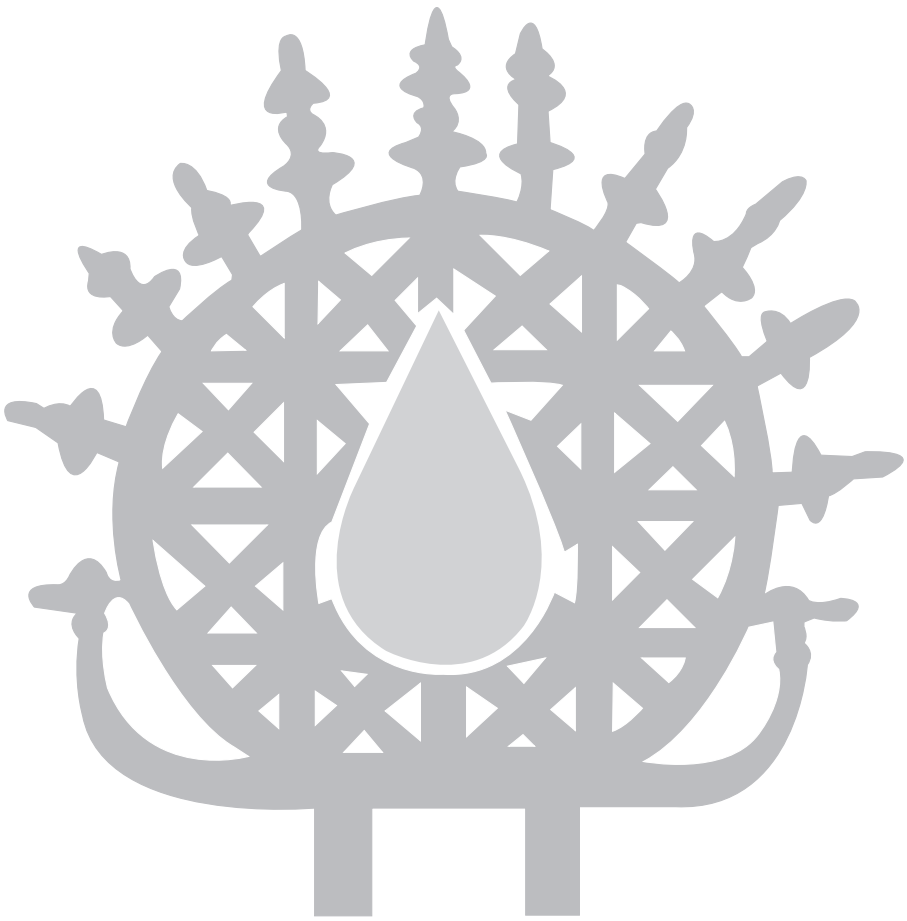
3rd International Congress on Leukemia – Lymphoma – Myeloma

May 11 – 14, 2011 • İstanbul, Turkey

Proceedings & Abstract Book



Turkish Society of Hematology

Organizing Committee

Congress President

Muhit Özcan
Ankara University, School of Medicine, Department of Hematology & BMT Unit, Ankara, Turkey

Congress Secretary

Mutlu Arat
İstanbul Bilim University, School of Medicine, Department of Hematology, İstanbul, Turkey

Scientific Chairs - Program Planners

Multipl Myeloma	Bart Barlogie *University of Arkansas, Arkansas, United States of America*
Pediatric Acute Myeloid Leukemia	Ursula Creutzig *University Children's Hospital Muenster, Muenster, Germany*
Myelodysplastic Syndromes	H. Joachim Deeg *Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America*
Chronic Lymphocytic Leukemia	Peter Dreger *University of Heidelberg, Heidelberg, Germany*
Infections	Dan Engelhard *Hadassah University Hospital, Jerusalem, Israel*
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	Craig Moskowitz *Memorial Sloan-Kettering Cancer Center, New York , United States of America*
Chronic Myeloid Leukemia	Oliver Ottman *Universitatsklinik Frankfurt, Frankfurt, Germany*
Pediatric Acute Lymphoblastic Leukemia	Ching-Hon Pui *St. Jude Children's Research Hospital, Memphis, United States of America*
Aggressive Lymphomas	Anna Sureda *Addenbrooke's Hospital, Cambridge, United Kingdom*
Acute Myeloid Leukemia	Martin Tallman *Memorial Sloan-Kettering Cancer Center, New York , United States of America*
Chronic Myeloproliferative Disorders	Ayalew Tefferi *Mayo Clinic, Minnesota, United States of America*

**Listed alphabetically by surname.*

Dear Colleagues and Friends,

It gives us great pleasure to host the 3rd International Congress on Leukemia-Myeloma- Lymphoma 2011 (ICLLM 2011) in İstanbul, Turkey. In this midst of this exciting new era, the 3rd 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 covers topics from all the different fields of clinical and laboratory hematology on Lymphoma Leukemia and Myeloma. State of the art lectures and satellite symposia covering the latest developments on hematology will be the main parts of the program. The education program is a well-balanced teaching program focusing on the needs of clinical hematologists. Again world renowned 14 hematologists (organization committee) created the scientific program with top 42 specialists in hematology research; ensure to make an unforgettable meeting. This meeting has been accredited by the European Hematology Association (EHA).

ICLLM is held biannually since 2007. Every year there has been a substantial growth in numbers. In 2009 we had over 500 attendees and about %75 were specialists and the rest were industry representatives and accompanying persons. Majority of the specialists attended are from university hospitals. This year there will be participants from 40 different countries. With each year, ICLLM becomes an increasingly more important event.

İstanbul 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 İstanbul for cultural and artistic projects will visit the city's cultural riches, mosques, churches, palaces and museums. The unique geography of İstanbul gives the opportunity to meet where the two continents meet.

On behalf of the Organizing Committee, I would like to welcome you to the 3rd International Congress on Leukemia-Myeloma- Lymphoma 2011 in İstanbul. 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 Istanbul spring.

Sincerely,
Muhit Özcan
Congress President

Contents

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3rd International Congress on Leukemia – Lymphoma – Myeloma

May 11 – 14, 2011 • İstanbul, Turkey

SCIENTIFIC PROGRAM

May 12, 2011, Thursday

TIME — MEETING HALL A

08:30-10:00 **Multipl Myeloma**
Scientific Chairs: ***Bart Barlogie*** *(University of Arkansas, Arkansas, United States of America)*
Yıldız Aydın *(İstanbul University, İstanbul, Turkey)*
Speakers: Genomics in Myeloma: ***Bart Barlogie*** *(University of Arkansas, Arkansas, United States of America)*
High Risk Myeloma–The Challenge for the Future: ***Jean-Luc Harousseau*** *(University of Nantes, Nantes, France)*
The Curability of Myeloma: ***Bart Barlogie*** *(University of Arkansas, United States of America)*

10:00 - 10:30 **COFFEE BREAK**

10:30 - 12:00 **Acute Myeloid Leukemia**
Scientific Chairs: ***Martin Tallman*** *(Memorial Sloan-Kettering Cancer Center, New York , United States of America)*
Zafer Gülbaş *(Anadolu Health Center, John Hopkins Hospital, Kocaeli, Turkey)*
Speakers: Genetic Heterogeneity of AML: Making Sense of it All: ***Ross L. Levine*** *(Memorial Sloan-Kettering Cancer Center, New York , United States of America)*
Novel Transplant Strategies in AML: ***Jacob M. Rowe*** *(RAMBAM Health Care Campus, Haifa, Israel)*
Crossing the "Great Divide" in AML in the Genomic Era: ***Martin Tallman*** *(Memorial Sloan-Kettering Cancer Center, New York , United States of America)*

12:00 - 14:00 **LUNCH**

14:00 - 15:30 **Diffuse Large B-Cell Lymphoma**
Scientific Chairs: ***Craig Moskowitz*** *(Memorial Sloan-Kettering Cancer Center, New York , United States of America)*
Muhit Özcan *(Ankara University, Ankara, Turkey)*
Speakers: An Update on Relapsed DLBCL: ***Christian Gisselbrecht*** *(Hôpital Saint Louis,Paris,France)*
An Update on Interim FDG-PET Scanning in DLBCL: ***Michel Meignan*** *(Hôpital Henri Mondor, Université Paris Est Créteil, Creteil, France)*
An Update on Untreated DLBCL: ***Craig Moskowitz*** *(Memorial Sloan-Kettering Cancer Center, New York , United States of America)*

15:30 - 16:00 **COFFEE BREAK**

16:00 - 17:30 **Chronic Myeloproliferative Disorders**
Scientific Chairs: ***Ayalew Tefferi*** *(Mayo Clinic, Minnesota, United States of America)*
Levent Ündar *(Akdeniz University, Antalya, Turkey)*
Speakers: New information on Pathogenetic Mechanisms in Myeloproliferative Neoplasms: ***Ross L. Levine*** *(Memorial Sloan-Kettering, New York , United States of America)*
Diagnosis and Management of BCR-ABL-Negative Myeloproliferative Neoplasms: ***Ayalew Tefferi*** *(Mayo Clinic, Minnesota, United States of America)*
Diagnosis and Management of Eosinophilic and Mast Cell Neoplasms: ***Ayalew Tefferi*** *(Mayo Clinic, Minnesota, United States of America)*

MEETING HALL B

12:00 - 14:00 **NOVARTIS SATELLITE SYMPOSIUM**
New Insights in CML
Scientific Chair: ***İbrahim Haznedaroğlu*** *(*Hacettepe University, Ankara, Turkey*)*
Speakers : Significance of Molecular Response in CML: ***Martin Mueller*** *(Mannheim, Germany)*
Continuing Superiority of Nilotinib in CML: ***Richard Clark*** *(Liverpool, United Kingdom)*

18:00-19:00 **OPENING CEREMONY**

May 13, 2011, Friday

TIME — MEETING HALL A

08:30-10:00 **Acute Lymphoblastic Leukemia**
Scientific Chairs: ***Nicola Gökbuget*** *(J.W. Goethe University Hospital, Frankfurt, Germany)*
Ahmet Öztürk *(Acıbadem Hospital, İstanbul, Turkey)*
Speakers: What is State-of-the-Art Diagnosis for ALL and Which Information Comes from New Molecular Markers?: ***Elizabeth McIntyre*** *(St. Louis hospital, Paris, France)*
Management of Ph+ ALL : ***Oliver Ottmann*** *(Universitatsklinik Frankfurt, Frankfurt, Germany)*
Management of Adult ALL with Risk Adapted and Individualised Approaches: ***Nicola Gökbuget*** *(J.W. Goethe University Hospital, Frankfurt, Germany)*

10:00 - 10:30 **COFFEE BREAK**

10:30 - 12:00 **Hodgkin Lymphoma**
Scientific Chairs: ***Andreas Engert*** *(University Hospital Cologne, Cologne, Germany)*
Mehmet Ali Özcan *(Dokuz Eylül University, İzmir, Turkey)*
Speakers: Early Stages: ***Andreas Engert*** *(University Hospital Cologne, Cologne, Germany)*
Advanced Stages: ***Franck Morschhauser*** *(Service des Maladies du Sang -CHRU de Lille, Lille, France)*
Relapse and New Drugs: ***Peter Borchmann*** *(Klinik I Für Innere Medizin Universitatsklinikum, Köln, Germany)*

12:00 - 14:00 **LUNCH**

14:00 - 15:30 **Myelodysplastic Syndromes**
Scientific Chairs: ***H. Joachim Deeg*** *(Fred Hutchinson Cancer Research Center, Seattle, United States of America)*
Osman İlhan *(Ankara University, Ankara, Turkey)*
Speakers: Old and New Diagnostic Approaches to MDS: ***Torsten Haferlach*** *(MLL Munich Leukemia Laboratory, Munich, Germany)*
Treatment of Low and High-Risk MDS: ***Uwe Platzbecker*** *(University Hospital Dresden, Dresden, Germany)*
Hematopoietic Cell Transplantation for Patients with MDS: ***H. Joachim Deeg*** *(Fred Hutchinson Cancer Research Center, Seattle, United States of America)*

15:30 - 16:00 **COFFEE BREAK**

16:00 - 18:00 **Infections**
Scientific Chairs: ***Dan Engelhard*** *(Hadassah University Hospital, Jerusalem, Israel)*
Ali Zahit Bolaman *(Adnan Menderes University, Aydın, Turkey)*
Speakers: Viruses - The Invisible Enemies: ***Per Ljungman*** *(Karolinska University Hospital, Stockholm, Sweden)*
Fungi – The Good, The Bad and The Ugly: ***Catherine Cordonnier*** *(Henri Mondor University Hospital, Créteil, France)*
Bacteria - The Threat of Superbugs: ***Dan Engelhard*** *(Hadassah University Hospital, Jerusalem, Israel)*

MEETING HALL B

12:00 - 14:00 **CELGENE SATELLITE SYMPOSIUM**
Optimizing Treatment Strategies with Revlimid in Multiple Myeloma
Scientific Chair: ***Meral Beksaç*** *(Ankara University, Ankara, Turkey)*
Speakers: ***Michel Attal*** *(Hospital Purpan, Toulouse, France)*
Hakan Göker *(Hacettepe University, Ankara, Turkey)*

May 14, 2011, Saturday

TIME	MEETING HALL A
08:30-10:30	**Indolent Lymphomas** Scientific Chairs: ***Robert Marcus*** *(King's College Hospital, London, United Kingdom)* ***Önder Arslan*** *(Ankara University, Ankara, Turkey)* Speakers: Molecular Pathogenesis of Follicular Lymphoma: ***Andreas Rosenwald*** *(Würzburg University, Würzburg, Germany)* Pathological Insights into Clinical Practice: ***Ronald Levy*** *(Stanford University, California, United States of America)* New Clinical Studies in Follicular NHL: ***Anas Younes*** *(MD Anderson Cancer Center, Texas, United States of America)* Introduction and Current Therapy for Follicular Lymphoma: ***Robert Marcus*** *(King's College Hospital, London, United Kingdom)*
10:30 - 11:00	**COFFEE BREAK**
11:00 - 12:30	**Chronic Myeloid Leukemia** Scientific Chairs: ***Oliver Ottmann*** *(Universitatsklinik Frankfurt, Frankfurt)* ***Teoman Soysal*** *(İstanbul University, İstanbul, Turkey)* Speakers: Current Treatment: Rise of the Second Generation TKIs: ***Oliver Ottmann*** *(Universitatsklinik Frankfurt, Frankfurt, Germany)* Novel Drug Development in Resistant CML and New Strategies Directed Towards Disease Cure: **Ali Turhan** *(University of Poitiers, Hopital Jean Bernard, France)* Stem Cell Transplant in Imatinib Era: Any Sign for Revival?: ***Ahmet Elmaağaçlı*** *(University Hospital of Essen, Essen, Germany)*
12:30 - 14:30	**LUNCH**
14:30 - 16:00	**Chronic Lymphocytic Leukemia** Scientific Chairs: ***Peter Dreger*** *(University of Heidelberg, Hamburg, Germany)* ***Osman Özcebe*** *(Hacettepe University, Ankara, Turkey)* Speakers: Tentative Topics are Standard Treatment and Indications: ***Emili Montserrat*** *(University of Barcelona, Barcelona, Spain)* Novel Perspectives for Resistant Disease: ***Eva Kimby*** *(Karolinska Institute Huddinge University, Karolinska, Sweden)* Stem Cell Transplantation: ***Peter Dreger*** *(University of Heidelberg, Hamburg, Germany)*
16:00 - 16:30	**COFFEE BREAK**
16:30 - 18:30	**Aggressive Lymphomas** Scientific Chairs: ***Anna Sureda*** *(Addenbrooke's Hospital, Cambridge, United Kingdom)* ***Burhan Ferhanoğlu*** *(İstanbul University, İstanbul, Turkey)* Speakers: Pathology and Pathophysiology of T-cell Lymphomas: ***Philippe Gaulard*** *(Henri Mondor Hospital, Créteil, France)* Conventional Therapy in T-cell Lymphomas: ***Norbert Schmitz*** *(Asklepios Klinik St.Georg, Hamburg, Germany)* New Drugs in the Treatment of T-Cell Lymphomas: ***Francesco d'Amore*** *(Aarhus University Hospital, Aarhurs, Denmark)* The Role of Stem Cell Transplantation in T cell Lymphomas: ***Anna Sureda*** *(Addenbrooke's Hospital, Cambridge, United Kingdom)*

May 14, 2011, Saturday

TIME	MEETING HALL B
10:30 - 11:00	**COFFEE BREAK**
11:00 - 12:30	**New Advances in Pediatric ALL** Scientific Chairs: ***Ching Hon- Pui*** *(St. Jude Children's Research Hospital, Memphis, United States of America)* ***Hale Ören*** *(Dokuz Eylül University, İzmir, Turkey)* Speakers: New Genetic Abnormalities in ALL and Their Clinical Implications: ***Robrecht Pieters*** *(Sophia Children's Hospital, Rotterdam, the Netherlands)* Treatment Strategies of High-Risk Childhood ALL: ***Ching-Hon Pui*** *(St. Jude Children's Research Hospital, Memphis, United States of America)* Treatment Strategies of Adolescents and Young Adults with ALL: ***James Nachman*** *(University of Chicago Children's Hospital, Chicago, United States of America)*
12:30 - 14:30	**LUNCH**
	PFIZER SATELLITE SYMPOSIUM **Early Management of Invasive Fungal Diseases: Special Focus to Latest Practice Guidelines** Scientific Chair: **Hamdi Akan** *(Ankara University, Ankara, Turkey)* Speaker: **Zekaver Odabaşı** *(Marmara University, Istanbul, Turkey)*
14:30 - 16:00	**Pediatric Acute Myeloid Leukemia** Scientific Chairs: ***Ursula Creutzig*** *(University of Münster, Münster, Germany)* ***Mehmet Ertem*** *(Ankara University, Ankara, Turkey)* Speakers: The Place of Stem Cell Transplantation in 1st Remission in Pediatric AML: ***Brenda Gibson*** *(Royal Hospital for Sick Children, Glasgow, United Kingdom)* Relapse Treatment and New Treatment Options: ***Gertjan Kaspers*** *(VU University Medical Center, Amsterdam, Netherland)* Risk Adapted Treatment in Pediatric AML: ***Ursula Creutzig*** *(University of Münster, Münster, Germany)*
16:00 - 16:30	**COFFEE BREAK**

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PROCEEDINGS

Multipl Myeloma

On behalf of the 3rd International Congress on Leukemia, Lymphoma and Myeloma, it is my distinct pleasure to welcome you to the session on Multiple Myeloma. Three timely topics will be covered during this session.

1. *Professor John Shaughnessy of the Myeloma Institute will address the enormous progress in understanding myeloma genetics and biology, defining disease, and projecting prognosis through genome-wide array analysis of plasma cells and the bone marrow micro-environment.*

2. *Professor Jean-Luc Harousseau of the University of Nantes will focus on the treatment of high-risk myeloma, now recognized as a common terminal event also in low-risk disease after multiple relapses.*

3. *Professor Bart Barlogie of the Myeloma Institute will provide evidence of myeloma curability with an emphasis on the benefits of early recognition and subsequent identification of optimal treatment strategies.*

Bart Barlogie, MD

BART BARLOGIE, M.D., Ph.D.

PRESENT TITLE AND AFFILIATION: Professor of Medicine and Pathology University of Arkansas for Medical Sciences; Director, Myeloma Institute for Research and Therapy
BIRTH DATE AND PLACE: May 10, 1944 Eitorf/Siegkreis, GERMANY
CITIZENSHIP: United States
OFFICE ADDRESS: 4301 W. Markham #816 TELEPHONE: (501) 526-2873
Little Rock, AR 72205 FAX: (501) 526-2273
MARITAL STATUS: Wife - Melisa Kathleen; Children - Britta, Eva and Bart
EDUCATION: Heidelberg University, Medical School Physikum, 1963-1965
Munchen University, Medical School, 1965-1966
Heidelberg University, Staatsexamen, (M.D.) 1966-1969
Max-Planck-Institute for Med. Research
Ph.D. Thesis, 1970 (Magna cum Laude)
POSTGRADUATE TRAINING: University of Munich Internship in Internal Medicine, May, 1970 - February, 1971 University of Muenster Medical School - Residency in Internal Medicine Rheumatology, Nephrology and Cardiology Hematology and Infectious Diseases Gastroenterology, March, 1971 -June, 1974
POSTGRADUATE TRAINING: M.D. Anderson Hospital and Tumor Institute, Department of Developmental Therapeutics Clinical Fellowship in Oncology July, 1974 - June, 1976
PROFESSIONAL APPOINTMENTS:
- Project Investigator, Department of Developmental Therapeutics, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, July, 1974. Faculty Associate, Department of Developmental Therapeutics, July 1, 1976.
- Assistant Professor of Medicine, Department of Developmental Therapeutics, M.D. Anderson Hospital and Tumor Institute, September 1, 1977 to August, 1979.
- Acting Chief of Oncology Service, Assistant Professor, Department of Internal Medicine, University of Texas Medical School at Houston, June 1, 1978 to August 31, 1982.
- Associate Professor of Medicine with Tenure, Department of Developmental Therapeutics, M.D. Anderson Hospital and Tumor Institute, September 1, 1979 to August 31, 1983.
- Associate Professor of Medicine, Department of Internal Medicine, University of Texas Medical School at Houston, September 1, 1979 to August 31, 1983.
- Professor of Medicine, Graduate School of Biomedical Sciences, University of Texas at Houston, September 1, 1978 to August 31, 1989.
- Clinical Associate Professor, Department of Natural Sciences and Mathematics, University of Houston, January 4, 1978 to June, 1980.
- Professor of Medicine, Department of Hematology, M.D. Anderson Hospital and Tumor Institute, September 1, 1983 to August 31, 1989.
- Chief, Cytometry Center, Department of Hematology, Division of Medicine, M.D. Anderson Hospital and Tumor Institute, September 1, 1984 to September, 1985.
- Professor of Pathology, Department of Pathology, M.D. Anderson Hospital and Tumor Institute, April 1, 1985 to August 31, 1989.
- Ad Interim Chairman, Department of Hematology, Division of Medicine, M.D. Anderson Hospital and Tumor Institute, September 1, 1985 to January, 1987.
- Chief, Section of Experimental Hematology, Department of Hematology, Division of Medicine, M.D. Anderson Hospital and Tumor Institute, September, 1985 to August 31, 1989.
- Professor of Medicine and Pathology, and Director, Division of Hematology/Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, September 1989 to present.
- Director of Research, Arkansas Cancer Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, September 1989-1998.
- Adjunct Professor of Medicine (Hematology), Division of Medicine, Department of Hematology, M.D. Anderson Hospital and Tumor Institute, September 1989 to present.
- Director, Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, January 1, 1997-1998.
- Director, Arkansas Cancer Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, July 15, 1998-2001.

