting. In order to avoid overlaps, we have decided to devote this other one to three distinct entities with a well known aggressive behaviour: Mantle Cell Lymphoma (MCL), Peripheral T Cell Lymphoma (PTCL) and Primary Central Nervous System Lymphoma (PCNSL).

The first presentation entitled "Inside the Mantle Cell. Treatment of High-Risk Mantle Cell Lymphoma" will be given by Prof. Olivier Hermine from Hopital Necker, Paris, France. MCL is one of the lymphomas with the worse prognosis (median survival 3-5 years) as it has an aggressive evolution and at the same time is incurable. Biologically it is characterized by the t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1. Unfortunately, there are still a lot of controversial aspects in the management of the disease: how to recognize the small subgroup of cases with an indolent course, which treatment is suggested for the young and fit or for the elderly, the role of CNS prophylaxis, rituximab maintenance, the indications to allogeneic transplantation and the place of new active anti-lymphoma drugs. Some of them will be extensively discussed in this talk.

Prof. Norbert Schmitz from Asklepios St Georg in Hamburg, Germany will be the responsible expert leading the discussion of "The Role of Stem Cell Transplantation in Peripheral T Cell Lymphomas". PTCL is a heterogeneous group of non-Hodgkin's lymphoma that carries, except for ALK-positive anaplastic large cell lymphoma, a poor prognosis. Only a third of patients live 5 years post diagnosis. The incidence of PTCL has been increasing during the last two decades. In recent years, there was a rising interest in PTCL manifested by the abundance of publications dedicated exclusively to this disease. Given the poor outcomes of PTCL patients, high-dose chemotherapy and autologous stem-cell transplantation (HDT/ASCT) have been used in the up-front and salvage settings, with different success rates. However, there are no prospective randomized controlled trials addressing the role of HDT/ASCT in a PTCL-restricted population. The same principle applies to the use of allogeneic stem cells both in the relapse setting and as consolidation therapy in patients responding to first line therapy.

Last but not least, Prof. Gerald Illerhaus (University of Freiburg, Freiburg, Germany) will go through many of the still open questions in PCNSL with his presentation entitled "Biology, Prognostic Factors and Treatment of Primary Central Nervous System Lymphoma". Recent studies addressing the molecular characteristics of PCNSL have significantly improved our understanding of the pathogenesis of this lymphoma entity, which is associated with an inferior prognosis as compared with DLBCL outside the CNS. This unfavorable prognosis has stimulated intense efforts to improve therapy and induced recent series of clinical studies, which addressed the role of radiotherapy and various chemotherapeutic regimens.

We really hope that this session, although the last one in the program of this very intensive meeting will be of your interest and we cordially invite you to make it as interactive and lively as possible during the Q&A time after each one of the presentations. Looking forward to meeting all of you in Istambul.

Anna Sureda MD PhD
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CURRICULUM VITAE

Olivier Hermine

Olivier Hermine is Professor of Hematology at Paris Descartes university, director of the department of Adult Hematology of Hospital Necker, member of the scientific board of the Imagine institute, coordinator and founder of the reference centre for mastocytosis (CEREMAST), vice director of the CNRS UMR 8147 unit "Cytokines, hematopoiesis, virus and immune system regulation" at Necker Hospital. He is founder and coordinator of the Laboratory of Excellence on red cells (GRex), which has been granted by the French ministry of research. He is an active member of the Lysa and the EMCL particularly involved in studies of Mantle cell lymphoma and virus related lymphoma. He is author and co-author of **421 publications** in peer-reviewed journal including Nature, Journal of experimental medicine, New England journal of Medicine, Lancet oncology, Journal of clinical oncology, and blood. His topics of basic science and clinical research cover erythropoiesis regulation and erythroid disorders, immune regulation, mast cell and mastocytosis, lymphomagenesis and leukemogenesis, and treatment of haematological disorders.