LOCAL, STATE, NATIONAL, INTERNATIONAL COMMITTEES:
- 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:
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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

TEACHING EXPERIENCE:
- Medical Students, House Staff and Fellows in Medical Oncology during affiliation with UTMS as in-patient attending physician (generally 4-6 months per year)

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Cancer Genetics Lectures for Sophomore Medical Students
Clinical Correlates of Disease
Residents' Lecture Series UAMS

Pharmacogenomics of Bortezomib in Multiple Myeloma

Bart Barlogie

University of Arkansas, Arkansas, United States of America

Much of the recent progress in the treatment of multiple myeloma has been attributed to the introduction of several novel agents which, when combined with standard cytotoxic agents and each other, have imparted a high frequency of clinical responses. We have previously reported on the superior survival outcomes in Total Therapy 3A (TT3A), with added bortezomib (Bz), compared with Total Therapy 2 (TT2), which randomized patients to a control arm or an experimental thalidomide arm of a multi-agent chemotherapy and tandem autograft-supported high-dose melphalan program. The major advance with TT3A was observed in the 85% of patients presenting with gene expression profiling (GEP)-defined low-risk myeloma and. As part of TT3A, pharmacogenomic investigations of Bz, using GEP analysis pre- and post-48 hr test-dosing, were performed in an attempt to further delineate low- versus high-risk disease.

Pharmacogenomic investigations after test-dose applications of Bz have revealed that high expression levels of proteasome genes are linked to inferior prognosis in both of our TT3 protocols. The GEP80 model discriminated outcomes whether applied to post-Bz or baseline samples. These findings, observed in TT3A, were validated in TT3B and also applied to both arms of TT2 (control and thalidomide).

Employing post-Bz and baseline samples in TT3, the GEP80 model provided segregation of high-risk subsets of 9% and 3%, respectively, in the GEP70 low-risk group and low-risk subsets of 41% and 55%, respectively, in the GEP70 high-risk setting. In TT2, the GEP80 model failed to discern a low-risk subset among the patients with GEP70 high-risk disease, and the GEP80 model discriminated only one patient with high-risk status among those identified to have GEP70 low-risk disease.

We found a significant upregulation in the expression of proteasome genes following a 48-hour Bz test dose. *PSMD4* was only one of three genes common to both GEP70 and GEP80 models. *PSMD4* and other proteasome genes were uniquely upregulated by Bz but not by dexamethasone, immunomodulatory agents, and melphalan. Prognostically, GEP80(BL)-defined high-risk status was the sole genetic parameter that survived multivariate PFS and OS models, along with low albumin and high LDH, although all the other standard and both cytogenetic and molecular genetic variables also contributed when examined alone.

We have previously reported that both the copy number and the percentage of cells with amp1q21 invariably increase when comparing samples obtained at diagnosis and at relapse. Genes residing on chromosome 1q21 contribute critically to the high-risk designation in the GEP70 model. Consistent with this, we have noted that the GEP70 score inevitably increases at relapse and a shift from low to high risk imparts a significantly shorter post-relapse survival.

In summary, pharmacogenomic investigations of the short-term effects of Bz in TT3 have revealed insights into novel mechanisms of resistance to this agent. As we have embarked on GEP-defined risk-based assignments of therapy in TT4 and TT5, we are also performing pharmacogenomic analyses after test-dosing of melphalan toward identifying the basis for synergistic interaction of this genotoxic drug with novel agents.

Jean-Luc Harousseau
Date of birth: June 1st 1948 to Nantes
Married, 2 children
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Fax number : 33 2-40-67-97-01
E-mail : jl-harousseau@nantes.fnclcc.fr
- Graduated MD (1976)
- Assistant Professor (1976-1977)
  Hospital St Antoine - Paris (Pr J. DEBRAY)
- Assistant Professor (1977-1980)
  Hospital St Louis - Paris (Pr J. BERNARD)
- Professor of Hematology (since 1980)
  University of Nantes
- Member of the Conseil National des Universités (since 2006)
- Head of the Department of Hematology at University Hospital – Hôtel Dieu –Nantes (1984 - 2008)
- Director of the Cancer Center René Gauducheau since October 2008

Jean-Luc Harousseau is Professor of Hematology at the University of Nantes, France.

He has been Head of the Department of Clinical Haematology for 24 years and is now Director of the Cancer Center René Gauducheau and President of the Institut du Cancer Nantes Atlantique at Nantes. He is member of the Scientific Advisory Board of the French National Cancer Institute and President of the Clinical Research in Oncology National Committee He was a founder member of the Groupe Ouest-Est Leucémies Aigues et Maladies du Sang and of the Intergroupe Français du Myélome and is currently President of this internationally renowned cooperative group. Professor Harousseau is a member of the European Haematology Association, the European Group for Blood and Marrow Transplantation, the American Society of Hematology and the American Society of Clinical Oncology.
He is member of the Scientific Advisory Board of Multiple Myeloma Research Foundation and of International Myeloma Foundation. His fields of interest are Therapy of Acute Myeloid Leukemia and of Multiple Myeloma. He received the 2005 Waldenström Award and the 2009 Robert Kyle Award for his scientific contribution in the field of Multiple Myeloma. He has contributed to more than 400 peer-reviewed publications.

High Risk Myeloma–The Challenge for the Future

Jean-Luc Harousseau
University of Nantes, Nantes, France

Multiple Myeloma is a very heterogeneous disease and, in the historical period, the median overall survival (OS) was in the range of 3 years, but in some patients disease evolution was smoldering with OS of more than 10 years while in other cases the prognosis was dismal with a fulminant course leading to death in less than one year. A large number of prognostic factors have been described, in relation to patient's characteristics, tumor mass, disease progression kinetics and response to therapy. Among the different published classifications that have been published, only two have been widely used in clinical practice, the Durie-Salmon (DS) and the International Staging System (ISS)which is based on β2-microglobulin and albumin levels [1] . Currently the ISS is progressively replacing the older DS classification since it is very simple and easily reproducible.

However, it is now clear that the genetic changes that are associated with MM have a major prognostic significance. There are different ways to identify genetic changes. High-throughput molecular technologies are probably the most powerful since they analyze all abnormalities . However these technologies (gene expression profiling, comparative genome hybridization arrays, single nucleotide polymorphisms arrays) require plasma cell purification and highly dedicated platforms and therefore are available only at very specialized centers. In clinical practice, only more conventional approaches, such as conventional karyotyping and interphase in situ hybridization (FISH), are available to many physicians and may be used for MM prognostication.

Conventional karyotyping provides information not only on genetic changes but also on plasma cell proliferation. Unfortunately it is informative in one third of cases only. FISH also requires plasma cell purification and analyzes only a limited number of well defined abnormalities. This explains why genetic changes are not always analyzed and have not yet been included into a widely accepted prognostic classifications, Currently FISH is the most frequently used technique and the most common genetic features associated with a poor outcome are del (13), t(4;14) and del(17p).

Until now prognostic factors have been validated in the context of chemotherapy, either conventional chemotherapy or high-dose therapy followed by autologous stem cell transplantation (ASCT). Dramatic improvements have been achieved in the past few years with the introduction of three novel agents, thalidomide, bortezomib and lenalidomide. The key question is therefore : are novel agents changing MM prognostic factors and how can we define high-risk MM in the era of novel therapies ?

Thalidomide

There is relatively few data as regards prognostic factors in patients treated with thalidomide. Available results show that prognostic factors that are associated with a poorer outcome with chemotherapy remain unchanged with thalidomide; As an example, in the IFM study which showed the benefit of thalidomide maintenance after ASCT, patients with del(13) by FISH analysis did not benefit from thalidomide maintenance [2] . More recently, in a randomized study testing thalidomide before and after ASCT, the British MRC group showed that patients with poor risk cytogenetics had no progression-free survival (PFS) benefit and a worse OS in the thalidomide arm [3].

The Italian group recently showed that the use of thalidomide-dexamethasone (TD) in combination with double ASCT did not improve the prognosis of patients with t(4;14) and/or del (17p) (5-year PFS 28% versus 45% in patients without these abnormalities) [4].

Bortezomib

1) In the context of ASCT

Several groups have shown that the use of bortezomib in the induction treatment prior to ASCT did increase the complete remission (CR) or the CR plus very good partial remission (VGPR) rates compared to classical chemotherapy or to TD. This was mostly explained by a significanrly higher CR or CR/VGPR rate in poor prognostic subgroups. In the IFM 2005-01 trial comparing bortezomib-dexamethasone (VD) and VAD as induction treatment prior to ASCT, the CR/VGPR rate was significantly better in the VD group for patients with ISS3. [5] Interestingly, while the CR/VGPR decreased from ISS1 to ISS3 in the VAD group, it remained unchanged in the VD group (Table 1). The CR/VGPR was also significantly superior in patients with poor-risk cytogenetics by FISH: del(13), t(4;14) and /or del (17p), and in patients with both del (13) and β2-microgrnobulin >3mg/L (Table 1).

Table 1. CR/VGPR rates after induction in the IFM 2005-01 trial

	VAD	VD	p-value
With			
ISS1	21%	37%	0.32
ISS2	13%	36%	0.043
ISS3	7%	40%	<0.0001
Del (13)	15%	46.5%	<0.0001
T(4;14) and/or Del (17p)	17%	40%	0.04
β2-mic >3 plus del (13)	15%	43%	0.006

Other groups have shown that bortezomib-containing induction treatments significantly improve the CR or CR/VGPR rates in patients with poor-risk cytogenetics compared to VAD[6] or to TD [7,8]. The consequence is that the CR or CR/VGPR is the same in patients with or without poor-risk cytogenetics, mostly t(4,14) and or del (17p).

An important question is to determine whether this better initial tumor reduction with bortezomib-containing induction treatments translates into prolonged PFS as well.

In the IFM experience, patients with t(4;14) had a significantly longer PFS with a VD induction prior to ASCT (median PFS 28 months) than with a VAD induction (median 16 months p<0.001) [9] . However, the presence of t(4;14) remained associated with a poorer outcome in patients treated with VD induction, both for PFS and OS . Thus, a short induction with bortezomib did partially overcome the poor prognosis associated with t(4;14). As regards del(17p), bortezomib induction failed to improve PFS compared to VAD induction and PFS and, OS of del(17p) positive patients remained significantly worse compared to PFS and OS of del(17p) negative patients, even with VD induction.

In the Italian experience patients with t(4;14) and/or del(17p), PFS was significantly longer with bortezomib- thalidomide-dexamethasone (VTD) given both for induction and for post-ASCT consolidation than with TD [7] . Moreover, in the VTD group, patients with t(4;14) had the same 3-year PFS than patients without t(4;14).

One can conclude that bortezomib may overcome the poor prognosis associated with t(4;14); espe-

cially if given both for induction and consolidation . However, there is no convincing evidence that bortezomib is useful in patients with del(17p).

2) In the context of non-intensive therapy

In the Vista trial, borrtezomib-melphalan-prednisone (VMP) was superior to melphalan-prednisone (MP) for all efficacy parameters (CR, PFS and OS) [10,11], The outcome was not different in the VMP group between patients with or without t(4;14), del(17p) or t(14;16) but the number of patients with poor-prognostic cytogenetic abnormalities was small.

In a recent trial from the Spanish group, patients with adverse cytogenetic abnormalities had a shorter PFS than patients without these abnormalities (24 months versus 33months) despite bortezomib treatment both for induction (VMPor VTP) and for maintenance (VT or VP) [12].

In elderly patients not eligible for ASCT, based on available data, there is no convincing evidence that bortezomib (as it is used) is as useful in patients with t(4;14) as in the field of ASCT.

Lenalidomide

There are less results with lenalidomide.

In relapsed patients treated with lenalidomide-dexamethasone, results are conflicting. In the IFM study, patients with del(13) or t(4;14) had a lower response rate and a shorter PFS and OS than patients without these abnormalities[13]. In another study, patients with del(13) and t(4;14) had a median PFS and OS comparable with patients without these abnormalities. However, in this study patients with del(17p) still had a dismal outcome [14].

In newly diagnosed patients, current results are unclear. In the Mayo Clinic experience patients with high-risk disease did not benefit from initial treatment with lenalidomide-dexamethasone (median PFS 18.5 months versus 36.5 months for patients with standard-risk MM) [15].

In the IFM 2005-02 trial , low-dose lenalidomide maintenance dramatically improved PFS compared to placebo in patients with at least stable disease after ASCT. Subgroup analysis showed that the benefit of lenalidomide was observed across all prognostic subgroups defined by the stratification at time of randomization (β2-microglobulin level and presence of del(13) by FISH)[16]. Moreover, patients with either t(4;14) or del(17p) had a significantly longer PFS in the lenalidomide group compared to the placebo group (median 27 months versus 15 months and 29 months versus 14 months respectively) [17] .However, in the lenalidomide group, PFS was still significantly shorter in patients with these abnormalities.

Bortezomib and lenalidomide improve the outcome of high-risk MM simply defined by β2-microglobulin level or by ISS. As regards poor-risk cytogenetic features as defined by FISH, bortezomib appears to partly overcome the poor prognosis related to t(4,14) . Lenalidomide maintenance may also partially increase PFS in patients with t(4;14)or del (17p).

However patients with these abnormalities still have a worse outcome and better approaches are still needed for those patients.

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The Curability of Myeloma

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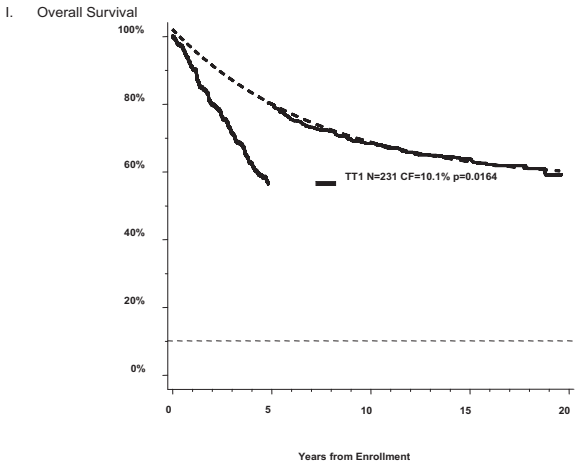
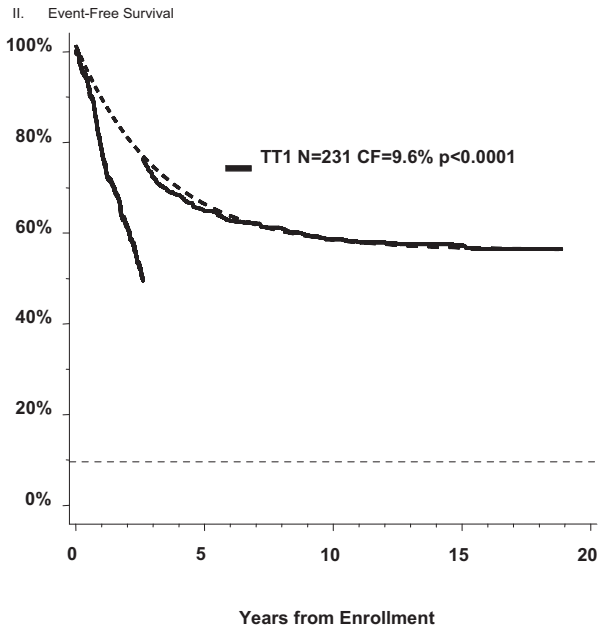
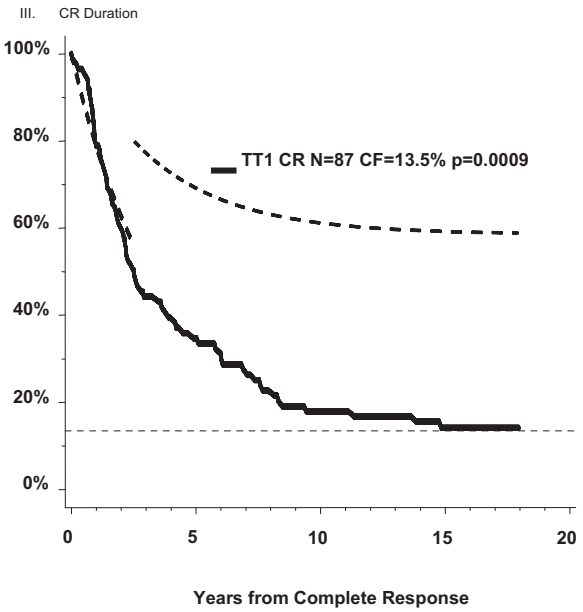
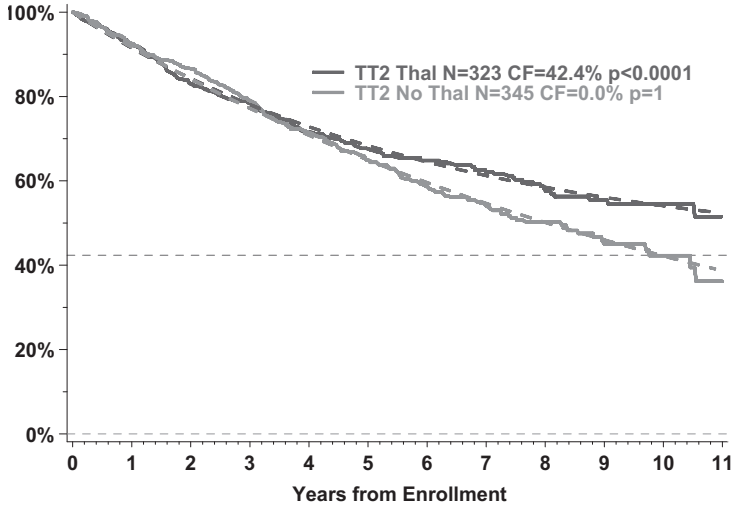
The perceived lack of curability of multiple myeloma (MM) motivated the analysis of 1202 newly diagnosed patients treated on consecutive Total Therapy (TT) protocols. Cure fractions were estimated from Kaplan–Meier plots of overall survival (OS), event-free survival (EFS) and complete response duration (CRD). Cure fractions (CF) were computed from all 3 endpoints in TT1 (n=231) (OS:10.1%, P=0.016; EFS: 9.6%, P<0.0001; CRD: 13.5%, P=0.0009), from 2 in TT2's control arm (n=345) (OS: 0.0%, P=1; EFS-CF=10.6%, P=0.05; CRD-CF=23.5%, P=0.02) and 3 in its thalidomide arm (n=323) (OS: 42.4%, P<0.0001; EFS: 24.7%, P=0.0002; CRD: 32%, P=0.002), and from all 3 endpoints in TT3 incorporating both thalidomide and bortezomib (n=303) (OS: 43.9%, P=0.056; EFS: 53.9%, P<0.0001; CRD: 65.4%, P=0.0007). In the case of Inter-Group trial S9321, EFS-based CF was 7.2% (P<0.0001); no CF was computed for OS. Multivariate analyses identified several variables in TT protocols (presence of cytogenetic abnormalities [CA], high levels of beta-2-microglobulin [B2M] and lactate dehydrogenase [LDH] and, in a subset, gene expression profiling [GEP]-defined high-risk MM) as being significantly linked to reduction in odds ratio estimates of CF. CF results were supported by estimates of relapse hazard rate approaching zero-values and relative survival ratio reaching unity-values for all TT protocols.







I. Overall Survival



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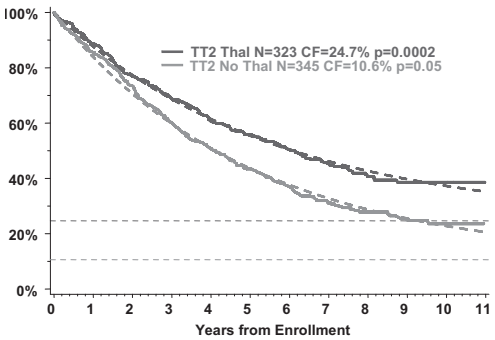

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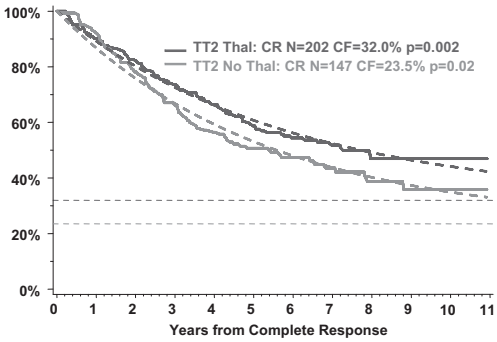
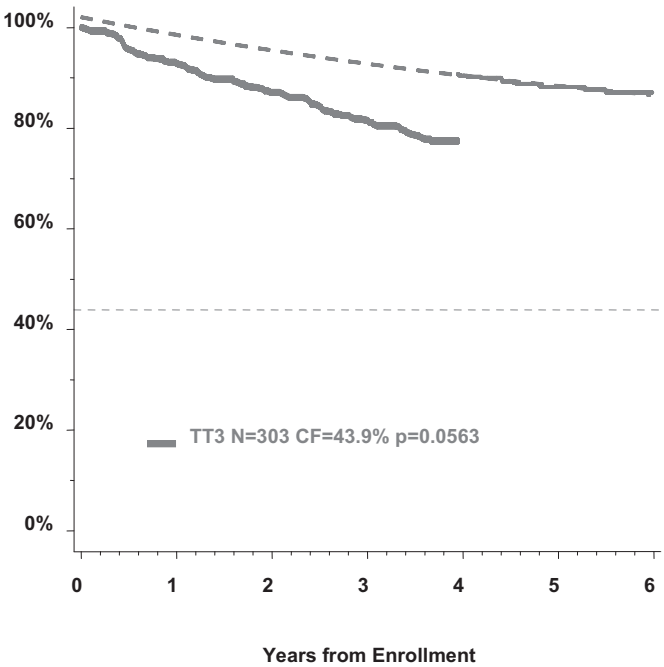


I. Overall Survival



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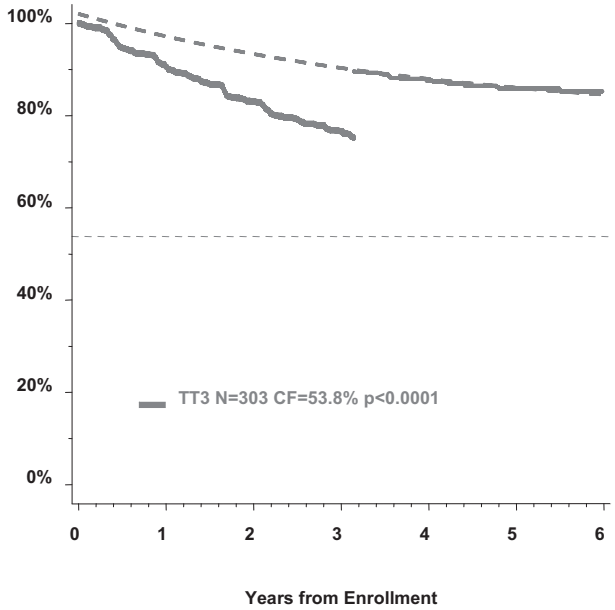

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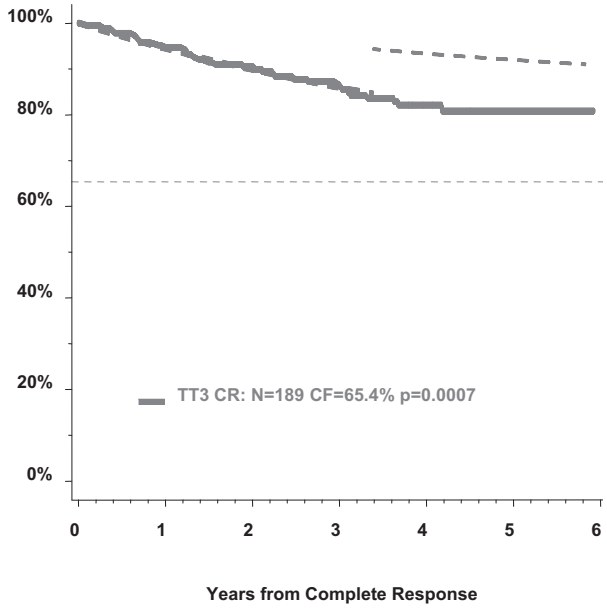

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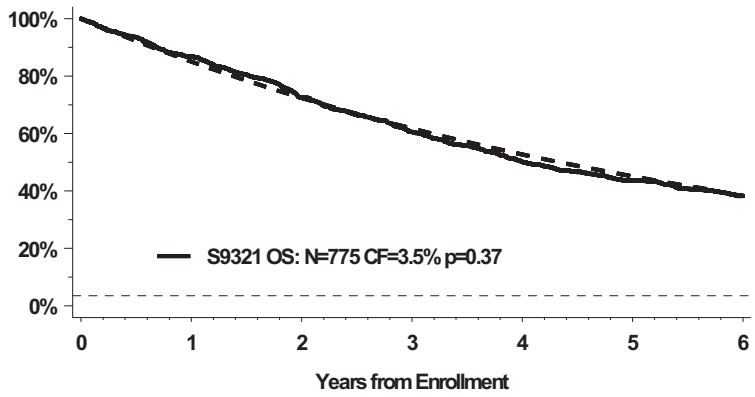

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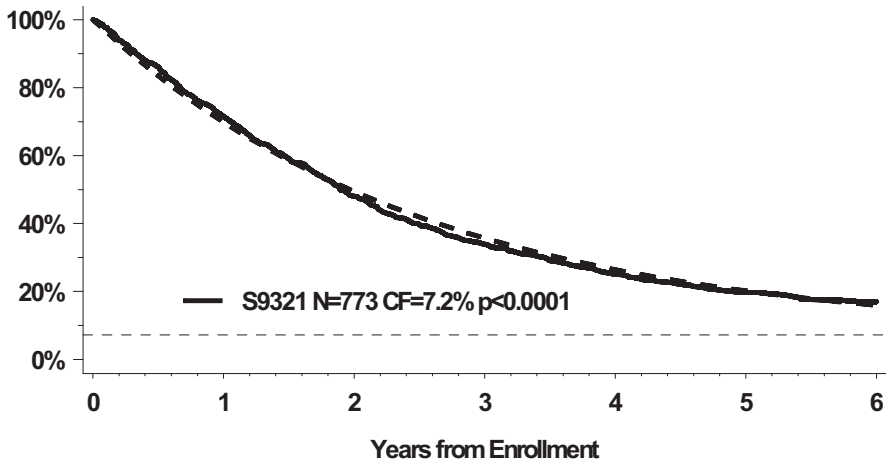

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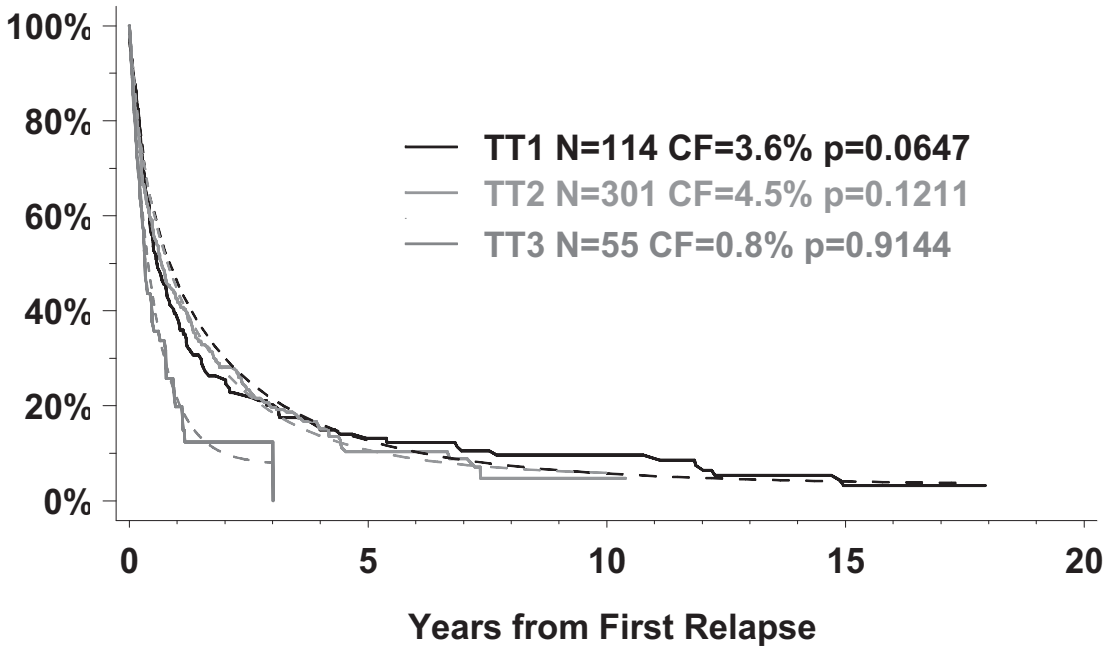

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a heterogeneous group of clonal myeloid malignancies with acquired genetic abnormalities important in the pathogenesis of the disease. There is great variability in both clinical manifestations and outcome. The outcome for most subtypes remains unsatisfactory. Only patients with acute promyelocytic leukemia have the excellent apparent cure rates desired by patients and their physicians. However, major advances have occurred in the last several decades, particularly in four areas. These include deciphering the molecular biology of the leukemia cell, identifying prognostic factors predictive of outcome with various therapies, developing drugs with novel mechanisms of action, and expanding availability of hematopoietic cell transplantation. This session with address these four areas. Dr. Ross Levine, Assistant Member, Leukemia Service and Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY, will discuss: Genetic Heterogeneity of AML: Making Sense of it ALL. Dr. Martin S. Tallman, Chief, Leukemia Service, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY, will address: Crossing the Great Divide in AML in a Genomic Era. Finally, Dr. Jacob Rowe, Director, Department of Hematology and BMT, Rambam Medical Center, Haifa, Israel, will present important new information on: Novel Transplant Strategies in AML. We hope that this session will provide the attendees with the most important and useful new information in AML and will inspire continued study of this fascinating disease.

Martin Tallman, MD.

Ross L. Levine, M.D.

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Education and Training

2002-2005 Dana Farber Cancer Institute/Partners Cancer Care, Boston, MA
Fellow, Hematology/Medical Oncology

1999-2002 Massachusetts General Hospital, Boston, MA.
Intern/Resident in Internal Medicine

1994-1999 Johns Hopkins University School of Medicine, Baltimore, MD.
Doctor of Medicine

1990-1994 Harvard College, Cambridge, MA. A.B., Biology, *magna cum laude*

Research/Fellowships

2003-2007 Postdoctoral Research Fellow
The molecular genetics of myeloproliferative disorders and acute leukemia
Brigham and Women's Hospital/Harvard Medical School
D. Gary Gilliland, Ph.D. M.D., Professor of Medicine, Investigator, Howard Hughes Medical Institute

1997-1999 Howard Hughes Medical Institute Research Training Fellowship
The molecular pathogenesis of endometrial carcinoma
Johns Hopkins University School of Medicine
Lora Hedrick Ellenson, M.D., Associate Professor of Pathology, Gynecology and Obstetrics, and Oncology

1991-1994 Undergraduate Research Assistant
Clinical research in neuroendocrinology
Brigham and Women's Hospital/Harvard Medical School
Gary S. Richardson, M.D., Instructor in Medicine

Honors and Awards

2007 Geoffrey Beene Junior Chair
2007 Howard Hughes Medical Institute Early Career Award
2006 Doris Duke Charitable Foundation Clinical Scientist Development Award
2006 American Society of Hematology Basic Research Fellow Award
2006 American Society of Clinical Oncology Young Investigator Award
1999 *Alpha Omega Alpha,* Johns Hopkins School of Medicine
1998-1999 Howard Hughes Medical Institute Award for Completion of Medical Studies
1994 Harvard University, *magna cum laude*
1991-1994 Harvard University, John Harvard Scholarship

Licensure and Board Certification

2002 Certification, Internal Medicine (American Board of Internal Medicine)
2005 Certification, Hematology (American Board of Internal Medicine)
2005 Certification, Medical Oncology (American Board of Internal Medicine)
2007 Medical License, State of New York, #245520

Professional Societies

2002- Member, American Society of Hematology
2008- Member, American Association for Cancer Research

National Committees

2007- ASH Scientific Committee on Hematopoiesis, (Vice Chair 2010, Chair 2011)
2007- International Working Group on Myelofibrosis
2010- AACR National Meeting Educational Committee

Study Sections

2008- Leukemia and Lymphoma Society Translational Research Program
2008- American Society of Hematology Scholar Award

Editorial Board

2008- *American Journal of Hematology*
2010- *Blood*

Ad Hoc Reviewer

New England Journal of Medicine, Science, Nature, Nature Genetics, Nature Medicine, Cancer Cell, Molecular Cell, Proceedings of the National Academy of Sciences, Journal of Clinical Investigation, Leukemia, Cancer Research, Clinical Cancer Research

Genetic Heterogeneity of AML: Making Sense of It All

Ross L. Levine

Memorial Sloan-Kettering Cancer Center, New York , United States of America

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adult patients and is associated with poor outcome. Despite clear evidence of clinical and biologic heterogeneity, a small number of cytogenetic and molecular lesions have sufficient relevance to influence clinical practice. The prognostic relevance of cytogenetic abnormalities has led to the widespread adoption of risk stratfication into three cytogenetically-defined risk groups which guide post-induction therapeutic decisions. More recently, mutations in FLT3, NPM1, and CEBPA were found to have clinical and therapeutic relevance in patients without karyotypic abnormalities. Although recurrent cytogenetic and molecular abnormalities are of clinical/therapeutic significance, there are significant limitations to current AML biomarkers including the absence of prognostic lesions in many AML patients and the heterogeneous clinical outcome seen in currently defined favorable, intermediate, and unfavorabel risk groups. These observations suggest there are additional molecular alterations with prognostic and therapeutic relevance in AML.

Two recent phase II trials demontrated that dose-intensified induction therapy with 90 mg/m2 daunorubicin and cytarabine improved outcomes compared to standard induction therapy with 45 mg/m2 daunorubicin and cytarabine in adults with AML. It would be beneficial, therefore to further refine the molecular biomarkers which better define AML patients who derive benefit from dose-intensified induction therapy and which are associated with adverse/favorable outcome in AML. We therefore performed mutational analysis of 18 genes in 398patients with de novo AML younger than 60 years of age randomized to receive induction therapy with high dose or standard dose daunorubicin. ASXL1 (p=0.005), and PHF6 (p=0.02) mutations were associated with impaired overall survival. Patients with the IDH2 R140Q allele or with co-occuring IDH1/2 and NPM1 mutations had favorable outcome . We were able to identify novel predictors of outcome, including TET2, PHF6, DNMT3A, and IDH2 mutations which allowed us to develop a novel AML risk stratificaiton model. In addition we found that high dose daunorubicin therapy improved survival in AML patients withDNMT3A mutations or MLL translocations(p=0.008), but not in patients without these genetic lesions(p=0.448).

We have also gone on to use this data to provide novel insights into AML pathogenesis. Specifically, we found that TET2 and IDH1/2 mutations are mutually exclusive, and that the oncometabolite produced by IDH mutant alleles inhibits TET2 function. Moreover, mutations in IDH or TET2 resulted in increased stem cell proliferation, and TET2 loss in vivo results in increased stem cell function and myeloid transformation. These data suggest mutations in epigenetic modifiers contribute to AML pathogenesis.

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Married, 4 children

Present Position

- **Chief, Department of Hematology and Bone Marrow Transplantation,** Rambam Healthcare Campus, Haifa, Israel
- **Dresner Professor of Hemato-oncology**, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
- **Adjunct Professor of Medicine,** Department of Medicine, Northwestern University, Chicago, IL

Education

1969-1971	University College London, London, UK, Pre-clinical Medicine
1971-1972	University College of London, London, UK, Pharmacology, **B.Sc. (First Class Honors)**
1972-1975	University College Hospital Medical School, London, UK, Clinical Medicine, M.B., B.S.

Postdoctoral Training

1975-1976	House Physician, University College Hospital, London, UK
1976-1977	House Surgeon, Chaim Sheba Medical Center, Tel Hashomer, Israel
1977-1978	Resident, Internal medicine, Hadassah University Hospital, Mt. Scopus, Jerusalem, Israel
1978-1981	Hematology/Oncology Fellow, University of Rochester School of Medicine & Dentistry, Rochester, NY
1980-1981	Chief Medical Resident and Oncology Fellow, St Mary's Hospital, University of Rochester, Rochester, NY

Honors

1986	**Alpha Omega Alpha**, elected by University of Rochester students, 1986
2000	**Excellency Achievement Award**, presented by Nobel Laureate Dr. E.D. Thomas at Thirteenth Symposium on Molecular Biology of Hematopoiesis and Treatment of Leukemia and Cancer, New York, July, 2000.
2003	**Kent Kiekow Memorial Award and Leukemia Lecture.** "Maintenance therapy in acute leukemia". Northwestern University, Chicago, USA, April, 2003.
2006	**Emanual G. Rosenblatt Award for Scientific Achievements (The Israel Cancer Association – USA).** Palm Beach, Florida, February 2, 2006.
2008	**Blood: Journal of the American Society of Hematology. Award for Top Reviewer in 2008**. December 2008.
2010	**The Israel Ministry for Immigrant Absorption Award for Outstanding Scientists – 1990-2010.** Tel Aviv, Israel, October 2010.
2010	**Blood: Journal of the American Society of Hematology. Award for Top Reviewer in 2010**. December 2010.
2010	**Leukemia Research Reviewer Award "Reviewer of the Year 2010"**

Faculty Appointments

1978-1981	Instructor in Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY
1981-1987	Assistant Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY
1987-1991	Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY
1991-1997	**Professor of Medicine**, University of Rochester School of Medicine and Dentistry, Rochester, NY
1997-2002	**Adjunct Professor of Medicine,** University of Rochester School of Medicine and Dentistry, Rochester, NY
1996-pres	**Professor**, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
1998-pres	**Incumbent, Dresner Chair of Hemato-oncology,** Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
2002-2003	**Visiting Professor of Medicine,** Northwestern University, Chicago, IL
2004-pres	**Adjunct Professor of Medicine,** Department of Medicine, Northwestern University, Chicago, IL
2006-2009	**Vice Dean for Clinical Appointments,** Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

TEACHING EXPERIENCE

McS and PhD students

2005-2009	PhD student, Dina Stroopinsky. Functional characteristics of activated T cells compared with naturally occurring regulatory T cells, Laboratory of Stem Cell Transplantation, Department of Hematology, Rambam Medical Center (primary supervision; secondary supervision - Dr. Tami Katz and Dr. Irit Avivi)
2010	McS student. Neta Pery. Identification and characterization of leukemic sub-population which are rarely dividing (primary supervision).

Teaching

1994 - present Hematology clerkship 4th – 6th year students, Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
1994 - present Hematology Courses (4th year students), American -Technion program.
1994 - present Course of hematology, 3rd -year students, lectures, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
1999 - present Integrative course of hemato-oncology, 4th year students, lectures, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
1994 – present Extended teaching to hematology trainees; bedside and frontal courses.

Supervision of Research by Medical Residents

2010 Ofrat Beyar. Clinical course of favorable AML. Department of Hematology, Rambam Medical Center

Licensure

New York State Permanent Medical Licensure No. 139041 Britain 1976
Israel Medical Association, No 27567

Professional Board Certification (ABIM)

1980 Internal Medicine
1982 Hematology

Professional Hospital and Administrative Appointments

1983-1983 Director of Internal Medicine Residency Program, St. Mary's Hospital, University of Rochester, Rochester, NY
1981-1996 Attending Physician/Admitting Privileges, Strong Memorial Hospital, Rochester, NY
1989-1990 Founding Medical Director, Bone Marrow Transplant Program, University of Rochester, NY
1989-1996 Director of Clinical Services, Hematology Unit, Strong Memorial Hospital, Rochester, NY
1992-1996 Director, Medicine Treatment Center, Department of Medicine Strong Memorial Hospital, Rochester, NY
1993-1996 Acting Medical Director, Bone Marrow Transplant Program, Strong Memorial Hospital, University of Rochester Medical Center
1994-pres Chief, Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, Haifa, Israel
2006-2009 Vice Dean for Clinical Appointments, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

Membership in National and International Academic Professional Organizations

1975-1985 British Medical Association
1981-1983 Association of Program Directors in Internal Medicine
1981-pres American College of Physicians (Fellow)
1981-pres American Society of Hematology
1989-1994 American Society of Hematology, Committee on Practice
1983-pres American Society of Clinical Oncology
1985-1994 American Medical Association
1986-2006 Monroe County Medical Society
1984-pres Eastern Cooperative Oncology Group, Leukemia Committee
1987-pres Eastern Cooperative Oncology Group, Leukemia Core Committee
1988-1993 Eastern Cooperative Oncology Group, Leukemia Committee, Co-Chairman
1993-1997 Eastern Cooperative Oncology Group, Leukemia Committee, Chairman
1989-pres Eastern Cooperative Oncology Group, Bone Marrow Transplant Core Committee
1990-1995 Association of Program Directors in Hematology and Oncology
1990-1993 American Medical Association, CPT Advisory Committee
1990-pres European Bone Marrow Transplant Group (EBMT)
1991-1995 Harvard Resource-Based Relative Value Scale (RBRVS)-Technical Expert Panel, American Medical Association
1992-1996 Advisory Committee, Autologous Bone Marrow Transplant Registry (ABMTR)
1992-pres International Society of Experimental Hematology
1992-1996 Eastern Cooperative Oncology Group, Chairman, Subcommittee on Recertification of Bone Marrow Transplant Centers
1994-1997 National Marrow Donor Program, Acute Leukemia Sub-Committee
1994-pres American Society for Blood and Marrow Transplantation, Member
1995-pres Israel Medical Association, Member
1994-pres National Oncology Council, Israel, Member
1995-pres National Oncology Council, Israel, Sub-Committee on Bone Marrow Transplantation, Member
1995-pres Hematology Advisory Committee, Scientific Council, Israel Medical Association, Member
1999-pres Appeals Subcommittee, Hematology, Israel Ministry of Health, Member.
2001-2003 Medical Subcommittee, Israel National Commission on Kishon River Cancer Deaths.
2001-2005 Technion Senate Evaluation and Promotion Committee
2008-pres American Society of Hematology, Educational Affairs Committee.
2009-pres Israel Ministry of Health Appeals Committee for Health Services Outside Israel.
2009-pres Chairman, Ethics Committee of Clinical Trials in Human Subjects, Technion, Israel Institute of Technology, Haifa Israel

Novel Transplant Strategies in AML

Jacob M. Rowe

RAMBAM Health Care Campus,Haifa, Israel

Table 1. Suggested indications for allo-HSCT among young adults with AML in first complete remission

Cytogenetic Risk Factors	HLA-matched sibling	MUD / haplo / cord
Favorable, all except	NO	NO
c-KIT	YES	Possible
Intermediate, all except	YES	Possible
NPM+/ FLT3-ITD-	Possible	NO
Biallelic CEBPA+/ FLT3-ITD-	Possible	NO
FLT3-ITD+	YES	YES
Unfavorable	YES	YES

Adapted from Rowe JM, Am Soc Hematol Educ Program, 2009

Fig.1

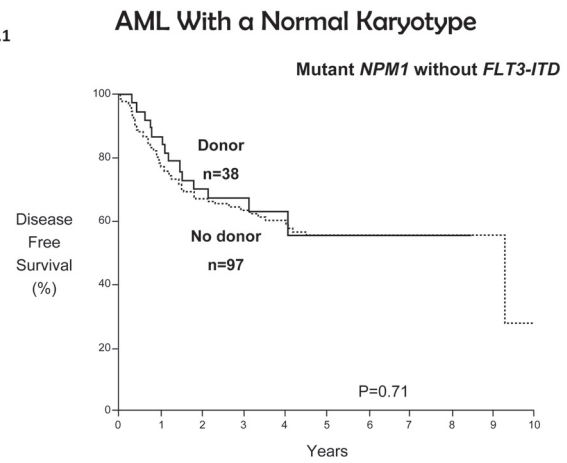
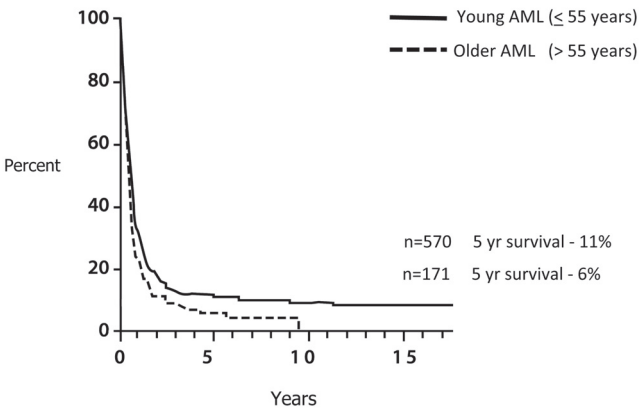


Fig 2.



Martin Tallman

Memorial Sloan-Kettering Cancer Center and Weill Medical College of Cornell University

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
Office Fax:	212-639-3841
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
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	Northwestern University	1980-1981
Internal Medicine	Evanston Hospital/McGaw Medical Center Evanston, IL	
Resident		Northwestern University
Internal Medicine	Evanston Hospital/McGaw Medical Center Evanston, IL	1981-1983
Chief Resident	Northwestern University	1983-1984
Department of Medicine	Evanston Hospital/McGaw Medical Center Evanston, IL	
Fellow	University of Washington	1984-1987
Hematology/Oncology	Fred Hutchinson Cancer Research Center Seattle, WA	

2. Academic Positions (teaching and research)

Title	Institution name and location	Dates held
Instructor	Department of Medicine	1983-1984
	Evanston Hospital, Northwestern University, Feinberg School of Medicine, Evanston, IL	
Acting Instructor	Division of Hematology University of Washington Seattle, WA	1987-1988
Assistant Professor	Division of Hematology/Oncology	1988-1996
	Northwestern University, Feinberg School of Medicine, Evanston, IL	
Member	Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Evanston, IL	1988-2010
Associate Professor	Division of Hematology/Oncology	1996-2002
(tenure)	Northwestern University, Feinberg School of Medicine, Evanston, IL	
Co-Director	Hematologic Malignancy Program	2001-2010
	Robert H. Lurie Comprehensive Cancer Center Northwestern University, Evanston, IL	
Professor	Division of Hematology/Oncology	2002-2010
(tenure)	Northwestern University, Feinberg School of Medicine, Evanston, IL	
Associate Chief	Division of Hematology/Oncology	2006-2010
	Northwestern University, Feinberg School of Medicine, Evanston, IL	

Member	Memorial Sloan-Kettering Cancer Center New York, NY	2010-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	1993-Present Pharmaceuticals Research Institute, Raritan, NJ
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	1995-Present
Department of Health and Human Services	
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)	2006-Present
Myeloid Growth Factor Panel	
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	1992
2-Chlorodeoxyadenosine (2-CdA): An Effective New Therapy for Hairy Cell Leukemia and Other Lymphoproliferative Disorders	
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

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,
May 2000, 2001, 2002

Crossing the "Great Divide" in AML in the Genomic Era

Martin Tallman

Memorial Sloan-Kettering Cancer Center, New York , United States of America

Introduction

Among younger patients (less than age 55-60 years of age) with acute myeloid leukemia (AML), conventional cytotoxic chemotherapy results in a complete remission (CR) rate of 60 to 80%[1-3]. However, only approximately 40 to 45% of such patients remain alive at 5 years. Among older patients (more than 55-60 years of age), the CR rate is approximately 40-50% and approximately 10-15% remain alive at 5 years. Consolidation chemotherapy with intensive cytotoxic chemotherapy often, but not always, confined to high-dose ara-C, is standard therapy for younger patients, but does not appear benefit those patients with high-risk cytogenetics[4]. Allogeneic hematopoietic cell transplantation (HCT) is an important and potentially curative approach for many patients in first CR. Reduced-intensity conditioning and alternative donors have expanded the population of patients who can benefit from the graft-versus-leukemia effect. New insights into the molecular biology of AML have contributed to rapid drug discovery has been rapid.