Inside the Mantle Cell. Treatment of high-risk mantle cell patients

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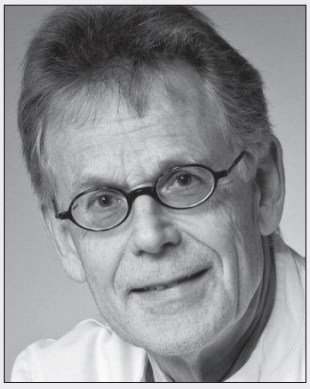
Mantle cell lymphoma (MCL) is an individualized entity that is well characterized at the molecular level and considered to be a disease of elderly patients. However, about half of patients are less than 65 years of age and may benefit from intensive therapies. Although MCL has been considered during the last three decades as an incurable disease with current chemotherapy regimens, in young patients recent intense chemo-immunotherapy (CIT) induction regimens including highdose cytarabine with consolidation with autologous stem cell transplantation (ASCT) have increased significantly the outcome of patients with the disease; some may experience long-term survival free of disease and may even be cured. In elderly patients rituximab maintenance has improved significantly survival.

In addition, new drugs targeting some pathways, including molecular alterations of the disease, are being progressively incorporated into the therapeutic armamentarium of the disease and will certainly contribute to further improve prognosis. In the near future, more individualized approaches are foreseen that will take into account risk factors present at diagnosis, biomarkers representative of the molecular alterations, as well as quality of the response assessed by molecular residual diseases analysis. Current therapeutic approaches with classical CITs, the role of autologous and allogeneic stem cell transplantation, and the main new drugs that target major molecular pathways alterations of the disease, as well as their positioning during induction, consolidation, and maintenance in first-line treatment and in relapsing younger patients with MCL, will be discussed.



CURRICULUM VITAE

Norbert Schmitz, M.D., born in Aachen, Germany, April 11, 1951.

Degrees

1977	M.D. at the University of Giessen, Germany.
1989	Postdoctoral thesis (habilitation), title: Analysis of haematopoietic chimerism after allogeneic bone marrow transplantation in patients with chronic myelogenous leukaemia at the Christian-Albrechts-University Kiel, Kiel, Germany.
1996	Professor of Medicine at the University of Kiel, Kiel, Germany.

Positions

1976-1977	Resident in Internal Medicine at the District Hospital Braunfels/Lahn, Braunfels, Germany.
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1979-1980	Resident at the Department of Internal Medicine of the University of Giessen, Giessen, Germany.
1981-1985	Resident at the 2nd Department of Internal Medicine of the University of Kiel, Kiel, Germany.
1982	Visiting physician at the Department of Hematology and Bone Marrow Transplantation, City of Hope National Monument, Duarte, California, USA.
1983	Head of the Bone Marrow Transplant Unit of the Departments of Paediatrics and Internal Medicine II of the University of Kiel, Kiel, Germany.
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German Society of Hematology and Oncology
German Cooperative Group for Blood and Bone Marrow Transplantation
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American Society of Hematology (ASH)
European Haematology Association (EHA)

Other Important Functions

1989 -	Regular reviewer for the Journal of Clinical Oncology, BLOOD, Lancet, Annals of Hematology, Haematologica, Annals of Oncology
1992 -	Co-ordinator of studies for patients with relapsed Hodgkin's disease in Germany and Europe.
2002 - 2004	Chairman of the German High-Grade Non-Hodgkin-Lymphoma Study Group (DSHNHL)
1992 – 1998	Secretary of the European Group for Blood and Marrow Transplantation (EBMT)
1998 - 2004	Chairman of the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT)
2005 ongoing	Chairmen of the T-cell lymphoma subcommittee of the WP Lymphoma

Scientific Publications

More than 300 articles in national and international journals, 420 abstracts, 50 book chapters

Stem Cell Transplantation for Peripheral T cell Lymphomas. How, Who and When?

Norbert Schmitz

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2012	Director, Stuttgart Cancer Center
2013	Director, Clinic of Hematology/Oncology Klinikum Stuttgart

MEMBERSHIPS

- Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)
- Berufsverband deutscher Internisten
- Deutsche Krebsgesellschaft
- Arbeitsgemeinschaft für internistische Onkologie (AIO)

Biology, Prognostic Factors and Treatment of Primary Central Nervous System Lymphoma:

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Primary CNS lymphoma (PCNSL) is a rare disorder defined by involvement of the cerebral parenchyma, leptomeninges, eyes, or spinal cord without evidence of systemic disease. In the United States, PCNSL account for 2.7-3,1% of all primary brain tumors and 2-3% of all Non-Hodgkin´s lymphomas.[1] Its incidence rose nearly three-fold between 1973 and 1984[2] with slightly stabilisation over the last years.[3] The median age at diagnosis is 61 years[4, 5] rising in patients > 60 years.[6, 7] The vast majority (95%) of PCNSL are B-cell lymphomas classified as diffuse large-cell lymphomas (DLBCL), with indolent B-cell lymphomas and T-cell lymphomas are much rarer.[8, 9] The pathogenesis of PCNSL is being debated, and some maintain that clonal proliferation might occur among normal B lymphocytes drawn to the CNS, a theory supported by the occurrence of white matter brain lesions that herald brain lymphoma.[10] Alternatively, a clone of malignant systemic lymphocytes displaying specific adhesion molecules might travel and penetrate the brain.[11-13] The International Extranodal Lymphoma Study Group (IELSG) identified the following parameters as independent factors for a poorer outcome: age over 60 years; ECOG performance status greater than 1; elevated serum LDH; high CSF protein concentration; and tumor location within the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum). Patients with 0 or 1, 2 or 3, or 4 or 5 of these adverse risk factors had 2-year overall survival (OS) rates of 80%, 48%, or 15%, respectively (Fig 1).[5] Another evaluation identified three distinct prognostic classes: class 1 (patients < 50 years), class 2 (patients ≥ 50; Karnofsky performance score [KPS] ≤ 70) and class 3 (patients ≥ 50; KPS≤ 70).[4]

For diagnostic evaluation patients should have undergone contrast enhanced brain magnetic resonance imaging (MRI, Fig. 2), and if a lumbar puncture can be performed safely, cytologic evaluation and flow cytometry of CSF. All patients should undergo a slit lamp examination as well as CT-scans of the chest, abdomen, and pelvis and a bone marrow biopsy to exclude systemic disease. For histological diagnosis of PCNSL, the procedure of choice is a stereotactic needle biopsy because patients derive no clinical benefit from surgical resection and the deep-seated nature of most lesions increases the risk of surgical complications. [14] Patients with PCNSL usually present with a brief disease history of often only a few weeks. Most patients had focal neurologic deficits and neuropsychiatric symptoms; symptoms of increased intracranial pressure and seizures are less frequently. [15] In case of leptomeningeal involvement at the time of PCNSL diagnosis, most show no clinical obvious signs. Approximately 20% of patients will have ocular involvement at the time of PCNSL diagnosis, with both eyes affected in most patients. Patients with intraocular lymphoma generally complain of floaters, blurred vision, diminished visual acuity, and painful red eyes.[16] About a third of patients present with disseminated disease that revealing itself in highly diverse deficits.

Untreated, median survival is only a few months. Historically, radiotherapy (RT) has been the standard treatment for PCNSL.[17] Despite the high complete remission rate, almost all patients relapse after a few months after RT with a median survival of 12 months.[18] High-dose MTX (MTX > 1,5 g/m²) is considered the single most effective substance for treating PCNSL. [5, 19] Several studies have demonstrated response rates between 70 and 100% and a prolongation of median survival to as many as 55 months. The addition of chemotherapy to RT has been recommended to improve survival of PCNSL patients.[5, 19] Several studies attempted to improve outcome by adding other drugs to HD-MTX.[20] However, at least partially due to their poor blood-brain barrier (BBB) penetration, the most effective drugs against NHL, doxorubicin and cyclophosphamide, are associated with unsatisfactory results.[21-23] The combination of MTX-based

chemotherapy protocols with whole brain radiotherapy has also shown very high response rates, but they are associated with a considerable risk of neurotoxicity (30% of all patients and 40-50% of those over 60 years).[24] Cognitive deficits as serious as dementia, gait disturbances and incontinence are the most common symptoms of the post therapeutic leukoencephalopathy, which as disabling as the lymphoma itself and associated with a 30% of related mortality.[25] The main risk factors for leukoencephalopathy are radiotherapy, age >60 years, intrathecal therapy, and chemotherapy after WBRT.[24, 26, 27]

There is some preliminary evidence in PCNSL literature supporting a role for rituximab, an anti-CD20 hybrid monoclonal antibody useful against different types of B cell lymphomas. In fact, the addition of rituximab to CHOP has significantly improved therapeutic results in patients with diffuse large B-cell lymphoma.[28] However, there are many doubts about the capability of this antibody to cross the BBB and the large French randomized trial comparing CHOP with R-CHOP did not show any role for this drug to prevent CNS dissemination.[29] A prospective experience suggest that rituximab is active against relapsed PCNSL, while a prospective phase II trial from the MSKCC demonstrates that the rituximab-methotrexate combination is feasible and active[30], but the precise role of rituximab in PCNSL remains to be defined, perhaps in a randomized study.