New Prognostic Factors

Correlation of a variety of recently described mutations with outcome after conventional chemotherapy among may guide therapy. Patients with normal karyotype whose cells do not express the *FLT3-ITD* mutation, but do express the *NPM1* mutation do not appear to benefit from HCT in a donor-versus-donor analysis, but such a conclusions warrants further studies[5]. Patients with core binding factor (CBF) leukemias, a group for whom allogeneic HCT has not generally been recommended, with a mutation of *c-KIT* may have a considerably less favorable outcome than those patient with CBF AML without a *c-KIT* mutation and may be considered for transplantation or other novel therapy such as a tyrosine kinase inhibitor[6, 7]. Patients with a bi-allelic *CEBPa* mutation appear to have a reasonably good outcome with conventional chemotherapy and may not benefit from allogeneic HCT. Patients with poor-risk cytogenetics and other mutations which confer a poor prognosis with conventional chemotherapy do not have a favorable outcome with chemotherapy alone and may benefit from allogeneic HCT[8]. The outcome of patients with *FLT3* mutations appears to depend on the allelic ratio. The benefit from allogeneic HCT has not been clearly established among such patients although most clinicians recommend such an approach[9].

Induction Chemotherapy

A recent large randomized cooperative group trial has addressed daunorubicin dose intensification in younger patients. Daunorubicin in a daily dose of 90 mg/m^2 for 3 was compared with 45 mg/m^2 for 3 both in combination with standard dose ara-C given for 7 days[10]. This resulted in a significantly better CR rate in the 90 mg arm (70.6% vs 57.3%: p=0.001) without any addition toxicity. Survival at a median of 24 months was also improved (23.7 vs 15.7 months: p=0.003). The benefit was not observed in those patients with poor-risk cytogenetics. Two studies have explored the addition of antibody directed chemotherapy with the immunoconjugate, gemtuzumab ozogamicin, a humanized anti-CD33 monoclonal antibody which is chemically linked to the potent toxin calicheamicin. In a large study reported by the Medical Research Council (MRC), 1,113 patients were randomized to one of three induction regimens, either Daunorubicin plus Ara-C or Daunorubicin plus Ara-C and Etoposide or FLAG-Ida, with or without GO at a dose of 3mg/m^2 [11]. There was no improvement in CR rate or OS. However, there was a significant OS benefit in patients with favorable-risk cytogenetics. Due to toxicity issues and lack of sufficient efficacy in a second trial, SWOG S0106, testing the benefits of GO in induction when combined with chemotherapy in younger patients[12], the drug was removed from the market.

Consolidation Therapy

One standard consolidation chemotherapy regimen often includes high-dose ara-C[4]. However, the optimal dose and schedule and number of cycles to administer have not been established and the addition of other agents is not clearly beneficial [13]. The MRC

Table 1. New Agents in Acute Myeloid Leukemia

Agent	Mechanism	Comments
XIAP antisense oligo[17]	Apoptosis inhib	Effective w/chemo
CPX-351	Liposomal fixed ratio of dauno/ara-C	High response rate and reduced mortality
DOT1L inhibitor[19]	Histone H3K79 methyltransferase	Preclinical data against *MLL*
Sorafenib[20]/AC220[21]	Multikinase inhib	CRs w/single agent
Clofarabine[22]	Nucleoside analog	Effective in older adults with unfav. Prog. Factors
Sapacitabine[23]	Nucleoside analog	CRs w/single agent
Elacytarabine[24]	Eliadic ester of ara-C	Modest remission in adv disease

conducted a randomized comparison of ara-C dose, 3 g/m^2 versus 1.5 g/m^2, which showed no apparent benefit for the higher dose of ara-C suggesting that a new standard may be established if additional studies confirm these results. A large randomized trial of 4 versus 5 courses of intensive consolidation showed no benefit for longer regimen[13].

Hematopoietic Cell Transplantation

In general, patients with favorable-risk cytogenetics do not benefit from HCT and patients with poor-risk cytogenetics do appear to benefit. The role of allogeneic HCT in intermediate-risk patients may depend on a specific molecular genetic genotype. Several important recent advances in allogeneic HCT have occurred. Firstly, there is evidence which suggests that the TRM has decreased during the past 30 years related to a decrease in organ damage, infections and graft-versus-host disease[14]. Secondly, the outcome for transplantation from well-matched unrelated donors appears to be associated with similar outcomes as those associated with matched related donors even among patients with high-risk disease[15, 16]. Thirdly, the introduction of reduced-intensity conditioning (RIC) allogeneic HCT, whereby the chemotherapy administered as conditioning is not intensive and myeloablative and the benefits rely more on the putative graft-versus-leukemia effect, has expanded the population of patients who may not otherwise have had the opportunity to benefit.

Novel Promising Agents

A wide variety of new agents with unique mechanisms of action have been discovered. These include antisense oligonucleotides[17], CPX-351 (a liposomal formation of a fixed molar ratio of daunorubicin and ara-C)[18], DOT1L inhibitors (histone H3K79 methyltransferase inhibitor) which appears to target *MLL*[19], *FLT3* inhibitors such as Sorafenib[20] and AC22[21], novel purine analogs such as Clofarabine[22] and Sapacitabine[23] and elacytarabine (elaidic ester of ara-C)[24]. The purine nucleoside Clofarabine induced CR in 38% of previously untreated adults aged >/= 60 years with at least 1 adverse prognostic feature (age >/=70 years, antecedent hematologic disorder, PS of at least 2, and/or intermediate or poor-risk karyotype) with a 30-day all cause mortality rate of 10%[25]. The overall response rate (ORR) was 42% among patients with poor-risk cytogenetics. CPX-351 is a liposomal formulation of a 5:1 fixed molar ratio of daunorubicin and Ara-C[29]. Among previously untreated adults aged 60-75, receiving CPX-351, the ORR was 66.7% with a CR rate of 40.5%. The 30-day and 60-day mortality rates were 3% and 4.7%, respectively, compared to 7.3% and 14.6% for patients treated with conventional cytotoxic chemotherapy in a randomized trial. Further studies of these agents alone exploring alternative doses and schedules or combined other novel agents or chemotherapy are underway. There is a Great Divide between our understanding of the molecular pathogenesis of AML and effective treatment. The advances described here will facilitate crossing that divide. The heterogeneity of AML will mandate close collaboration among both clinical investigators and laboratory-based scientists for the design of important information studies and the accrual of enough patients with a given molecular subtype of AML.

References

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Advances in Acute Myeloid Leukemia. J Clin Oncol 29 (5) : 487-494, 2011
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12. Petersdorf S, Kopechy K, Stuart R K et al. Preliminary results of Southwest Oncology Group Study S0106: An international intergroup phase 3 randomized trials comparing the addition of Gemtuzumab Ozogamicin to standard induction therapy versus post-consolidation Gemtuzumab Ozogamicin versus no additional therapy for previously untreated Acute Myeloid Leukemia. Blood.114, 326-327, 2009
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ICLLM2011

Diffuse Large B-Cell Lymphoma

Since the report by the GELA in 2001, the use of rituximab-based chemotherapy programs are standard of care in DLBCL, however; the 10 year PFS is <45%. There are 3 critical issues that will be discussed in this seminar. First, Dr. Moskowitz will discuss the results of large phase II and III risk-adapted studies evaluating new treatment strategies to improve outcome in untreated DLBCL. Dr. Gisselbrecht will update us on the management of relapsed and primary refractory DLBCL in the wake of the results of the CORAL trial and discuss novel strategies in this setting. Lastly Dr. Meignan will review the controversial area of FDG-PET imaging including it use as part of staging, interim evaluation and determination of remission status.

Craig Moskowitz, MD

Christian GISSELBRECHT

Professor of Hematology, Paris University, Hemato-Oncology-Department, Hôpital Saint Louis, Paris, France

Christian Gisselbrecht, MD is a professor of hematology at Paris University in the Hemato-Oncology Department at the Hôpital Saint Louis in Paris, France. He received his MD from Creteil University. At the University of Paris, he completed a residency in hematology and served as chief resident. Dr Gisselbrecht also earned a molecular biology certificate from the University of Sciences Paris VII and an oncology certificate from Saint-Louis-Paris VII University. He is co-founder of the Groupe d'Etude des Lymphomes de l'Adulte (GELA), a French-Belgian cooperative group which has organized numerous randomized trials in lymphoma since 1984. Dr Gisselbrecht and his research group are currently undertaking prospective trials to investigate the combination of dose-intensive chemotherapy and new monoclonal antibodies in lymphoma.

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 numerous peer-reviewed papers and several book chapters and is on the editorial board of a number of highly respected journals.

An Update on Relapsed Diffuse Large B Cell Lymphoma

Christian Gisselbrecht

Hôpital Saint Louis,Paris,France

Introduction

Aggressive lymphoma patients who relapse or fail to achieve a CR have a poor outcome with a life expectancy of 6 months. Since < 10 %t of these patients obtain long-term disease-free survival with a salvage regimen alone, it has long been established before rituximab era, that salvage chemotherapy should, whenever possible be followed in a chemosensitive patient by consolidation with HDT and then ASCT.

All patients are now treated with front line rituximab (R) and chemotherapy. The analysis of randomized studies and registry data from patients treated with R CHOP confirmed that a major improvement in the treatment of diffuse large B cell lymphoma is observed in the general population.

Fewer relapses are seen among patients with 0-2 IPI factors (10-20%) however 50% of relapses are still seen for patients with more than 2 IPI factors.

In the absence of transplantation the outcome of relapsing patients is still poor. In the long-term analysis of data from the LNH 98-5 trial, comparing CHOP and R CHOP in patients over the age of 60 years[1] survival after progression, whatever the type or progressive disease, is poor for most of the patients. Median OS after progression was 0.6 month and 0.7 month for CHOP and R-CHOP respectively. Most of late relapse received a rituximab containing regimen. However, some patients responded to salvage therapy and had a long survival after progression: 10 year survival was 10.5% and 8.6% for CHOP and R-CHOP respectively.

In younger or fit elderly patient, the initial approach to relapsed DLBCL management is to determine if the patient is a candidate for high-dose therapy (HDT) and autologous stem cell transplant (ASCT). In 1995, the PARMA trial evaluated a salvage chemotherapy with platinum and cytarabine based (DHAP) regimen alone or in combination with ASCT [2]. Both EFS and OS were significantly superior in the transplant group versus the 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. Induction therapy before HDT/ASCT consists in salvage regimens and several important issues to obtain the best CR are still in question: first the type of salvage regimen to choose; second, the efficacy of rituximab used in an era when R-CHOP is accepted as standard care in frontline therapy; third the risk factors as second line age-adjusted IPI (s-aaIPI) or relapse less than 12 months from diagnosis. When patient is not candidate to HDT/ASCT, other therapeutic options such as new biological therapies may be considered. Improvements in outcome may potentially be achieved through a greater understanding of the genetic abnormalities specifically associated with poorer-prognosis, and of factors that lead to unresponsiveness to chemotherapy.

Selecting a salvage regimen

Various old and new drugs are treatment options for DLBCL in the salvage setting. The effectiveness of these agents has been evaluated mainly in non-randomized studies and the difficulty of obtaining a cure or a prolonged disease-free period with conventional salvage chemotherapy may explain the large number of phase II studies that have been conducted in this setting. Consequently, salvage regimens outcomes are generally expressed as response rates and the possibility of collecting stem cells for ASCT. Survival data very often represent a mixture of transplanted patients and those not eligible for transplantation. No clear superiority of one regimen over the other has been demonstrated in the absence of randomized study.

Advances in salvage therapy are needed for two reasons: first, to overcome resistance to chemotherapy, enabling more patients to achieve a CR, thus allowing suitable candidates to proceed to transplantation and, second, to optimize transplantation procedures.

The addition of rituximab to CHOP chemotherapy has significantly improved the CR rate, event-free and overall survival rates compared to CHOP alone, as first-line treatment of aggressive NHL, without increasing toxicity. Thus combining rituximab with ICE (R-ICE), one of the most effective salvage regimens, has been given to patients with relapsed/refractory disease. Results from the first 36 assessable patients who had relapsed (n=23) or refractory (n=13) disease following a single standard anthracycline-based treatment for diffuse large B-cell lymphoma, have been reported [3,4].

The overall response rate was 78% and the CR rate 53%. The CR rate was significantly higher for patients receiving R-ICE than historical controls, with a similar second-line IPI given ICE (p=0.006). Patients with relapsed disease had a significantly higher overall response rate than those who had primary refractory disease (96% vs 46%, p=0.01). Multiple phase 2 studies with various regimens have been reported going in the same direction. (Table1).

The clear demonstration of the addition of rituximab to platinum-based salvage regimens was provided by a prospective randomized trial. In the 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. Analysis of 225 patients evaluable, 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 ($p \leq 0.01$). Post-transplantation PR/CR was obtained in 50% and 73% of the patients, respectively (p=0.003). A marked difference in favour of the R –DHAP arm was observed at 24 months for failure-free survival, 50%vs24% (p<.001) but not for OS 52%vs 59% (p=0.15). Cox regression analysis demonstrated a significant effect of rituximab treatment on FFS and overall survival when adjusted for time since upfront treatment, age, performance status and secondary age adjusted IPI. However, at the time of the study less than 5% of the patients have been previously exposed to Rituximab [5].

What is the optimal chemotherapy regimen to combine with rituximab as salvage therapy for DLBCL? The CORAL intergroup trial compared the association rituximab, Ifosfamide, etoposide, carboplatinum, R-ICE and rituximab dexamethasone aracytine and cisplatinum R-DHAP. DLBCL CD 20+ in first relapse or patients' refractory after first line therapy were randomized between R-DHAP and R-ICE. Responding patients received BEAM and ASCT and were randomized between observation or maintenance with rituximab for 1 year. Intent to treat analysis was made on the first 396 pts randomized in 11 countries (R ICE:202; R DHAP:194) [6].

Table I. Rituximab in combination with platinum-containing regimens

Regimen	Disease status	*n*	ORR/CR	ASCT performed	Survival in ASCT patients
R-ICE	DLBCL	36	78%/53%	70%	67% OS at 2 years
R-ICE	Aggressive B NHL	8	75%/ 50%	100%	Not given
R-various (mostly ICE)	DLBCL	59	Not given	100%	81% OS at 2 years
R-ICE	Aggressive B NHL	11	89%/67%	27%	Not given
R-DHAP	Aggressive B NHL	53	62%/32%	38%	Median 20.4 months OS
DHAP/VIM/DHAP ± R	Aggressive B NHL	225	75%/46% *versus* 54%/35% ± R, respectively	63% *versus* 46% ± R, respectively	At 2 years FFS 50%versus 24% in favour of R (p<.001)
R-ESHAP	DLBCL/MCL/HD	24 (15 = DLBCL)	Not given	79%	DFS = 53%
R-ESHAP	DLBCL/MCL	6	100%/67%	Not done	Not applicable
R-ESHAP	Aggressive B NHL	26	92 %/46%	88%	median OS and PFS not yet reached
R-ESHAP	Aggressive B NHL	18	56%/28%	38%	Not stated
R-ICE or R-DHAP	DLBCL	10	60%/10%	Not done	Not applicable
R-ASHAP	Aggressive B NHL	20	75%/45%	25%	Not stated
R-DHAOX	NHL	43	48%/10%	Not stated	Not stated
R-ICE or R-DHAP followed by HDT (BEAM) and ASCT ± R maintenance	Relapsed DLBCL	396	63%/38%	52% (*n*= 204)	49% OS at 3 years

* Planned interim analysis for the first 400 patients.
ASCT: autologous stem cell transplant; ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; CR; complete response, DFS: disease-free survival; FFS: failure –free survival; DHAOX: dexamethasone, oxaliplatin; DHAP: dexamethasone, cytarabine, cisplatin; DLBCL, diffuse large B-cell lymphoma; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; FU: follow-up; HD, Hodgkin's disease; ICE: ifosfamide, carboplatin, etoposide; HDT: high dose therapy; MCL, mantle-cell lymphoma; NHL, non-Hodgkin's lymphoma; ORR: overall response rate, OS: overall survival; PFS: progression-free survival; R: rituximab; VIM: etoposide, ifosfamide, methotrexate.

The median age was 55 years. In 225 patients a relapse >12months was observed after initial complete remission. In 166 cases patients did not achieve initial complete remission (refractory) or had an early relapses < 12 months. 244 patients were treated with combination chemotherapy with prior exposure to rituximab. At the time of inclusion in the study there were 240 patients with Stage 3-4; 198 patients with elevated LDH. At relapse 226 patients had a secondary IPI 0-1 and 149 patients sIPI 2-3. Patients with prior exposure to rituximab had more refractory disease and adverse prognostic factors. The overall response rate was 63%, with 38% complete remission. There was no difference in response rate between R-ICE 63.5% (CI: 56-70%) and R-DHAP 62.8% (CI: 55-69%), and in mobilization adjusted response rate 52% vs 54%. Factors significantly affecting response (p<0.0001) were: refractory/relapse < 12 months with a response rate of 46 % vs 88 %, secondary IPI >1: 52% vs 71% and prior exposure to rituximab: 51% vs 83%. There were fewer serious adverse events in the RICE regimen when compared to R DHAP.

From this first randomized study on relapses which was recently updated, there was obviously no difference in response rate and the ability to mobilize stem cell between the two major regimens used around the world in DLBCL.

In a retrospective study the (GEL/TAMO) [7] reported also that prior exposure to rituximab was an independent adverse prognostic factor for both PFS and OS in 163 relapsed patients with DLBCL treated with R-ESHAP (rituximab plus etoposide, cytarabine, cisplatin, and methylprednisolone); PFS rate was at 4 years 57% in rituximab-naïve patients vs. 17% in previously rituximab-exposed patients, and OS rate at 4 years 64% vs. 38%, respectively . The results of these trials indicate that patients, who do not respond to rituximab-containing regimens as first-line therapy, may be much more difficult to salvage with rituximab in the second-line treatment.

Rituximab as post-transplantation maintenance/ consolidation

Despite transplantation, the rate of progression was in the CORAL study at 3 years 39%. Progress should be made to prevent relapses. Mainte-

nance rituximab post-ASCT has been evaluated as a means to reduce minimal residual disease. Two institutions have independently reported improvements in DFS and OS rates with use of rituximab post-ASCT. In the first study [8], rituximab was introduced at the dose of 1000mg/m² before collection of peripheral blood stem cell and after transplant on day 1 and 8. The DFS rate after a median follow-up of 20 months was 67%, compared with 43% in a historical control group (p=0.004). The 2-year OS rate was 80%, compared with 53% in historical controls who underwent ASCT without rituximab (p=0.002). In the second study [9] rituximab was given once-weekly at weeks 4–8 after salvage ASCT (and repeated if needed over 4 weeks at month 6) to 21 patients with relapsed or refractory large-cell lymphoma. After a median follow-up of 30 months, the EFS rate was 81% and the OS rate was 85% [63]. It should be noted that there was an increased risk of prolonged neutropenia complicated with infection and hypogammaglobulinemia. In the CORAL study, after a second randomization post transplant with or without rituximab after HDT/ASCT, rituximab was given at the dose of 375 mg/m² every two months for one year. At the first interim analysis there was no difference between the two arms, especially in patients with prior rituximab exposure at first line treatment. These results were confirmed in the final analysis, with however a significant benefit according to women in favour of rituximab. (Personal communication)

New approaches

Is there a place for RIC allograft ?

A number of studies showed that it was only advisable to proceed to an autograft if the patient had responded to initial salvage therapy with response being defined by clinical and CT criteria .With CT/PET scanning now widely available, it appears that autografts are of major benefit only in those patients with no metabolically active disease [10], and further attempts with standard dose therapy should be made to achieve such a state before proceeding to an autograft. In the CORAL study, for the patients who had a CT/PET before transplant there was also an advantage in PFS to PET negative patients with a 3 year PFS at 62%, however not all the patients with PET positive experienced a relapse with a 3 year PFS at 35% (p<0.0001). The patients failing to achieve a metabolic CR after initial salvage therapy clearly represent a poor prognostic group, and there is enthusiasm for considering these patients for reduced intensity allografts. One study has suggested that the allograft procedure overcomes the poor prognosis associated with a persistently positive PET scan but this requires confirmation [11].

Currently the major role of reduced intensity allogeneic transplantation (RIT) is in those patients who have failed an autograft or in whom an autograft is not possible, and the results from some centres are encouraging. However, less favourable results have been reported from some other centres, and stringency of patient selection is likely to be a major reason for such discrepancies.

Unlike ASCT, allogeneic SCT (alloSCT) generates an allogeneic graft-versus-lymphoma effect that reduces the likelihood of disease relapse following transplantation. 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. Although RIC alloSCT has only been used for a few DLBCL patients, the results suggest that it may be beneficial. In previously published studies of RIC alloSCT, the rates of relapse at 2 or 3 years ranged from 33 to 79 % [12].

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 reported [13]. The overall survival at 4 years was 47%. Recently, the French Society of Marrow Transplantation and Cellular Therapy reported on 68 patients [14].

They had received a median of 2 regimens of therapy prior to RIC alloSCT, and 54 (79%) had already undergone ASCT. Prior to transplantation, 32 patients (47%) were in complete remission (CR). For all patients but one, conditioning regimens were based on Fludarabine, which was combined with other chemotherapy drugs in 50 cases (74%) and with total body irradiation in 17 (25%). For 56 patients (82%), the bone marrow donor was an HLA-matched sibling, and peripheral blood was the most widely used source of stem cells (57 patients, 84%). With a median follow-up of 49 months, estimated 2-year OS, PFS and the cumulative incidence of relapse were 49, 44, and 41% respectively. The 1-year cumulative incidence of non-relapse mortality was 23%. According to multivariate analysis, the patients in CR before transplantation had a significantly longer PFS and a lower cumulative incidence of relapse than those transplanted during partial remission or stable or progressive disease. Given the poor prognosis of this subset of patients when treated by conventional therapy,these results sug-

gest that RIC alloSCT is an attractive therapeutic option for patients with high-risk DLBCL. An exciting finding of this bone marrow transplantation study is that a history of anti-CD20 therapy prior to allogeneic transplant did not significantly affect the incidences of disease progression or relapse (2–yr PFS: 40 vs 48%, p=0.59). the results of all these studies can be considered encouraging.

How to use new agents in combination

We now better understand that the treatment of DLBCL must take into account individual factors related to biological characteristics of tumors and patients. Although DLBCL is a well-defined entity and has been characterized since the first classification of NHL, the complexity and heterogeneity of the disease has just been demonstrated over the past 10 years: according to the most recent WHO classification, it includes no less than 15 different sub entities [15].

Prognostic discrimination can also be achieved through gene expression profiling (GEP) [16], subdividing DLBCL lymphoma into the germinal center (GC) type, the activated B-cell (ABC) type and primary mediastinal B-cell lymphoma. The prognostic stratification between GC and ABC subtypes remains valid in patients receiving chemoimmunotherapy with a 3-year OS of 84 and 56%, respectively. However, GEP is technically demanding, and robust kits have not entered the routine use, either for broad-based diagnosis or for DLBCL sub categorization.

Although there are technical limitations, immunophenotyping is an essential diagnostic method that can identify DLBCL and further classify DLBCL into the GC type (CD10 + or CD10-, BCL6+ MUM1-) and the non-GC (ABC) type (CD10- BCL6- or CD10 – BCL6+ MUM1+) [17].

In the CORAL study, the analysis of a subset of 235 patients with GCB DLBCL (116) according to Hans's algorithm had a better PFS than patients with non-GCB DLBCL (119) (p=0.09). A more comprehensive and global view of molecular heterogeneity of the tumor and of the host response will help us to design more accurate and rational approaches to successfully treat these patients by targeted therapies.

It would be preferable to use one drug to treat patients with DLBCL, regardless of their subsets. However, it has not yet been clearly elucidated whether there are common factors among the subsets to target or whether we have to treat patients using different strategies. The rate of relapse and failure was dramatically reduced with the combination of rituximab and chemotherapy, mostly in the GCB group. Salvage chemotherapy is less effective in patients with previous exposure to rituximab . Therefore, new therapies should focus on patients with the high-risk IPI or the ABC subtype. There is an unmet need for this population, and new drugs could be evaluated in patient more quickly. However, despite the large amount of data collected in the last 10 years by wide-genomic analyses, only a few identified targets have progressed to phase II trials for DLBCL [18,19].

Of the many new agents developed for lymphoma, that are not monoclonal antibodies, some have been shown to be promising for future therapy of DLBCL and that are now under clinical investigations. These new drugs include immunomodulators and mTOR as well as kinase, proteasome, and histone deacetylase inhibitors, most of which have been tested in indolent lymphomas or mantle cell lymphoma, showing significant single-agent activity.

Multiple new agents targeting various pathways have shown some clinical activity in lymphoma. When the limit of standard chemoimmunotherapy treatment is reached, we need to incorporate these agents in the armamentarium, taking into account the additive toxicity. Understanding the relationship of tumor biology to outcome is important for the identification of molecular targets and for improvement of therapy. Recent advances in GEP confirmed that patients with the ABC subtype are less likely to respond well to CHOP-based regimens than those with GCB subtype. Hypothesis proposed by Wilson et al for a different result of infusional R-EPOCH with a better efficacy in GC B-cell like DLBCL than ABC like DLBCL was due to a prolonged exposure of agents. In contrast, the poor outcome of ABC like DLBCL may relate to the constitutive activation of the nuclear factor-k B pathway [20].

In the CORAL study, the subgroup of patients with GCB profile by immunohistochemistry had a better outcome under RDHAP regimen, but difference was observed for the ABC subtype. These findings underlined the need to study the effect of new drugs according to DLBCL subtypes.

However, at the present stage, most of the studies were conducted in a limited number of refractory patients. The response rate in DLBCL was in the order of 30%, with few complete remissions and a short du-

ration. Most of these agents appeared to be less toxic than chemotherapy or showed a different spectrum of toxicity. However, hematotoxicity with thrombocytopenia remained one of the most common toxicities. Many of these agents are cytostatic rather than cytotoxic. Their benefit might be only detectable when they are combined with standard regimens.

The easiest and most logical approach is to combine these agents with rituximab, given its low toxicity. The combination of lenalidomide and rituximab increased the response rate in follicular lymphoma and is worthwhile to be tested in DLBCL. Rituximab and temsirolimus also appeared to be promising in mantle cell lymphoma. However, assessing the real benefits of these combinations will be proven only in randomized studies.

The addition of new agents to well-established chemoimmunotherapy may improve the baseline results and is easier to apply to patients not heavily pre-treated. Bortezomib has been incorporated in several standard regimens: RCHOP, R CVP, R bendamustine. The rationale for treating DLCBL is that the ABC subtype is sensitized to chemotherapy under exposition to bortezomib.

Lenalidomide can also be incorporated to RCHOP or other combination chemotherapy, with the possible goal of achieving a better activity in ABC-DLBCL. The use of lenalidomide is now being tested in a large randomized study after RCHOP.

Another attractive approach is the combination of new agents. Combining agents that inhibit cell growth through different mechanisms should be developed, although this is also an enormous challenge that should be supported by reliable preclinical models *in vitro* and *in vivo*.

It must be kept in mind that the approval of two drugs in combination requires outstanding results and cost effectiveness. The number of drugs to be tested is enormous, and all too often, companies are conducting similar studies in similar patient populations, using molecules with similar targets. For diseases such as lymphoma, the incidence is too low for all of the different studies, and there is a risk of increasing the cost and significantly delaying the clinical development of new drugs[18].

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An update on Interim FDG-PET Scanning in DLBCL

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During the last ten years, ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) has proved to be a powerful tool in the management of lymphoma, both in patients with Hodgkin disease and patients with non-Hodgkin lymphomas. This is mainly due to the fact that the majority of the lymphomas subtypes are FDG avid as it has been recently confirmed by Weiler Sagie[1]. Though the level of uptake is highly variable according to the aggressive or indolent character with different degree of tumor SUV, the FDG avidity is especially high in DLBCL.

Therefore an impact of FDG-PET on staging has been expected. Indeed FDG-PET has been shown more sensitive than CT to detect lymphoma lesions particularly in DLBCL. Raanani has reported on 68 NHL patients studied retrospectively an upstaging in 31% of the cases with a resulting 25% change in treatment. For these reasons PET is currently used in pretreatment evaluation in DLBCL[2]. However it should be pointed out that there is a therapeutic impact only if a stage II CT is increased to stage III or IV by PET given that stage I and II and III and IV are taken together in the IPI which determined the risk stratification. Moreover it should also be known that even in DLBCL, bone marrow infiltration can be missed by PET in case of small cells infiltrate[3]. Nevertheless pre treatment PET is mandatory as a base line study for optimizing PET reporting at end treatment or interim evaluation and is helpful in directing the biopsy to a site missed by CT.

FDG-PET is also currently used at the two main steps of the treatment evaluation: the evaluation at the end of first line therapy and the interim evaluation during the first few cycles of chemotherapy. At the end of treatment residual masses are frequent but only a minority of patients relapses; on the other hand some patients in apparent complete remission based on CT criteria are relapsing. From morphological imaging with CT and IWC we know that the residual masses have a PPV as low as 30% as many are fibrotic and that many patients are on CR undetermined. Since early treatment of residual active disease may improve survival there is a need for an accurate and sensitive tool to detect residual disease.

Actually with PET we have moved from morphological to metabolic imaging. PET has the capability to detect the persisting viable tumour cells into the residual mass; therefore the IWC response criteria have been revised in 2007[4]. These new International Harmonization project criteria (IHP) are based on PET positivity or negativity. They use two reference backgrounds to detect true positive residual foci. Depending on residual tumor size larger or smaller than 2 cm, PET is positive if the tumor residual activity is greater than the MBP or greater than the nearby background usually much lower than MBP for taking in account the underestimation of the residual activity in a small structure. These IHP criteria were based on a study from Juweid[5].

In a small retrospective series of patients with DLBCL with a median follow up of 5 years Juweid shown in 2005 that using PET to classify the response at end treatment the Cru category disappeared and that 40% of patients in PR were classified in CR. The outcome was modified for the PR category which was split in patients with true PR and bad outcome and patients in CR. Even if one study has claimed that in the Rituximab era due to inflammatory reactions induced by Rituximab the results of end treatment PET were not predictive of the outcome with a very low PPV for relapse,[6] this has been recently challenged and FDG PET/CT is now considered the standard for the evaluation of the response at end treatment.

Interim PET is a rather different issue. In the context of new drugs, increased survival, will to decrease the drug's adverse effects, the interim PET is proposed as a tool to obtain during first line an a posteriori prognostic index and a chemosensitive indicator allowing early escalation or de –escalation. It is indeed a unique imaging method tracking the evolution of glucose metabolism of the tumor.

The first results published ten years ago were encouraging in this regards. In DLBCL Haioun showed in 2005 that early PET performed after two cycles could separate responder and non responder patients and that PET results were predictive of the outcome[7]. A difference in EFS was found both for low/low–intermediate risk patients (p=0.01) and for high/high-intermediate-risk patients (p=0.004). Since then many trials interim PET driven are ongoing but, as the time goes by, whereas a high negative predictive is still reported in NHL the positive predictive value is highly variable with a PPV as low as 26 % in a recent study leading to ask whether we should biopsy all PET+ lesions even if in the biopsy yield was 13% [8,9]. By contrast a study from Zinzani showed recently a high NPN and PPV of mid treatment PET [10].

These discrepancies are due to the lack of standardized criteria for interim PET. It must be highlighted that with interim PET we evaluate the kinetic of the FDG metabolism during the tumour destruction produced by the first few cycles of chemotherapy. The results after one, two, three, four cycles should not be mixed and a minimal residual uptake is expected. This residual uptake has several meanings. It can be due to tumour cells or to inflammatory cells of the tumour's microenvironment. The problem is obviously the threshold of minimal residual uptake that we can tolerate at interim to decide if a patient is responder or not responder. When PET is reported visually it depends on the reference background to which the residual activity is compared. We have proposed during two meetings in Deauville and Menton to report interim PET by using the 5-point scale defined by the group of the Saint Thomas hospital [11-13]. The residual activity is graded without any reference to the size of the residual lesion but with reference to the mediastinal blood pool and liver activities.

Due to difficulties in visual assessment in DLBCL and to kinetics of the tumour destruction during chemotherapy we had better to use a quantitative analysis in this type of lymphoma by computing the delta SUV between baseline and 2-4 cycles. With a delta SUV cut off of 66% after two cycles we have shown a dramatic improvement of the prognostic value of interim PET by reducing the number of false positive studies found with visual analysis [14]. This has been recently confirmed by Casanovas in a series of 220 patients with DLBCL[15]. The ratio between the residual and the liver activities could be another promising alternative[16].

It can be concluded that for end treatment evaluation of DLBCL, PET is now the standard and that there are now many reasons to think that FDG-PET will be probably extensively used in the next few years for guiding therapeutic strategy during first line treatment.

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Craig Howard Moskowitz MD

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Citizenship:	USA

EDUCATIONAL BACKGROUND

1. Degree(s)(B.A. and above), institution name and location, dates attended, and date(s) of award *(in chronological order beginning with B.A. or equivalent)*

Degree	Institution name and location	Dates attended	Year Awarded
BS (Chemistry)	Brooklyn College, Brooklyn, NY	09/76-06/80	1980
MD	Wayne State University School of Medicine Detroit, Michigan	08/84-05/88	1988

PROFESSIONAL POSITIONS AND EMPLOYMENT

1. Post-doctoral training including residency/fellowship

Title	Institution name and location	Dates
Internship & Residency Internal Medicine	Bronx Municipal Hospital/Jacobi Medical Center Albert Einstein College of Medicine, Yeshiva University, Bronx, NY	07/88-06/91
Chief Resident Internal Medicine	Bronx Municipal Hospital/Jacobi Medical Center Albert Einstein College of Medicine, Yeshiva University, Bronx, NY	06/91-07/92
Fellow Hematology/Oncology	Memorial Sloan Kettering Cancer Center, New York, NY	07/92-03/95
Fellow Clinical Hematology	Weill Medical College of Cornell University, New York, NY	07/93-09/93

2. Academic positions:

Title	Institution name and location	Dates
Instructor	Weill Medical College of Cornell University, New York, NY	03/95-05/96
Clinical Assistant	Memorial Sloan Kettering Cancer Center, New York, NY	05/96-12/99
Assistant Member	Memorial Sloan Kettering Cancer Center, New York, NY	12/99-01/05
Assistant Professor of Medicine	Weill Medical College of Cornell University, New York, NY	12/99-11/05
Associate Member	Memorial Sloan Kettering Cancer Center, New York, NY	01/05-
Associate Professor of Medicine	Weill Medical College of Cornell University, New York, NY	12/05-

3. Hospital positions:

Title	Institution name and location	Dates
Instructor	Memorial Sloan Kettering Cancer Center, New York, NY	04/95-05/96
Assistant Attending Physician	Memorial Sloan Kettering Cancer Center, New York, NY	05/96-01/05
Associate Attending Physician	Memorial Sloan Kettering Cancer Center, New York, NY	01/05-

4. Other Employment:

Title	Institution name and location	Dates
Ambulatory Care Administrative Coordinator	Brookdale University Hospital Medical Center, Brookdale, NY	1981-83

LICENSURE, BOARD CERTIFICATION, MALPRACTICE

1. Licensure

a. State	Number	Issue date	Last registration	Expiration Date
NY	179435	1989	6/30/10	6/30/12

b. DEA number: BM2176926

c. NPI number: 1053402503

2. Board Certification

Full Name of Board	Certificate #	Date
Internal Medicine	136244	1999, 2001
Medical Oncology	136244	1995, 2005
Medical Hematology	136244	2001

3. Malpractice insurance

Do you have Malpractice insurance? Yes

Name of Provider: MSK Insurance Ltd.

Premiums paid by: institution (Memorial Sloan Kettering Cancer Center)

PROFESSIONAL MEMBERSHIPS

Member/officer	Name of Organization	Dates
Member	American Medical Association	1988-
Member	American College of Physicians	1988-
Member	American Society of Hematology (ASH)	1992-
Member	American Society of Clinical Oncology (ASCO)	1992-
Member	American Society for Blood and Marrow Transplantation	1998-
Member	European Society for Medical Oncology	2002-

HONORS AND AWARDS

Name of award	*Date awarded*
Gordon B. Meyers Award in Internal Medicine	1988
The Leo Davidoff Society Award	1989
The Paul Sherlock Housestaff Teaching Award, MSKCC	1993
Chief Fellow, Hematology/Oncology, MSKCC	1993-94
New York State Society of Medical Oncologists & Hematologists Award	1994
ASCO Merit Award for Outstanding Abstract (ICEMAN trial)	1995
Hematology Attending Fellows Teaching Award, MSKCC	2003-04
Hematology Attending Fellows Teaching Award, MSKCC	2007-08

INSTITUTIONAL/HOSPITAL AFFILIATION

Primary Hospital Affiliation:	Memorial Hospital for Cancer and Allied Diseases
Other Hospital Affiliations:	None
Other Institutional Affiliations:	None

EMPLOYMENT STATUS

Name of Employer(s): Memorial Sloan Kettering Cancer Center

Employment Status: Full-time salaried

Administrative duties

Activity	Dates
Research Council Member, MSKCC	2002-
Department of Medicine Steering Committee Member, MSKCC	2007-
Investigational New Drug (IND) Committee Member, MSKCC	2007-
Clinical Director, Division of Hematologic Oncology, Dept. of Medicine, MSKCC	2008-

An Update on Untreated DLBCL

Craig Moskowitz

Memorial Sloan-Kettering Cancer Center, New York , United States of America

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma and in fact most common hematologic malignancies approximately 27,000 newly diagnosed cases each year in the United States. The median age is 64, but it may present at any age, and is slightly more common in men than in women although one of the subtypes, primary mediastinal large B cell lymphoma (PMBCL) is more common in women and the median age in that subtype mirrors Hodgkin lymphoma.

We now know that DLBCL is a heterogeneous group of lymphoid diseases clinically, histologically and molecularly. The WHO subcategorizes DLBCL into 4 categories with subgroups and these include Diffuse large B-cell lymphoma, not otherwise specified (NOS), Diffuse large B-cell lymphoma subtypes, other lymphomas of large B cells, and borderline cases. Since DLBCL is a heterogeneous group of lymphomas there is no clear histologic criteria for subdivision. Adequate tissue is needed for histochemistry, immunohistochemistry, flow cytometry, and molecular diagnosis, therefore fine needle aspiration biopsy is not acceptable and excisional biopsy is preferred; core needle biopsies are reasonable if the site of disease would require a laparotomy.

Useful Prognostic Factors

Molecular Subclassification

Molecular profiling has subdivided DLBCL into germinal center-like (GC) and activated B-cell-like (ABC) tumors, and primary PMBCL. Using this molecular classification, investigators define the cell of origin of the underling DLBCL; GC tumors and PMBCL have a better prognosis than the ABC subtype, regardless of clinical risk factors. Currently, DNA microarray technology is not practical for the analysis of routine patient samples. This fact has led investigators to try to find simpler and more universally available techniques that could mirror the information garnered from GEP. A number of immunohistochemical algorithms have been published, most of which use a combination of antibodies against GCB- and ABC-specific antigens.

There is no single antibody that can be used to subdivide DLBCL or predict prognosis. For this reason, combinations of antibodies, or algorithms, have been developed based on subdivision of DLBCL by microarray analysis. The Hans and Choi algorithms are useful to determine the cell of origin for a given DLBCL and can separate patients with DLBCL into prognostic groups, with or without the use of BCL6. A new algorithm that tallies antibody results without order precedence also has an excellent ability to predict the cell of origin and separate DLBCL patients into prognostic groups.

Double-Hit Lymphomas

Double-hit lymphomas are characterized by dual translocations of MYC and BCL2 Clinically, this type of lymphoma presents with high risk IPI (international prognostic index) score. Clinical outcome of double-hit lymphomas is extremely poor with less than 20% of patients cured, and most series report a median survival of less than one year despite aggressive therapy that may include a transplant. Recent evidence suggests that up to 10% of DLBCL may have this entity and if possible patients with high risk IPI disease with abnormalities of BCL-2 should have either cytogenetics or FISH done prior to therapy initiation; at our center these patients would receive a consolidative autotransplant (ASCT) in first remission.

International prognostic index

Clinical risk is still defined by the IPI, which identified 5 factors: age greater than 60, ECOG performance status >1, elevated LDH, stage III/IV disease, and >1 extranodal site of disease as predicting outcome. Patients are then categorized into low, low-intermediate, high intermediate and high risk disease based upon the number of risk factors. With rituximab-based chemotherapy, however, patients can probably be divided into 3 groups: 0-1 risk factor, 2 risk factors and 3-5 risk factors; interestingly OS > 50% even in the most unfavorable cohort demonstrating that immunochemotherapy has had a major impact on all risk groups.

TREATMENT

A pivotal trial conducted in 1998 by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) demonstrated that combining rituximab with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy significantly improved response, event-free survival, and overall survival compared with CHOP alone in elderly patients. These results have been confirmed by three additional randomized trials in both younger and older patients with diffuse large B-cell lymphoma.

The question in 2011 is should we still be administering R-CHOP-21. Some of the research studies include giving additional cycles of R-CHOP-21, maintenance therapy after R-CHOP-21, intensifying R-CHOP-21 by shortening the interval or adding more rituximab, adding additional agents to R-CHOP-21, targeting specific patient groups by using induction followed by consolidation treatments and evaluating autotransplant in first remission.

These options will be discussed at the symposium.

ICLLM2011

Chronic Myeloproliferative Disorders

"The myeloproliferative neoplasms session conducted by Professor Ayalew Tefferi from Mayo Clinic, Rochester, Minnesota, USA and Dr. Ross Levine from Memorial-Sloan-Ketterling Cancer Center, New York, New York USA will provide state-of-the-art review in the science and practice of essential thrombocythemia, polycythemia vera, myelofibrosis, mastocytosis and eosinophilic disorders".

Ayalew Tefferi, MD

New Information on Pathogenetic Mechanisms in Myeloproliferative Neoplasms

Ross L. Levine

Memorial Sloan-Kettering, New York , United States of America

The discovery of somatic mutations in the JAK-STAT signaling pathway in human myeloproliferative neoplasms (MPN) provided important insight into the molecular pathogenesis of polcythemiavera (PV), essential thrombocythemia, and primary myelofibrosis (PMF), and suggests that activation of JAK2 signaling is an important pathogenetic event in PV, ET, and PMF. Although these discoveries have provided important insight into the pathogenesis of these disorders, important questions remain regarding these MPN including the role of additional inherited and acquired alleles in MPN pathogenesis. We will present recent data demonstrating that novel inherited disease alleles, including a MPN predisposition haplotype within the JAK2 locus, contribute to MPN predisposition and phenotypic pleiotropy. In addition, we will review recent data demonstrating that acquired somatic mutations in recently discovered oncogenes and tumor suppressors, including TET2, ASXL1, IDH1, and ISH2, contribute to MPN pathogenesis and to progression from MPN to AML. We will also review the current status of the development of JAK2-targeted kinase inhibitors for the treatment of MPN. We will also present new data suggesting that alternate therapeutic approaches which target the JAK-STAT signaling pathway and other pathways involved in MPN pathogenesis may offer benefit for the treatment of patients with PV, ET, and PMF.

Dr. Ayalew Tefferi

Dr. Ayalew Tefferi was born in Addis Ababa, Ethiopia and migrated to the United States in 1982 after completing his medical school education at the University of Athens in Athens, Greece. Dr. Tefferi received his Hematology training at the Mayo Clinic in Rochester, MN before joining the staff at the Mayo Clinic College of Medicine, Division of Hematology in the Department of Medicine. He has been a full professor in Hematology and Internal Medicine since 2001.

Dr. Tefferi is primarily engaged in direct patient care and sees patients every afternoon. His clinical and laboratory interests focus on myeloid disorders including polycythemia vera, essential thrombocythemia, myelofibrosis, chronic myeloid leukemia, myelodysplastic syndromes, acute leukemia, eosinophilic disorders and systemic mastocytosis. He also serves as division resource for anemia, porphyria, hemochromatosis and hemoglobinopathies.

Dr. Tefferi's academic and research achievements include over 1000 publications including books, book chapters, original articles, reviews, editorials, letters, and abstracts. Dr. Tefferi serves as associate or section editor for the *Mayo Clinic Proceedings*, *Leukemia*, *American Journal of Hematology*, *European Journal of Hematology, and Hematological Oncology*. He is also in the editorial board of several other journals including *Journal of Clinical Oncology*, *Blood, Cancer, Leukemia Research, Acta Haematologica, and Leukemia and Lymphoma* . Dr. Tefferi has given more than 700 national and international invited lectureships and serves as faculty for the annual Hematology and Oncology Board review courses at George Washington University in Washington DC, Cancer medicine and Hematology offered by Harvard institutes in Boston MA, and MD Anderson Cancer Center in Houston TX.

Ayalew Tefferi, M.D., Staff physician in Hematology and Internal Medicine, Mayo Clinic and Mayo School of Medicine (1989-present)
TITLE: Professor of Medicine and Hematology (2001-present)
WORK ADDRESS: Mayo Clinic, 200 First Street, SW, Rochester, MN 55905
VISA STATUS: United States Citizen

MEDICAL TRAINING:
1975 - 1982, University of Athens Medical School, Athens, Greece
1983 - 1986, Internal Medicine residency, St. Joseph Hospital, Chicago, IL.
1986 - 1989, Hematology fellowship, Mayo Graduate School, Rochester, MN.