Consolidation after induction chemotherapy probably represents the best role for RT.[19, 31] Since PCNSL is often multifocal, the target for RT is the whole brain, whereas the added value of the "tumour-bed boost" is questionable.[17] The combined chemoradiation therapy is associated with relevant risk of severe neurotoxicity. With the intention to reduce the risk of severe leukoencephalopathy some investigators propose replacing WBRT with other strategies as consolidation treatment. High-dose chemotherapy supported by autologous stem cell transplantation (ASCT) is one of these strategies. In a multicenter French trial, patients with PCNSL relapsed after first-line treatment with a HD-MTX-containing regimen have been treated with intensive chemotherapy followed by ASCT. Twenty-six of 27 patients who completed the planned treatment achieved a CR. With a median follow-up of 36 months, the median overall survival was 18.3 months in the overall population, and 58.6 months among transplanted patients.[32] Similar strategies have been used as part of front-line treatment in PCNSL patients with encouraging results, mostly when thiotepa-based conditioning regimens have been used.[33] After a median follow-up of 63 months, the 5-year survival rate for all patients was 69%, and for those who completed high-dose chemotherapy, 87%. Over time, 5/30 patients developed leucoencephalopathy. In a consecutive pilot study, cytostatic therapy was intensified and consolidating radiotherapy was restricted to patients not responding completely to the previous chemotherapy, containing HD-MTX followed by cytarabine and thiotepa.[34] Seven out of 11 patients were in complete remission following ASCT, and 3 in partial remission received radiotherapy as consolidation treatment. After a median follow-up of 25 months, 3 years disease-free survival as well as overall survival was 77%. None of the patients suffered from severe neurotoxicity during the follow-up period. Both trials demonstrated a curative effect from HD chemotherapy in young patients. This new approach has being taken in a multicenter phase II trial with 79 included patients in Germany.[35] Preliminary results showed an overall remission rate (ORR) for the intend-to-treat population of 91% (77% CR and 14% PR), for patients treated with HDT and ASCT (n=73) ORR was 91%. After a median follow up of 35 months the 3 year overall survival was 77.6% for all patients and 87.1% for patients after HDT. Benefit and side effects of these consolidative strategies, that is, conventional WBRT and high-dose chemotherapy supported by ASCT, deserve to be compared in a randomized trial so as to draw definitive conclusions on the role of consolidation both on efficacy and neurotoxicity in patients with newly-diagnosed PCNSL.

MTX-based therapy should also play a role in the treatment of older patients with PCNSL. Contrary to the widely-held opinion that MTX is overly toxic in older patients, we have observed that, provided their kidney function is not impaired, MTX is not excessively toxic. Combinations with the oral alkylating agents CeCeNu and procarbazine raise response rates and survival: median survival of 15 months and 30% cures have been reported with such therapy.[36, 37] Whole-brain radiation should only be considered as a last resort in older patients with refractory disease due to its highly neurotoxic properties; however, formal studies confirming the value of this strategy have not been reported.

Conclusion

In summary, PCNSL is a rare form of extranodal non-Hodgkin's lymphoma. Initial diagnosis is supported by MRI; definitive confirmation should be based on stereotactic biopsy findings. .

Clinical presentation depends on where the tumor

is located. Methotrexate-based, multi-agent chemotherapy is currently the treatment of choice leading to high remission rates, although most patients relapse. Consolidation therapy may improve survival, the whole-brain radiotherapy commonly employed is associated with a high risk of treatment-related neurotoxicity, especially in older patients. Consolidating high-dose chemotherapy with autologous stem-cell transplantation has highly curative potential in patients under 65 years. Benefit and side effects of these consolidative strategies, that is, conventional WBRT and high-dose chemotherapy supported by ASCT, deserve to be compared in a randomized trial to draw definitive conclusions on the role of consolidation on both efficacy and neurotoxicity in patients with newly-diagnosed PCNSL.

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