PECIALTY CERTIFICATION:
American Board of Internal Medicine, 1987
American Board of Hematology, 1988

AWARDS AND HONORS:
The William Summerskill Award, 1989, Mayo Medical Center
Teacher of the Year 1992, Mayo Medical School
Teacher of the Year 1992, Internal Medicine, Mayo Medical Center
Teacher of the year 1994, Internal Medicine, Mayo Medical Center
Teacher of the year 1995, Internal Medicine, Mayo Medical Center
Teacher of the year, Hall of fame, Internal Medicine, Mayo Medical Center 1995
Teacher of the year 1996, Mayo Medical School
Distinguished Mayo Medical School Service Award, 1996
Dean's Recognition Award, Mayo Medical School, 1999
Department of Medicine Medical School Education Award, 2000, Mayo Medical Center
Teacher of the year 2001, Mayo Medical School
Teacher of the year, 2004 Mayo Medical School
Department of Medicine Outstanding Mentorship award, 2004
elected Speaker, Masters in Medicine, Department of Medicine, 2007

Institutional positions:
Professor of Medicine and Hematology, Mayo Medical School and Medial Center [2001-]
Chairman, 1st year Hematopoietic Course, Mayo Medical School (1991-2005)
Associate Editor, Mayo Clinic Proceedings (2002-)
Director, Department of Medicine Medical grand Rounds (2003-)
Director, Medical Genomics Education Journal Publications and Grand Rounds (2003-)

Chair, Myeloproliferative Disorders Disease Group (2000-)

Institutional memberships:
Education committee of the Division of Hematology, 1989-2005.
Chronic lymphocytic leukemia study group, 1989-2005.
Acute leukemia study group, 1989-.
Myeloproliferative study group, 1989-.
Bone marrow transplant committee, 1990-2004.
Mayo Clinic Transplant Research Committee, 1999-2005.
The Mayo Medical School organ unit curriculum committee, 1992-2005.
Internal medicine resident evaluation committee, 1994-2005.
The Mayo Clinic Human Genomics Education Committee, 2000-.
Medical School Education Committee, 2002-2004.
Academic Appointments and Promotions Committee, 2002-2006.

Extramural memberships and positions
American Society of Hematology.
American Federation for Clinical Research
American Medical Association
Minnesota Medical Association
Zumbro Valley Medical Society
North Central Cancer Treatment Group (NCCTG)
Eastern Cooperative Oncology Group (ECOG)
cientific Advisory Board Member for Bio-reference Laboratories, New Jersey (2003-)
cientific Advisory Board Member for Apotex Inc. Toronto, Canada (2003-2005)
ASH Publications Committee Member (2003-2006)
Faculty-Annual Board Review at Harvard (2001-)
Faculty-Annual Board Review at George Washington University (1998-)
Faculty-Annual Board Review at MD Anderson Cancer Center (2003-)

PUBLICATIONS (published or in press)

Total (including abstracts)	702
Peer reviewed, pub-med accessible publications other than abstracts	435
Books, Book chapters, CD-ROM publications	46
Abstracts, Web of Science accessible	223
INTERNATIONAL INVITED LECTURES	**65**
NATIONAL INVITED LECTURES	**157**
TOTAL NATIONAL AND INTERNATIONAL INVITED LECTURES	**223**

Associate Editor:

1. Mayo Clinic Proceedings
2. European Journal of Hematology

ection Editor:
1. Current Hematology Reports

Editorial Board Member:
1. Mayo Clinic Proceedings
2. Blood
3. European Journal of Medicine
4. Leukemia and Lymphoma
5. Acta Haematologica
6. Current Hematology Reports
7. Journal of the Chinese Medical Association

Reviewer for the following journals

1. Mayo Clinic Proceedings
2. Nature Medicine
3. Proceedings of the Library of Science (PLOS)
4. New England Journal of Medicine
5. Lancet
6. Annals of Internal Medicine
7. Blood
8. Journal of Clinical Oncology
9. Experimental Hematology
10. Leukemia
11. British Journal of Haematology
12. Leukemia Research
13. American Journal of Hematology
14. European Journal of Haematology
15. Leukemia and Lymphoma
16. Haematologica
17. Seminars in Thrombosis and Haemostasis
18. Blood Coagulation and Fibrinolysis
19. Journal of Translational Medicine
20. Clinical Gastroenterology and Hepatology
21. International Journal of Dermatology
22. Acta Haematologica
23. Annals of Hematology

Diagnosis and Management of BCR-ABL-Negative Myeloproliferative Neoplasms

Ayalew Tefferi

Mayo Clinic, Minnesota, United States of America

Polycythemia Vera and Essential Thrombocythemia

Disease overview: Polycythemia Vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms primarily characterized by erythrocytosis and thrombocytosis, respectively. Other disease features include leukocytosis, splenomegaly, thrombohemorrhagic complications, vasomotor disturbances, pruritus and a small risk of disease progression into acute leukemia or myelofibrosis.

Diagnosis: Diagnosis is based on *JAK2* mutation status (PV and ET), serum erythropoietin (Epo) level (PV) and bone marrow histopathology (ET). The presence of a *JAK2* mutation and subnormal serum Epo level confirm a diagnosis of PV (Table 1). Differential diagnosis in ET should include chronic myelogenous leukemia and prefibrotic myelofibrosis (Table 1). Diagnosis of post-PV or post-ET MF is according to the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria (Table 2).

Table 1. World Health Organization (WHO) diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis[2]

2008 WHO Diagnostic Criteria						
		Polycythemia Vera*		Essential Thrombocythemia*		Primary Myelofibrosis*
Major criteria	1	Hgb > 18.5 g/dL (men) > 16.5 g/dL (women) or**	1	Platelet count ≥ 450 x 109/L	1	Megakaryocyte proliferation and atypia*** accompanied by either reticulin and/or collagen fibrosis, or†
	2	Presence of JAK2V617F or JAK2 exon 12 mutation	2	Megakaryocyte proliferation with large and mature morphology.	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
			3	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
			4	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	ubnormal serum Epo level			2	Increased serum LDH level
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

*PV diagnosis requires meeting either both major criteria and one minor criterion or the first major criterion and 2 minor criteria. ET diagnosis requires meeting all 4 major criteria. PMF diagnosis requires meeting all 3 major criteria and two minor criteria.
**or Hgb or Hct > 99th percentile of reference range for age, sex, or altitude of residence or red cell mass > 25% above mean normal predicted or Hgb > 17 g/dL (men)/ > 15 g/dL (women) if associated with a sustained increase of ³ 2 g/dL from baseline that can not be attributed to correction of iron deficiency
***Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.
†or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).
Key: BM, bone marrow; Hgb, hemoglobin; Hct, hematocrit; Epo, erythropoietin; EEC, endogenous erythroid colony; WHO, World Health Organization; CML, chronic myelogenous leukemia; PV, polycythemia vera; PMF, primary myelofibrosis; MDS, myelodysplastic syndromes; LDH, lactate dehydrogenase

Table 2. International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) recommended criteria for post-polycythemia vera and post-essential thrombocythemia myelofibrosis.[3]

Criteria for post-polycythemia vera myelofibrosis

Required criteria:

1 Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria (see table 2)

2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale) (see footnote for details)

Additional criteria (two are required):

1 Anemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy

2 A leukoerythroblastic peripheral blood picture

3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly

4 Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Criteria for post-essential thrombocythemia myelofibrosis

Required criteria:

1 Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria (see table 2)

2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale) (see footnote for details)

Additional criteria (two are required):

1 Anemia and a ≥ 2 g/dL decrease from baseline hemoglobin level

2 A leukoerythroblastic peripheral blood picture

3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly

4 Increased lactate dehydrogenase

5 Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Grade 2–3 according to the European classification:4 diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification:5 diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Table 3. Risk stratification in polycythemia vera and essential thrombocythemia and risk-adopted therapy

Risk categories	**Essential thrombocythemia**	**Polycythemia vera**	**Management during pregnancy**
Low-risk (age <60 years and no thrombosis history)	Low-dose aspirin	Low-dose aspirin + Phlebotomy	Low-dose aspirin + Phlebotomy if PV
Low-risk with extreme thrombocytosis (platelets >1000 x 10^9/L)	Low-dose aspirin provided ristocetin cofactor activity >30%	Low-dose aspirin provided ristocetin cofactor activity >30% + Phlebotomy	Low-dose aspirin provided ristocetin cofactor activity >30% + Phlebotomy if PV
High-risk (age ≥60 years and/or presence of thrombosis history)	Low-dose aspirin + Hydroxyurea	Low-dose aspirin + Phlebotomy + Hydroxyurea	Low-dose aspirin + Phlebotomy if PV + Interferon-α

Table 1. Somatic mutations in primary myelofibrosis (PMF) and the closely related BCR-ABL1-negative myeloproliferative neoplasms (MPN) including polycythemia vera (PV) and essential thrombocythemia (ET).[6-16]

Mutations	Chromosome location	Mutational frequency	Pathogenetic relevance
*JAK2*V617F exon 14 (Janus kinase 2)	9p24	PV ~ 96% ET~ 55% PMF ~ 65% Blast phase MPN ~ 50%	Believed to contribute to abnormal myeloproliferation and progenitor cell growth factor hypersensitivity
JAK2 exon 12	9p24	PV ~ 3% ET~ rare PMF ~ rare Blast phase MPN ~ rare	Believed to contribute to primarily erythroid myeloproliferation
MPL exon 10 (MyeloProliferative Leukemia virus oncogene) (encodes for thrombopoietin receptor)	1p34	PV ~ rare ET~ 3% PMF ~ 10% Blast phase MPN ~5%	Believed to contribute to primarily megakaryocytic myeloproliferation
TET2 mutations occur across several of the gene's 12 exons (TET oncogene family member 2)	4q24	PV ~ 16% ET~ 5% PMF ~ 17% Blast phase MPN ~ 17%	Might contribute to epigenetic modulation of transcription (TET1 catalyzes conversion of 5-methylcytosine to 5-hydroxymethylcytosine)
ASXL1 exon 12 (Additional Sex Combs-Like 1)	20q11.1	PV ~? ET~? PMF ~? Blast phase MPN ~ 19%	Believed to affect regulation of transcription and RAR-mediated signaling
CBL exons 8 and 9 (Casitas B-lineage lymphoma proto-oncogene)	11q23.3	PV ~ rare ET~ rare PMF ~ 6% Blast phase MPN ~?	Believed to alter the regulatory function of wild-type CBL against kinase signaling because of defective ubiquitylation of oncoproteins
IDH1/*IDH2* exon 4/exon 4 (Isocitrate dehydrogenase)	2q33.3/15q26.1	PV ~ 2% ET~ 1% PMF ~ 4% Blast phase MPN ~ 20%	Induces accumulation of 2-hydroxyglutarate, a possible oncoprotein
IKZF1 *(mostly deletions including intragenic)* (IKAROS family zinc finger 1)	7p12	PV ~ rare ET~ rare PMF ~ rare Blast phase MPN ~ 19%	Not clear
LNK exon 2 (encodes a membrane-bound adaptor protein)	12q24.12	PV ~ rare ET~ rare PMF ~ rare Blast phase MPN ~ 10%	Wild-type is a negative regulator of JAK2 signaling
EZH2 mutations occur across several exons (enhancer of zeste homolog 2)	7q36.1	PV ~ 3% ET~ ? PMF ~ 13% Blast phase MPN ~ ?	Wild-type encodes for a Polycomb-group protein, a histone-lysine N-methyltransferase

Risk stratification: Current risk stratification in PV and ET is designed to estimate the likelihood of thrombotic complications (Table 3): high-risk–age >60 years or presence of thrombosis history; low-risk–absence of both of these two risk factors. Presence of extreme thrombocytosis (platelet count >1000 x 10^9/L) might be associated with acquired von Willebrand syndrome (AvWS) and, therefore, risk of bleeding. Risk factors for shortened survival in both PV and ET include age >60 years, leukocytosis, history of thrombosis and anemia.

Risk-adapted therapy: Survival is near-normal in ET and reasonably long in PV. The 10-year risk of leukemic/fibrotic transformation is <1%/1% in ET and <5%/10% in PV. In contrast, the risk of thrombosis exceeds 20%. The main goal of therapy is therefore to prevent thrombohemorrhagic complications and this is effectively and safely accomplished by the use of low-dose aspirin (PV and ET), phlebotomy (PV) and hydroxyurea (high risk PV and ET). Treatment with busulfan or interferon-α is usually effective in hydroxyurea failures (Table 3).[1]

Table 2. World Health Organization (WHO) diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis

2008 WHO Diagnostic Criteria						
		Polycythemia Vera*		Essential Thrombocythemia*		Primary Myelofibrosis*
Major criteria	1	Hgb > 18.5 g/dL (men) > 16.5 g/dL (women) or**	1	Platelet count ≥ 450 x 10^9/L	1	Megakaryocyte proliferation and atypia*** accompanied by either reticulin and/or collagen fibrosis, or†
	2	Presence of JAK2V617F or JAK2 exon 12 mutation	2	Megakaryocyte proliferation with large and mature morphology.	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
			3	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
			4	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	ubnormal serum Epo level			2	Increased serum LDH level
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

*PV diagnosis requires meeting either both major criteria and one minor criterion or the first major criterion and 2 minor criteria. ET diagnosis requires meeting all 4 major criteria. PMF diagnosis requires meeting all 3 major criteria and two minor criteria.
**or Hgb or Hct > 99th percentile of reference range for age, sex, or altitude of residence or red cell mass > 25% above mean normal predicted or Hgb > 17 g/dL (men)/ > 15 g/dL (women) if associated with a sustained increase of ³ 2 g/dL from baseline that can not be attributed to correction of iron deficiency
***Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.
†or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).
Key: BM, bone marrow; Hgb, hemoglobin; Hct, hematocrit; Epo, erythropoietin; EEC, endogenous erythroid colony; WHO, World Health Organization; CML, chronic myelogenous leukemia; PV, polycythemia vera; PMF, primary myelofibrosis; MDS, myelodysplastic syndromes; LDH, lactate dehydrogenase

Myelofibrosis

Disease overview: Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by stem cell-derived clonal myeloproliferation, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis (EMH), constitutional symptoms, cachexia and leukemic progression. Since 2005, a number of mutations (Table 1) have been described in PMF but none of them have garnered either the pathogenetic or therapeutic relevance assigned to *BCR-ABL1* in chronic myelogenous leukemia.

Diagnosis: Diagnosis is based on bone marrow morphology (Table 2). The presence of fibrosis, *JAK2*/*MPL* mutation or +9/13q- cytogenetic abnormality is supportive but not essential for diagnosis. Prefibrotic PMF mimics essential thrombocythemia in its presentation and the distinction is prognostically relevant. Differential diagnosis of myelofibrosis should include chronic myelogenous leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia and acute myeloid leukemia.

Risk stratification: *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 (Table 3): age >65 years, hemoglobin <10 g/dL, leukocytes >25 x 10^9/L, circulating blasts ³1%, constitutional symptoms, red cell transfusion dependency, platelet count <100 x 10^9/L and unfavorable karyotype (i.e. complex karyotype or sole or two abnormalities that include +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p- or 11q23 rearrangement). The presence of 0,

Table 3. Risk stratification and risk-adapted therapy in primary myelofibrosis.

DIPSS-plus[17] risk groups PMF	Median survival	Management PMF
Low-risk *(No risk factors†)*	~15.4 years	Observation or Conventional drugs††
Intermediate-1 risk *(1 risk factor†)*	~6.5 years	Observation or Conventional drugs†† or Experimental drugs
Intermediate-2 risk (2 or 3 risk factors†)	~2.9 years	Allo-SCT or Experimental drugs
High-risk *(≥ 4 risk factors†)*	~1.3 years	Allo-SCT or Experimental drugs

Key: DIPSS, Dynamic International Prognostic Scoring System;17
†DIPSS-plus17 uses 8 risk factors for inferior survival: age > 65 years, hemoglobin < 10 g/dL, leukocyte count > 25 x 109/L, circulating blasts ³ 1% , presence of constitutional symptoms, presence of unfavorable karyotype, platelet count < 100 x 109/L and presence of red cell transfusion need. Please note that a transfusion-dependent patient automatically has 2 risk factors because of transfusion need (one risk point) and hemoglobin < 10 g/dL (one risk point).
††androgen preparations or thalidomide with prednisone for anemia; hydroxyurea for symptomatic splenomegaly

1, "2 or 3" and ³4 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.

Risk-adapted therapy: Observation alone is adequate for asymptomatic *low/intermediate-1 risk* disease (Table 3). Allogeneic stem cell transplantation or experimental drug therapy is considered for *intermediate-2/ high risk* disease (Table 3). Conventional or experimental drug therapy is reasonable for symptomatic *intermediate-1* 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. JAK inhibitor therapy is currently investigational and has promise in MF (Table 4).

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Table 4. JAK2 inhibitor ATP mimetics that have made it to clinical trials

Anti-JAK2 ATP mimetic	**Anti-JAK2 IC50 (JAK1/JAK3/TYK2 selectivity)**	**Non-JAK kinase targets**	**Clinical trials**	**Disease features shown to be favorably affected**	**ide effects**
INCB018424[18] (Phase 1/2 study)	5.7 nM (x1.0/x98/x9.3)	None of ~28 kinases evaluated	MF (n=155)[19] PV (n=34)[20] ET (n=39)[20]	plenomegaly Constitutional symptoms Pruritus Cachexia Erythrocytosis (PV)	Thrombocytopenia (DLT) Anemia "Acute relapse of symptoms and re-enlargement of spleen upon drug discontinuation" "Systemic inflammatory response syndrome (SIRS) upon drug discontinuation"
TG101348[21] (Phase 1/2 study)	3 nM (x35/x332/x135)	FLT3 RET	MF (n=59)	plenomegaly Constitutional symptoms Pruritus Leukocytosis Thrombocytosis *JAK2*V617F burden	Increased amylase/lipase (DLT) Anemia Thrombocytopenia Nausea/vomiting Diarrhea Increased transaminases
CEP-701[22,23] (Lestaurtinib) (Phase 2 study)	1 nM (x?/x3/x?)	FLT3 TrkA	MF (n=22) PV (n=27) ET (n=12)	plenomegaly Anemia (MF) Pruritus	Diarrhea Nausea/vomiting Anemia (MF) Thrombocytopenia (MF) Thrombosis (PV/ET) Leukocytosis (PV/ET) Thrombocytosis (PV/ET)
CYT387[24] (Phase 1/2 study)	18 nM (x0.6/x8.6/x?)	JNK1 CDK2	MF (n=36)	Anemia plenomegaly Constitutional symptoms Pruritus	Increased amylase/lipase (DLT) Headache (DLT) Thrombocytopenia Increased transaminases "First dose-effect characterized by transient hypotension and lightheadedness"
AZD1480[25] (Phase 1/2 study)	0.26 nM (x5/x15/x?)	TrkA Aurora A FGFR1	MF	Results pending	Results pending
B1518[26] (Phase 1/2 study)	22 nM (x58/x24/x?)	FLT3	MF (n=31)	plenomegaly	(DLT=GI symptoms) Diarrhea Nausea Thrombocytopenia
XL019[27] (Phase 1/2 study)	2 nM (x67/x98/x172)	cant literature	MF (n=21)	plenomegaly Constitutional symptoms Leukocytosis	Neuropathy (DLT) No myelosuppression
LY2784544 (Phase 1/2 study)	cant literature	cant literature	MF	Results pending	Results pending

Abbreviations: PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; MF, myelofibrosis and includes PMF and post-PV/ET MF; DLT, dose-limiting toxicity; GI, gastrointestinal;

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Diagnosis and Management of Eosinophilic and Mast Cell Neoplasms

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Introduction: The 2008 World Health Organization (WHO) classification system for hematological malignancies classifies systemic mastocytosis (SM) and chronic eosinophilic leukemia-not otherwise specified (CEL-NOS) as myeloproliferative neoplasms (MPN).[1] Diagnosis in both SM and CEL-NOS requires the absence of *BCR-ABL1*, dyserythropoiesis, granulocyte dysplasia, or monocytosis (^{3}1 x 10^9/L).

Diagnosis of SM: When SM is suspected, one should consider bone marrow examination with tryptase stain, bone marrow mast cell flow cytometry to look for phenotypically abnormal mast cells (i.e. CD25-positive), and if available, mutation screening for *KIT*D816V; a working diagnosis can be made in the presence of bone marrow aggregates of morphologically abnormal mast cells or, when histology is equivocal, the presence of either *KIT*D816V or phenotypically abnormal mast cells.[2]

Diagnosis of eosinophilic disorders: Comprehensive and accurate evaluation of primary eosinophilia requires bone marrow examination with tryptase stain, T cell clonal studies and immunophenotype, cytogenetic studies, and molecular studies to detect *FIP1L1-PDGFRA*.[3] These studies should enable one to distinguish between "molecularly-characterized myeloid neoplasms associated with eosinophilia", CEL-NOS, and hypereosinophilic syndrome (HES). The former category includes *PDGFRA*, *PDGFRB*, and *FGFR1* rearranged myeloid neoplasms associated with eosinophilia.[4-7] In the absence of these molecular markers, CEL-NOs or HES is considered; diagnosis in both requires the presence of ^{3}1.5 x 10^9/L PB eosinophil count, exclusion of secondary eosinophilia, exclusion of other acute or chronic myeloid neoplasm, and no evidence for phenotypically abnormal and/or clonal T lymphocytes.[8] In addition, diagnosis of HES requires absence of both cytogenetic abnormality, and > 2% peripheral blasts or >5% bone marrow blasts.[8]

Management of eosinophilic disorders: All individuals carrying the *FIP1L1-PDGFRA* or *PDGFRB* mutation achieve a complete hematologic remission with 100-400 mg/day of imatinib mesylate, which is considered first-line treatment in such patients. In contrast to the case with *PDGFR*-rearranged eosinophilia, *FGFR1*-rearranged eosinophilia is an aggressive myeloproliferative disorder frequently associated with T-cell lymphoblastic lymphoma and does not respond to either imatinib mesylate or any other currently available drug.[9] It is advised that such patients be managed aggressively with intensive chemotherapy and allogeneic stem cell rescue.

There is currently no consensus regarding the management of asymptomatic patients with HES with no evidence of organ damage. I currently prefer to closely monitor rather than to treat asymptomatic patients, regardless of the degree of eosinophilia. Accordingly, I recommend measurement of serum troponin level every 3 to 6 months and an echocardiogram every 6 to 12 months to detect early cardiac involvement. For the treatment of symptomatic patients with HES, first-line drug of choice is prednisone (starting dose of 1 mg/kg/day) because of the rapidity as well as reliability of its effect. However, despite a near 70% overall response rate [10], relapses off therapy are usual and either a substitute drug or a steroid-sparing agent soon becomes necessary. In this regard, interferon alpha (starting dose 3 million units three-times-a-week) [11-14] and hydroxyurea (starting dose 500 mg twice-a-day) [10] have respectively served these roles by producing remissions in the majority of treated patients and are currently considered second-line drugs of choice. In true HES (i.e. *FIP1L1/PDGFRA*-negative), low-dose gleevec (100 mg/day) is unlikely to produce durable complete remissions [5]. A higher dose of the drug (400 mg/day), however, might induce partial remissions [5] and in some instances a complete remission [15], thus making gleevec a reasonable third-line drug of choice.

In patients that are refractory to usual therapy in HES, I am inclined to consider one of two monoclonal antibodies; mepolizumab (SB 240563) targets IL-5 and alemtuzumab (Campath®) targets the CD52 antigen that is expressed by eosinophils but

not neutrophils. Both were effective in controlling blood eosinophilia as well as disease symptoms. However, while durable remissions were seen with maintenance therapy with alemtuzumab (30 mg every 3 weeks) [16,17], response to single dose mepolizumab therapy (1 mg/kg) was relatively short-lived and associated with rebound eosinophilia.[18-21]

Management of SM: Drug therapy has not been shown to favorably affect survival in MCD. Therefore, current therapy in WHO-defined MCD is palliative and directed at mast cell degranulation symptoms (e.g. pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks), skin disease (e.g. urticaria pigmentosa; UP), and/or organ dysfunction from mast cell tissue infiltration. In general, antihistamines and cromolyn sodium are equally effective (or ineffective) in controlling mast cell degranulation symptoms.[22] UP and pruritus respond modestly to topical corticosteroids or ultraviolet A phototherapy with (PUVA) or without (UVA1) psoralen.[23] I would also consider interferon alpha (IFN) therapy for mast cell degranulation symptoms and UP that are refractory to usual therapy.[24]

The presence of organ dysfunction (e.g. symptomatic hepatosplenomegaly, clinically-significant liver function test abnormalities, ascites, cytopenias, osteoporosis or osteolysis, diarrhea associated with weight loss) distinguishes indolent from aggressive SM. In general, I try to avoid use of cytoreductive agents in patients with "indolent SM", where survival is usually long and disease course non-progressive.[23] In contrast, cytoreductive therapy is usually employed in aggressive SM with the intention to decrease mast cell burden. In this regard, IFN and cladribine are the first-line drugs of choice and I expect response rates of > 50% with each drug.[23] Treatment with either IFN or cladribine has the potential to benefit all aspects of disease including mast cell degranulation symptoms, UP, symptomatic organomegaly and ascites. In the presence of osteoporosis or lytic bone lesions, I recommend, in addition, bisphosphonate therapy (e.g. pamidronate 90 mg IV monthly).[23]

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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 tyrosinekinase inhibitors. Further more molecular evaluation of ALL blasts has provided important insights into disease biology. Therefore the first presentation of the session by Elisabeth McIntyre covers the topic ' What is state-of-the-art diagnosis for ALL and which information comes from new molecular markers'.

Targeted therapy has contributed to the improved over all outcome of ALL. The use of tyrosinekinase 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 sub group of ALL andis a model for causal molecular therapy of acute leukemias. The second presentation by Oliver Ottmann will cover the topic , Management of Ph+ 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. The concept of ALL treatment in general will be discussed by Nicola Gökbuget in the topic' Management of adult ALL with risk adapted and individualized approaches'

Participants of the session will get a complete over view on state of the art management of ALL starting from diagnosis to sub group adjusted therapy.

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What is State-of-the-Art Diagnosis for ALL and which Information Comes from New Molecular Markers?

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The aim of any diagnostic process in Acute Leukemia (AL) is to make sure that the patient receives the minimum treatment necessary to maximise the chances of cure with a minimum number of undesirable side effects. This implies firstly that the diagnosis is made correctly, that prognostic risk within the diagnostic category is appropriately evaluated and finally that the response to treatment is measured objectively and sufficiently reproducibly, if treatment decisions are to be based on the kinetics of leukemic disappearance, commonly referred to as assessment of minimal residual disease (MRD). Ideally, diagnostic criteria would be made available rapidly, in order to be used for theranostic stratification even during induction therapy. Acute Lymphoid Leukemia (ALL) represent the most common paediatric cancer and approximately 85% of paediatric AL compared to less than 10% of adult AL. AL of the T lymphoid lineage is found in 15% of paediatric and 25% of adult ALL, but will be disproportionately presented here, in view of recent developments, personal research involvement and since BCR-ABL/Ph+ ALL is treated by other speakers within this session. This presentation will also disproportionately concern adult ALL.

Parallels with normal hematopoiesis and lymphopoiesis

Distinction between Acute Lymphoid Leukemia (ALL) and Acute Myeloid Leukemia (AML) or Acute non-Lymphoid Leukemia (ANLL) was classically made by morphological and cytochemical assessment and was based on models of hematopoiesis, whereby the original cellular dichotomy was between a myeloid precursor with granulocytic, monocyte/macrophage, erythroid and megakaryocytic potential and a common lymphoid precursor (CLP), with T, B and NK potential. This has increasingly been called into question with the identification of an initial dichotomy between an Erythroid/Megakarycytic precursor and an intermediate precursor with lymphoid and myeloid potential, initially in the mouse (Lymphoid primed multipotent progenitors or LMPP) [1] and more recently in man (Myeloid Lymphoid Precursors or MLP) [2]. Dendritic cells have long been recognised to have either a lymphoid or a myeloid origin and are now proposed to originate, along with macrophages predominantly from the human MLP [2].

If AL represent cells arrested during developement, classical hematopoietic models would have dictated that immature AML would demonstrate features of granulocytic, monocyte/macrophage, erythroid and megakaryocytic precursors and immature ALL features of B, T and NK precursors. In practise, co-expression of T lymphoid and myeloid or B lymphoid and myeloid/macrophage features are much more common than co-expression of B and T lymphoid features, and are more in keeping with current hematopoietic models and a MLP. Compatible with this, an intermediate with characteristics of an MLP has recently been identified in AML [3]and the Leukemia Clonogenic population of a murine model of CALM-AF10 AML was shown to have lymphoid potential [4]. In practical terms, the phenotypic distinction of immature AML and ALL should be revisited. This implies modernisation of the Immunophenotypic panels used at diagnosis of all Acute Leukemias. This procedure is ongoing, notably, but not exclusively, within the EuroFlow 6th PCRDT program.

With regard to normal lymphopoiesis, it is important to remember that B cell development takes place in the bone marrow, whereas the majority of T lymphoid development occurs in the thymus. Whether the leukemic clonogenic cell in T-ALL originates in the thymus or the bone marrow is not yet clear and will probably prove to be variable. Similarly, expression of a surface Ig/TCR (T Cell Receptor) is seen in 1% of B Cell Precursor (BCP), compared to approximately 25% of adult and 50% of pediatric T-ALL. The interface between BCP-ALL and Burkitt's lymphoma and between T-ALL and T lymphoblastic lymphoma merits closer evaluation, both with respect to understanding the factors which govern bone marrow or thymic egress and with respect to the most appropriate treatment.

Molecular screening at diagnosis

Molecular screening by RT-PCR in ALL became obligatory in the 1990s with the realisation that classical morphological karyotyping did not allow detection of all cases of Ph+ (BCR-ABL) BCP-ALL. It then became relatively simple to expand the number of fusion transcript targets to be screened from cDNA. Their detection by RT-PCR was complementary to FISH detection and allowed clinico-biological characterisation of each oncogenic subtype, most of which corresponded to a minor subgroup. The large and increasing number of somatic genetic abnormalites (reviewed in [5]), the small number of patients in each subgroup and the different behaviour of each fusion transcript when used as MRD markers, however, limited their specific management and individual therapeutic stratification, unless specific targeted therapy was available. For these reasons, the only frequent molecular subgroups (approximately 25%) were ETV6-RUNX1 (TEL-AML1) in pediatric and BCR-ABL in adult BCP-ALL and only the latter leads to therapeutic modification. No frequent fusion transcripts have been identified in T-ALL, with both CALM-AF10 [6] and MLL abnormalities occurring in less than 10% [7].

The second generation of molecular markers includes a large variety of transcripts with deregulated expression by promoter substitution. In T-ALL, many of these result from translocation with TCR loci, which are much more frequent than translocation with Ig loci in BCP-ALL. They include HOX11/TLX1, HOX11L2/TLX3, LMO1/2, TAL1 and a variety of rare targets (reviewed in [8]) . It is, however, sometimes difficult to distinguish physiological from pathological expression and quantitative expression of these transcripts does not always allow clear distinction of patient subgroups. Perhaps partly as a result of this, conflicting data regarding their prognostic impact is frequently reported. High level TLX1 expression is, however, reproducibly found to be of relatively good prognosis in adult T-ALL [9] and references therein. All of these markers are present in minor subsets. The advent of widespread gene-expression profiling (GEP) showed that transcriptional profiles often correlated with characteristic profiles in previously recognised oncogenic subgroups, although other subgroups, including BCR-ABL, were associated with relatively heterogeneous profiles. They also led to the identification of a range of transcripts reported to identify prognostically relevant subgroups, often without knowledge of the underlying oncogenic mechanisms. In a minority, these profiles led to identification of novel genomic abnormalities. GEP and confirmation of transcriptional profiles by quantitative RT-PCR have allowed significant advances in our understanding of leukemogenesis, but GEP has found little diagnostic application at a practical level, and the expression of individual transcripts tends to occur as a continuous variable, making cut-offs into reproducible subgroups difficult to apply, particularly on a multicenter basis. As an example, BAALC/ERG transcripts were identified from GEP in adult AML and subsequently T-ALL, when they were reported to identify poor prognosis adult T-ALL patients in the GMALL studies [10], but not in the GRAALL trials (Ben Abdelali et al., under revision).

The arrival of high resolution genomic quantification by CGH/SNP arrays (reviewed in [11] allowed the identification of a large number of copy number variations in both BCP and T-ALL, with deletions being more frequent than amplifications. The Ig/TCR recombinase is involved in a significant proportion of these deletions. Several of these deletions had already been recognised, but novel, frequent deletions included a large number of genes involved in normal B or T lymphoid development. There was also significant association between deletions and fusion transcripts. For example, IKAROS deletions co-segregate with BCR-ABL translocations, and confer a poor prognosis [12]. Increasing resolution continues to expand the large number of targets identified, and importantly, demonstrates that minor deletions which generate alternative isotypes with oncogenic consequences are increasingly identified. These will provide a mass of data on lymphoid oncogenesis within the coming years but once again, only a minority will translate into modified individual patient management. CGH/SNP arrays allow identification of hyperdiploid ALL, thus obviating the need for morphological karyotyping for this indication. Maintenance of a structural genomic mitosis bank is an invaluable resource for all ALL patients included in prospective clinical trials and has been, and will continue to be, a rich source of characterisation of novel structural abnormalities. It is, however, probably no longer necessary for individual stratification, if appropriate molecular and CGH/SNP screening is available.

Finally, point mutations with prognostic and sometimes therapeutic impact are increasingly recognised. Notch1 has a fundamental role in T lymphoid development and gain-of-function mutations of this gene are seen in 50-60% of T-ALLs [13]. The FBXW7 gene codes for a ubiquitin ligase which participates in Notch1 degradation. Loss of function FBXW7 mutations therefore lead to a Notch1 longer half life and as such converge functionally with Notch1 mutations . Notch1 and/or FBX1 mutations are seen in approximately 70% of T-ALLs (reviewed in [14]). They are generally associated with

a good prognosis, although this appears to be protocol dependent, and may be more striking in adult T-ALLs treated on pediatric inspired protocols [15] and Ben Abdelali et al. under revision.

Minimal Residual Disease management

MRD assessment needs to be applicable to the vast majority of patients within a given treatment arm. Apart from BCR-ABL, oncogenic markers have gradually been replaced by quantification of Ig/TCR markers from DNA. The robust value of reproducible Ig/TCR quantification of the kinetics of response to initial induction chemotherapy has long been recognised in pediatric ALL and is used for individual stratification in the majority of European clinical cooperative groups (reviewed in [16]). This is increasingly also the case in adult ALL, although the way in which MRD information is used is different, particularly with respect to the use of allogeneic stem cell transplantation. Reliable use of Ig/TCR quantification requires strict standardisation, as practised within the international EuroMRD group [17]. Recent developments in multicolour Flow cytometry will allow a complementary approach to MRD evaluation, on condition that they are proven to have inter-center reproducibility, including for the quantification of rare events.

Conclusion

Technological evolution continues to allow for rapid advances in our understanding of leukemogenesis and the transfer of a proportion of this understanding to individual patient management. Which proportion of the large number of diagnostic molecular markers should be transferred and how these analyses should be financed is a relevant issue which each individual health care system should address, in order to maximise the return on investment in terms of patient survival and well being.

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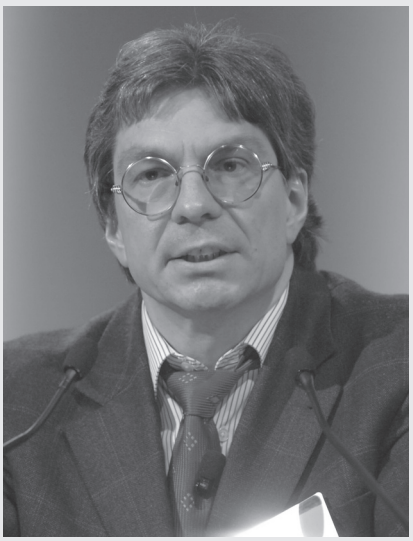

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Clinical Management of Philadelphia Chromosome positive Acute Lymphoblastic Leukemia (Ph+ALL)

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Administration of the tyrosine kinase inhibitor (TKI) imatinib as front-line treatment of Ph+ALL has increased the rate of complete remissions in newly diagnosed adult patients to approximately 95%. This magnitude of response is achieved irrespective of whether imatinib is given alone or in conjunction with various types of chemotherapy; however, the depth of these responses, as assessed by quantitative determination of bcr-abl transcripts, is higher following combined therapy. Maintaining these remissions has become the major challenge in treating Ph+ALL, and different approaches are being used depending on the group of patients considered. Overall, stem cell transplantation is the only therapeutic modality convincingly shown to have curative potential, but it is not available for a significant subset of patients, particular the elderly. With the recent introduction of more potent second generation TKIs directed against BCR-ABL, the role of additional intensive induction and consolidation chemotherapy and of stem cell transplantation will have to be redefined.

The concept of up-front treatment with single-agent TKI was initially explored in elderly patients with the aim of combining better tolerability with enhanced efficacy when compared with prevailing chemotherapy regimens. These studies indeed demonstrated the superiority of imatinib over chemotherapy with respect to reduced morbidity and mortality and excellent CR rates, acquired resistance to TKI were identified as the main clinical problems. It is still unclear whether dasatinib will resolve these shortcomings, as follow-up of studies is still short and resistance attributed to the T315I mutation of the bcr-abl tyrosine kinase domain appearing as a clinical problem. This problem of mutational resistance is not abrogated by the combination of TKI even with intensive chemotherapy; although results with imatinib-based regimens are superior to those obtained in historic controls, relapse remains the major cause of treatment failure even when imatinib or dasatinib are combined with intensive chemotherapy. Mutational analysis of relapse samples has consistently shown that bcr-abl

TKD mutations play a dominant role in clinical resistance to TKI, with preponderance of p-loop mutations and the T315I mutation. The spectrum of observed mutations depends on the TKI employed; thus, approximately 60% of partients who relapse on imatinib carry a p-loop mutation, whereas dasatinib is by far most frequently associated with the T315I mutation. It has become of central interest whether mutations are already present in TKI-naïve patients, and this frequently appears to be the case. These results supports a concept of mutations arising randomly as a consequence of a high genetic instability, while some of them confer a growth advantage under the selective pressure of TKIs.

The probability of patients undergoing allogeneic stem cell transplantation (SCT) in first CR has increased with the higher response and lower relapse rates achieved with TKI-based treatment. At present, SCT should be attempted in all patients with a compatible donor who are considered eligible for a transplant procedure. Given the high prevalence of bcr-abl TKD mutations in patients with Ph+ALL, the ability of allogeneic SCT to eradicate different types of TKD mutations is likely to determine the success of transplantation. In our hands, allogeneic SCT results in long-term elimination of mutant clones in the majority of patients, but patients remain at risk of relapsing with previously undetectable TKD mutations. Some of these mutations are responsive to second generation ABL TK inhibitors. This provides the rationale for the administration of TKI after SCT, although the exact modalities, e.g. type of TKI, dose, starting timepoint and duration of treatment remain to be resolved.

The importance of mutations in clinical resistance to available TKI has promoted the search for novel inhibitors, active particularly against the T315I gatekeeper mutation.

Interesting immunologic approaches are based on recently developed bispecific T-cell-engager (BiTE) antibodies that transiently engage cytotoxic T-cells for lysis of selected target cells. The bispecific antibody construct called blinatumomab links T cells with CD19-expressing target cells, resulting in a non-restricted cytotoxic T-cell response and T-cell activation. Preliminary results indicate that treatment with blinatumomab is able to convert MRD positive ALL into an MRD negative status, and that this is well tolerated. Current efforts also involve the optimisation of molecular techniques to quantitate minimal residual disease and identify resistance mechanisms. Optimal treatment results necessitate the integration of all available therapeutic and molecular diagnostic approaches into predefined, long-term strategies that take into account both patient and disease characteristics.

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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 more than 10 different Investigator-initiated trials in adult ALL and related diseases such as lymphoblastic lymphoma or Burkitt's lymphoma.
Nicola Gökbuget is founding member of the German Network for Acute and Chronic Leukemias supported by the German Ministery of Research and Education. 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 since the beginning of 2000 which is a major project of the network and responsible for distribution of leukemia specific informations for physicians, researchers, patients and the public. Furthermore she is founding member of the European Leukemia Network which is 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).

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Management of Adult ALL with Risk Adapted and Individualised Approaches

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Summary

Risk adapted therapy of adult ALL was invented in the 80ies [1] and has contributed to the improved outcome with complete remission (CR) rates of 85-90% and overall survival (OS) rates of 35-40% in recent trials (table 1) [2,3]. Improved chemotherapy regimens, the integration of stem cell transplantation (SCT) in frontline therapy, improved supportive care, optimised risk stratification and the use of targeted therapies were other important developments.

The major aim of "risk adapted therapy" was originally the identification of patients with poor prognosis who could benefit from treatment intensification by SCT. Nowadays the term has been extended and also includes age adapted therapy, subgroup adjusted therapy, targeted therapy and individualised therapy based on evaluation of minimal residual disease (MRD). Not only the term but also aims changed. Identification of patients with high risk of relapse it is still an important goals. In addition risk stratification aims to identify [1] patients with favour-

able prognosis in whom treatment reduction could be considered, [2] patients prone for specific toxicities e.g. by pharmacogenomic assessments and [3] for mortality after SCT e.g. by comorbidity scores. Overall these approaches lead to the development of more and more individualised therapy.

Table 1. Overall outcome of adult ALL

	N trials	N pts	CR	ED	OS/LFS
Younger pts	15	7262	84%	7%	35%
SCT (all with donor)	2696	84%		35%	
SCT (risk adapted)	2443	83%		36%	
Older pts	5	187	58%	16%	22%
Relapse pts	4	1494	~40%		6%

PROGNOSTIC FACTORS

The standardized, quality controlled, rapid diagnosis and classification of ALL is more than ever not only required for diagnostic confirmation but also to identify prognostic factors, markers for MRD evaluation and therapeutic targets. It includes morphology, immunophenotyping according to standardised criteria e.g. EGIL, cytogenetics and detection of molecular aberrations.

Age

Age is the most important prognostic factor (table 2). There is a continuous decrease in outcome with increasing age from childhood ALL (with the exception of infant ALL which is the poorest age group in pediatric ALL) to elderly patients. In adults OS ranges from 34-57% below 30 years to 15-17% above 50 years [4]. Above 70 years only few patients survive. In contrast to other prognostic factors age cannot be used to identify patients who could benefit from SCT as done by some groups because outcome of SCT also decreases with increasing age.

White blood cell count (WBC)

Elevated WBC at diagnosis (>30-50.000/µl) as poor prognostic feature[5] has been confirmed in various trials[2]. It was even considered as the most deleterious prognostic factor in B-precursor ALL with OS of 19-29%[6,7]. Some groups have used WBC as prognostic factor in T-ALL (>100.000/µl). In the GMALL studies the prognostic impact was outruled by immunophenotype in a multivariate analysis[6]. The biological reason for the highly resistant behaviour of B-precursor ALL with high WBC is unclear. Probably in the future additional molecular markers can help to clarify the underlying mechanisms. Due to the high relapse rate evaluation of MRD, use of experimental drugs and SCT modalities seem particularly important.

Immunophenotype

Immunologic subtypes of ALL are associated with different presentation and prognosis, distinct cytogenetic and/or molecular aberrations and surface markers are potential targets for antibody therapy. **Pro-B-ALL** and/or **t(4;11)** positive ALL is considered as poor prognostic subgroup in nearly all trials. It appears to be particularly susceptible to high-dose cytarabine based regimens and SCT as reported from the GMALL studies[8]. CD10-negative pre-B-ALL has been identified as a subgroup with similar features as pro-B-ALL[9]. **Common(c)/pre-B-ALL** bears a large proportion of Ph/BCR-ABL positive ALL (see below). Based on clinical and biologic factors c/pre-B-ALL can be subdivided into a standard and a high risk group with significantly different outcome of 50-60% survival for standard risk and 30-40% survival for high risk. The difference in overall outcome between pediatric and adult ALL is mainly due the poorer outcome in B-precursor ALL. **Mature B-ALL** is treated according to different concepts (see below).

Outcome of **T-lineage ALL** is generally considered superior compared to B-lineage[6,7,10]. Immunologic subtype of T-ALL was the most significant prognostic factor in the GMALL studies with leukemia free survival (LFS) of 25% for early T-ALL, 63% for thymic (cortical T-ALL) and 28% for mature T-ALL respectively[6]. Other groups observed inferior outcomes for early T-ALL[11,12] and coexpression of CD13, CD33 and/or CD34[11]. With current treatment regimens CR rates of more than 80% and a LFS above 50% can be achieved in T-ALL.

Interestingly also outcome after SCT appears to be influenced by immunophenotypes. In the GMALL studies the most favourable OS after SCT was achieved for pro B-ALL and early T-ALL whereas it was poorest in c/pre-B-ALL with high WBC[13].

Cytogenetics and molecular genetics

The most frequent cytogenetic aberrations in ALL are t(9;22)/BCR-ABL with about 20% (increasing with age) which is strictly correlated to B-precursor ALL and t(4;11)/ALL1-AF4 with 8-9% which is mainly correlated to pro-B-ALL. Both aberrations identify high risk patients. A recent analysis of cytogenetics

Table 2. Prognostic Factors for Risk Stratification of Adult ALL**

	Good	Adverse	
		B-lineage	T-lineage
At diagnosis			
Clinical Parameters	WBC < 30.000/μl	WBC > 30.000/μl	WBC > 100.000/μl (?)
Immunophenotype	Thymic T	Pro B (CD10-) Pre B (CD10-)	Early T (CD1a-, sCD3-) Mature T (CD1a-, sCD3+)
Cytogenetics / Molecular Genetics / Gene expression profiles	TEL-AML1 (?) HOX11* (?) NOTCH-1* (?) 9p del (?) Hyperdiploid (?)	t(9;22) / BCR-ABL t(4;11) / ALL1-AF4 Ikaros gene deletion t(1;19) / E2A-PBX (?) Complex aberrations (?) Low hypodiploid/near tetraploid (?)	HOX11L2* (?) CALM-AF4* (?) Complex aberrations (?) Low hypodiploid/near tetraploid (?)
Individual response during treatment			
Prednisone response	Good (?)	Poor (?)	
Time to CR	Early	Late (>3-4 wks)	
MRD after induction	Negative / < 10-4	Positive > 10-4	
Age			
	< 25 yrs, < 35 yrs	> 35 yrs, > 55 yrs, > 70 yrs	
Other factors			
Treatment realisation	Compliance, tolerability, delays, omissions etc.		
Drug resistance	Multidrug resistance overexpression, in vitro drug resistance (MTT assay), polymorphisms of drug metabolising genes etc.		

* overexpression of genes
** Generally accepted factors are printed in bold

in 782 adult ALL patients with Ph-negative ALL revealed a poor prognostic impact for low hypodiploid and near triploid karyotype (incidence: 4%), complex aberrant karyotype (5%) and t(8;14) (2%). The latter identifies patients with mature B-ALL/Burkitt's leukemia, who should be treated according to specific protocols. Del 9p (9%) and high hyperdiploid karyotype (10%) were associated with a favourable prognosis. A multivariate analysis identified age, WBC, t(8;14), low hypodiploid/near tetraploid and complex aberrant karyotype as independent prognostic factors for relapse and survival[14]. Generally there is the problem that cytogenetic aberrations refer to rare subgroups in an overall rare disease. In addition the prognostic impact depends on applied treatment protocol. Therefore uniform cytogenetic risk categories are difficult to establish.

Whereas cytogenetic aberrations are rarely detected in T-ALL a variety of molecular markers have been correlated to T-ALL subtypes such as HOX11, HOX11L2, SIL-TAL1 and CALM-AF10[15]. Many of those are not translocation breakpoints but are defined as overexpression of distinct genes, which makes a major difference in methodology. Thus overexpression of HOX11, which is associated with thymic T-ALL, may confer a favorable prognosis. Notch1 activating mutations with so far unclear prognostic relevance were identified in up to 50% of T-ALL cases[15]. Other groups observed inferior outcomes HOX11L2 and SIL-TAL positive T-ALL[12].

Recently deletions of the Ikaros gene have been described as poor prognostic feature first in childhood Ph-positive ALL[16], then in adult Ph-positive ALL[17] and finally in pediatric Ph-negative ALL[18]. Since the prognostic impact of molecular aberrations generally depends on the applied treatment regimen, future prospective evaluations will have to confirm the impact of this factor.

General condition and other "host" factors

Surprisingly the general condition of the patient has been rarely considered as prognostic factor. This may be due to the fact that in many, not population based trials, patients with poor general condition or relevant comorbidities are probably excluded. Poor general condition may be due to comorbidity, often

advanced age, late diagnosis or advanced stage with already pre-existing complications.

For SCT it has been demonstrated impressively that patients with extensive comorbidity most probably do not benefit at least from standard SCT procedures. Poor social conditions may prohibit patients to be included in clinical trials with adequate treatment in many countries and also may contribute to poor compliance with therapy.

Other "host" factors in adult ALL are not described sufficiently also they may have an impact on outcome such as gender or obesity.

Drug resistance

MDR-1 function has been associated with a poorer prognosis[11,19]. In-vitro sensitvity testing was able to identify patients with resistance to conventional cytostatic drugs which was associated with an inferior prognosis. More recently it was demonstrated that in-vitro drug resistance is even associated with distinct gene expression profiles[20]. In-vitro resistance testing is also increasingly used for effectivity testing of new cytostatic drugs.

Pharmacogenomics

Polymorphisms of drug metabolising enzymes can be associated with increased toxicity on one hand and increased or decreased efficacy on the other hand. The most prominent example is the thiopurinemethyltransferase (TPMT) polymorphism which is associated with increased toxicity of 6-mercaptopurine but also with increased efficacy indicated by improved relapse free survival. It was possible to correlate TPMT polymorphisms with MRD based response evaluation[21]. There is an increasing amount of evidence indicating that different polymorphisms could be associated with toxicities such as gastrointestinal, infections or also late effects such as avascular bone necrosis[22].

Treatment response and minimal residual disease (MRD)

Beside age the most relevant prognostic factor in ALL is still the achievement of CR. Further prognostic factors related to treatment response are delayed time to CR or response to prednisone therapy. A more accurate approach to assess individual response is MRD evaluation[23]. MRD not only gives an impression on individual chemotherapy sensitivity i.e. drug resistance but also covers a variety of other aspects such as individual realisation of therapy and unknown host factors. Longitudinal MRD-evaluation in adult ALL has three major aims [1] re-definition of clinical response, failure and relapse [2] utilisation as prognostic factor [3] basis of treatment decisions.

[1] In contemporary trials for adult ALL CR rates of 85-90% can be reached. The cytologic response rate is often favourable in all subgroups. Therefore more sensitive methods for evaluation of response are required. The molecular response defined as MRD below 10^{-4} after induction measured with two sensitive markers is about 70% and differences can be detected between subgroups[24]. Molecular CR may be an important new endpoint for efficacy evaluation.

Molecular relapse defined as MRD above 10^{-4} after prior achievement of molecular CR is highly predictive of cytologic relapse [25]. In clinical trials it should be treated similarly to cytologic relapse and molecular relapse could also serve as entry criterium for trials with experimental drugs. If MRD-based endpoints are used in clinical trials standardisation of methods and definitions is extremely important. More recently not only methodology of molecular MRD evaluation has been standardised [26] but also terminology regarding MRD based response evalution[27]. Now terms like molecular remission, molecular failure and molecular relapse can be defined according to common standards.

[2] MRD is at any time-point a significant prognostic marker. Very early achievement of molecular CR (during and after first induction) identifies a subgroup of patients with very favourable prognosis. However in the GMALL studies these were only 12% of standard risk patients[28]. Adult ALL patients reach molecular CR later than children and later timepoints are more predictive of relapse. In the GMALL studies 25% of the patients had a molecular failure after induction and first consolidation and this identified the most unfavourable subgroup[28]. MRD is an unfavourable prognostic factor before and also after SCT[29].

The use of MRD as risk factor is complicated by the fact that it is combined with "conventional" risk factors. MRD identifies additional high-risk patients in those without conventional risk factors but also good-risk patients in patients with conventional high-risk features, who are usually scheduled for SCT. Thus use of MRD as prognostic factor depends on the time-point, the treatment protocol, general risk stratification and the planned therapeutic consequences.

[3] MRD based treatment stratification is discussed below.

Recently it has been reported that in patients with extramedullary relapse MRD detection in the bone marrow reveals that the large majority of patients have involvement above the detection level. In pediatric ALL this is an unfavourable prognostic factor[30].

Risk Adapted Treatment

In the past decade risk adapted treatment was mainly focussed on indication for SCT. Three types of prospective trials were reported for adult ALL (table 1); [1]comparative analysis of the role of SCT with allogeneic SCT in all patients with sibling donor [2] optimisation of chemotherapy with SCT only for subgroups such as Ph+ ALL, [3] SCT indication based on prognostic models. Overall no difference can be detected between these general approaches. Moreover variables are changing constantly and the comparison of transplantation and chemotherapy depends on the quality of transplantation results on one hand and on optimisation of chemotherapy on the other hand.

New dimensions of risk adapted therapy

Contemporary risk stratification in adult ALL has two major problems [1] there is a variety of rare prognostic factors which also depend on the different treatment protocols and [2] not all of these factors identify patients in whom SCT is an option. A considerable number of new mainly molecular prognostic factors is proposed but all of these factors can impossibly be integrated in a conventional risk model. They may rather stimulate analysis of underlying mechanisms, drug targets or invention of treatment adaptations. Furthermore MRD evaluation measures individual response and therefore covers a variety of undetermined or undeterminable risk factors.

Risk adapted treatment of adult ALL will comprise new dimensions in the future [8]. Prognostic factors and patient characteristics no longer only serve for identification of candidates for SCT in first CR but to define individualized treatment approaches which will be discussed for examples in the following.

Risk adapted SCT indications

The optimal strategy is still not clear. The majority of study groups in Europe follow risk adapted approaches with indication of SCT in patients with high risk features including the persistence of minimal residual disease (www.leukemia-net.org). There are however conflicting proposals. On one hand there are plans to offer allogeneic sibling SCT particulary younger standard risk patients and on the other hands to offer these patients pediatric protocols with a very low transplantation frequency.

In general SCT indications have to keep the balance between the expected reduced relapse risk and increased mortality of 20-30% after SCT. Also late effects are more pronounced in SCT patients, the quality of life seems to be poorer. In the future probably additional prognostic models for outcome after SCT e.g. comorbidity, age will have to be considered and may help to decide on SCT modifications e.g. dose reduced conditioning[31,32].

Subgroup adjusted treatment

Mature B-ALL and Burkitt's lymphoma is treated in separate studies with short intensive cycles leading to an improvement of formerly <10% to >50% OS. With the addition of anti-CD20 the OS could be improved further to 70-80%[33-34].

Age adapted treatment

In similar ways subgroup adapted therapies have to be defined for patients at both ends of the age spectrum of adult ALL. The definition of age limits is very variable. In adolescents and young adults (defined up to 50 yrs in some studies) several study groups apply pediatric protocols. These studies are associated with considerable side effects. It remains open to question whether this approach will be feasible and lead to an improvement of results compared to intensified protocols for adults – which also nearly all are originally based on pediatric protocols.

In elderly patients above 55 or 65 years dose reduced specifically designed regimens are more successful than unmodified application of protocols for younger patients. Above an age limit of 70 to 75 years it remains open to question whether any long-term cure can be achieved but age-adapted protocols for palliative treatment may provide additional life-span with acceptable quality of life.

Individualised treatment

According to MRD: MRD as part of prospective risk stratification can be used in different ways for treat-

ment decisions regarding [1] time-point[2] the selection of patients for MRD risk stratification[3] combination of MRD-based and conventional risk factors and[4] the MRD-based treatment options. Most adult ALL trials combine MRD based and conventional risk factors. It is hardly possible to identify adult low risk patients in whom reduction of therapy would be justified. Thus the major aim in MRD-based studies is therefore to identify patients with high risk of relapse for treatment intensification by SCT. Molecular non-responders are by definition chemotherapy resistant and since outcome of SCT also depends on pretransplant MRD-level[29] it is questionable whether immediate SCT is really the best option. Experimental treatment may be useful to reduce MRD load. It is also important that MRD evaluation after SCT helps to identify patients who could benefit from additional treatment such as donor-lymphocyte infusions, maintenance therapy, experimental drugs.

On the other hand patients with conventional high-risk features, who are primarily candidates for SCT, may show excellent response and reach a negative MRD status. It is discussed whether in these patients SCT is still justified. Probably only controlled trials can help to answer this question. The best strategy remains open.

According to drug resistance or pharmacogenomics: For future trials modification of treatment regimens according to the results of in-vitro sensitivity testing or based on genetic polymorphisms for drug metabolising enzymes could be additional options for individualised treatment. The latter option is already reality in specialised centres for paediatric ALL

Targeted therapies

Ph/BCR-ABL positive ALL: The best example for targeted therapy is the use of Imatinib and other new kinase inhibitors which lead to a considerable improvement of this formerly most unfavourable subgroup. Treatment will be reviewed in a separate presentation.

Antibody therapy: ALL blast cells express a variety of specific antigens such as CD20, CD19,CD22,CD33,CD52 which may serve as targets for treatment with monoclonal antibodies (MoAb). The **anti-CD20** antibody has been successfully integrated in therapy of mature B-ALL. It is now also explored in several pilot studies for CD20-positive B-precursor ALL[35,36]. Ongoing and planned trials with antiCD20 and other antibodies will help to define optimal use and efficacy of antibody treatment in ALL:

Subgroup specific drugs: Particularly for T-ALL several new options for targeted therapy are coming up and based on results in phase I-II studies it will be necessary to define priorities. Thus the purine analogue Nelarabine could be soon integrated in front-line therapy studies as consolidation cycle.

Summary and future directions

Risk and subtype adjusted treatment strategies led to considerable improvement of outcome in mature B-ALL, T-ALL and Ph-positive ALL but to a lesser extent in adult patients with B-precursor ALL. The poorer outcome of B-precursor ALL is also the major factor contributing to the poorer overall outcome in adults compared to paediatric ALL patients.

Most of the adult ALL trials are originally based on paediatric protocols. In contrast to paediatric trials adult study groups to some extent focussed on high-dose therapies as used in acute myeloid leukemia and extensive use of SCT whereas in paediatric trials the major focus was on optimisation of intensive chemotherapy regimens. This is now again one important aim of several planned trials for adult ALL.

Intensive chemotherapy should be complemented by targeted and individualised treatment elements. A better adherence to protocols, support of patients to improve their compliance e.g. psycho-social counselling and documentation of compliance would be warranted in adult ALL.

Also the design of prospective trials will be challenging since they will even more focus on smaller subgroups of ALL and studies with new drugs. New endpoints for clinical trials are needed such as CR without platelet regeneration, realisation of SCT and quality of life. These new endpoints are also considered by regulatory authorities. Despite these short-term endpoints improvement of overall survival of the total patient population including all risk groups is the final proof of all new risk-adapted treatment approaches. Beyond this all patients should be followed for long-term effects and quality of life.

In order enable intergroup comparisons and international joint trials efforts similar to childhood ALL are required to define uniform criteria for diagnostic classification, definition of subgroups and prognostic factors. In Europe an important step towards this goal was made by the foundation of a European Working Group for Adult ALL (EWALL)[37].

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Hodgkin Lymphoma

Dear colleagues and friends,

It's my pleasure to invite you to the session on Hodgkin lymphoma during the 3rd ICLLM Conference in Istanbul. Hodgkin lymphoma is one of the best curable malignancies in adults and has become the disease with most cancer survivors. Thus, Hodgkin lymphoma is not only a role model for the development of successful treatment but also a disease to study long-term effects of anti-cancer treatment. The most relevant current aspects on Hodgkin lymphoma will be presented during this symposium.

We very much hope that you will enjoy the conference and this particular session on Hodgkin lymphoma. Looking forward to meeting with you in Istanbul I remain with best personal wishes

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Early-Stage Hodgkin Lymphoma

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Summary

The standard of care for patients with early-stage Hodgkin lymphoma (HL) has changed from wide-field radiotherapy alone to combined modality strategies consisting of a brief chemotherapy followed by involved-field radiotherapy (IF-RT). Since the vast majority of patients treated with this approach achieve permanent remission, cure rates can hardly be further improved. Therefore, the major goal of current clinical research is to minimize therapy-related acute and late toxicities such as secondary malignancies, infertility, heart failure and pulmonary dysfunction without compromising treatment efficacy. Different strategies are being pursued. A possible reduction of chemotherapy, the minimization of radiation dose and fields as well as the value of risk-adapted strategies based on PET imaging are currently investigated in ongoing clinical trials worldwide.

Introduction

Hodgkin lymphoma (HL) is a malignant disease of the lymphatic system with an incidence of 2-3/100.000/year in developed countries. Generally, HL occurs in all age groups but young adults are most often affected [1]. Two major subtypes can be distinguished, classical Hodgkin lymphoma (cHL) which accounts for about 95% of all cases and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) representing about 5% of cases [2].

Due to substantial treatment improvements over the past decades, HL has changed from an incurable disease to one of the adult malignancies with the best prognosis. This has lead to a steadily growing number of long-term survivors. Since these long-term survivors often suffer from treatment-associated late toxicity including secondary malignancies, infertility, heart failure and pulmonary dysfunction, reducing the frequency of long-term sequelae without compromising treatment efficacy has become the major challenge of today`s clinical research on HL [3]. This article should give an overview over the recent changes in the treatment of early-stage HL.

Risk factors

In Northern America, clinical stage I and II HL patients presenting with poor prognostic risk factors such as, large mediastinal mass, are usually treated very similar to patients diagnosed with advanced disease. In contrast, European study groups such as the German Hodgkin Study Group (GHSG) and the European Organisation for Research and Treatment of Cancer (EORTC) divide clinical stage I and II patients into an early favorable and an early unfavorable group. Patients with early favorable disease are those without risk factors while patients with early unfavorable disease are those presenting with risk factors. Risk factors usually are higher age, large mediastinal mass, three or more involved lymph node areas and an elevated erythrocyte sedimentation rate (ESR). They vary only slightly between study groups (table 1). The utility of the risk factors currently used to discriminate between early favorable and early unfavorable disease could be shown in a recent analysis by the GHSG. This analysis, compared progression-free survival (PFS) of patients included in the GHSG HD10 and HD11 trials for early favorable and early unfavorable stages who received four cycles of ABVD (unpublished) were compared. PFS was significantly worse in patients presenting with risk factors (age of more than 60 years, large mediastinal mass and elevated ESR in particular). Consequently, future treatment approaches in early favorable HL should aim at reducing treatment intensity whenever possible to prevent overtreatment in the majority of patients while a relevant portion of patients with early unfavorable disease might benefit from treatment intensification.

Radiotherapy

For many years, wide-field radiotherapy alone was considered treatment of choice for early favorable HL. With this approach, many patients achieved complete remission (CR) but relapse rate was high and overall survival (OS) not satisfying [4]. To improve treatment outcome, combined modality strategies were introduced and randomized trials demonstrated superiority when compared to radio-

Table 1. Definition of early favorable and early unfavorable HL according to study groups

Treatment group	EORTC	GHSG
Early favorable stages	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors
Early unfavorable patients	CS I-II with ≥ 1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥ 1 risk factors; CS IIB with risk factors C/D, but not A/B
Risk factors	(A) large mediastinal mass (B) age ≥ 50 years (C) elevated ESR (D) ≥ 4 nodal areas	(A) large mediastinal mass (B) extranodal disease (C) elevated ESR (D) ≥ 3 nodal areas

therapy alone [5-6]. Thus, there is currently no role for radiotherapy alone in HL except for the treatment of patients with stage IA NLPHL without risk factors. In this small subset of patients, analyses by the GHSG and the EORTC revealed no significant outcome differences between patients treated with 30 Gy involved-field radiotherapy (IF-RT) and patients treated with extended-field RT (EF-RT) or combined modality strategies [7-8]. Consequentially, the least toxic approach, 30 Gy IF-RT, was adopted as standard of care.

Combined modality approaches for early favorable HL

Randomized trials performed by different study groups showed the superiority of combined modality treatment over radiotherapy alone in patients with early favorable HL:

The HD7 trial conducted by the GHSG compared 30 Gy EF-RT and a 10 Gy XXXXXto the IF with two cycles of ABVD chemotherapy followed by the same radiotherapy. Tumor control was superior in patients treated with the combined modality approach resulting in a significantly better 7-year freedom from treatment failure (FFTF) (88% vs 67%, p<0.001) [6]. Reduction of radiation fields to IF without compromising treatment efficacy could be shown in a number of trials so that combined modality treatment including a brief chemotherapy such as ABVD followed by IF-RT has become accepted standard therapy in early favorable HL [9-10].

In the GHSG HD10 trial, patients were randomly assigned to receive either two or four cycles of ABVD followed by IF-RT with a radiation dose of either 20 Gy or 30 Gy. FFTF was very similar in all treatment arms so that the least toxic approach consisting in two cycles of ABVD followed by 20 Gy IF-RT was adopted as novel standard for early favorable HL within the GHSG (figure 1) [11].

The HD10 follow-up trial, HD13, aimed at decreasing toxicity from the ABVD backbone by reducing the number of drugs given. Patients were randomized between two cycles of ABVD, ABV, AVD or AV chemotherapy followed by 30 Gy IF-RT. A preplanned safety analysis performed in June 2006 detected a fourfold increase of events in the ABV and the AV arm, respectively, which could not be explained by chance. Consequentially, the ABV/AV arms were closed. Thus, as a preliminary result of the trial, dacarbazine must be considered an essential part of ABVD in the treatment of early favorable HL [12]. The question whether AVD is equivalent to ABVD will be answered in future analyses of this study.

Combined modality approaches for early unfavorable HL

Patients with early unfavorable HL are commonly treated with combined modality approaches. However, the optimal chemotherapy regimen and the number of chemotherapy cycles needed has been a matter of debate.

In the EORTC/Groupe d`etude des Lymphomes de l`adulte (GELA) H8U study, 996 patients were treated with either six cycles of MOPP-ABV plus IF-RT, four cycles of MOPP-ABV plus IF-RT or four cycles of MOPP-ABV plus subtotal nodal irradiation (STNI). All groups had similar 5-year event-free survival (EFS) (84% vs 88% vs 87%) and 10-year OS estimates (88% vs 85% vs 84%). Thus, four cycles of chemotherapy followed by IF-RT was proposed as standard treatment for patients with early unfavorable HL [13].

In the EORTC/GELA follow-up H9U study, patients were randomized into three treatment arms consisting of four cycles of ABVD, six cycles of ABVD or four cycles of BEACOPPbaseline each followed by 30 Gy IF-RT. An interim analysis at a median

follow-up of four years showed no significant differences regarding EFS and OS between the treatment arms while increased toxicity was observed with BEACOPPbaseline [14].

The final analysis of the GHSG HD11 trial led to similar results. In this trial, patients received chemotherapy consisting of either four cycles of ABVD or four cycles of BEACOPP in baseline dose followed by IF-RT with either 20 Gy or 30 Gy. As a result, FFTF after BEACOPPbaseline was superior compared to that observed after ABVD in case chemotherapy was followed by 20 Gy IF-RT. In contrast, no significant outcome differences between both chemotherapy protocols were detected in patients who received a radiation dose of 30 Gy. Treatment-related toxicity was more frequently observed in the BEACOPPbaseline arms. Due to this increased frequency of toxic events, BEACOPPbaseline was not adopted as novel standard chemotherapy protocol for early unfavorable HL within the GHSG [15].

In the subsequent HD14 trial, patients were randomized to either four cycles of ABVD followed by 30 Gy IF-RT or a more intensified treatment protocol consisting of two cycles of BEACOPPescalated followed by two cycles of ABVD ("2+2") and the same radiotherapy. In 2008, a planned interim analysis of the trial including data from 1010 patients at a median observation of three years was performed. This analysis revealed a significant superiority in terms of FFTF for the 2+2 concept compared to four cycles of ABVD so that the previous standard arm was closed prematurely [16]. The final analysis of the trial performed in 2010 including 1623 patients confirmed these results. At four years, the FFTF rate among patients who received the intensified 2+2 chemotherapy was significantly superior to that among patients who received four cycles of ABVD (94.7% vs 89.3%) [17].

Chemotherapy alone

Since it is well known that a number of severe long-term sequelae such as secondary malignancies, pulmonary fibrosis or hypothyroidism can potentially be caused by radiotherapy, several groups initiated randomized trials evaluating the impact of radiotherapy after adequate chemotherapy.

In a trial conducted by the National Cancer Institute (NCI) of Canada and the Eastern Cooperative Oncology Group (ECOG), 399 patients with limited HL (nonbulky clinical stages IA and IIA) were enrolled and randomly assigned to either receive four to six cycles of ABVD chemotherapy alone or ABVD combined with STNI. With a median follow-up of 4.2 years, freedom from disease progression was superior in patients receiving combined modality treatment (93% in the combined modality vs 87% in the chemotherapy alone arm) indicating a better tumor control by additional radiation after chemotherapy. There were no significant differences in terms of EFS and OS (88% vs 86% and 94% vs 96%, respectively) [18]. However, longer observation and documentation of patients included in this trial is required to draw final conclusions because follow-up is still too short to assess particularly radiotherapy-related long-term side effects.

Another study which was conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) led to similar results. A total of 152 patients with nonbulky clinical stages IA, IB, IIA, IIB and IIIA were prospectively randomized to either six cycles of ABVD chemotherapy alone or six cycles of ABVD followed by radiotherapy. Although no significant differences in terms of CR duration, freedom from progression (FFP) and OS could be detected, a tendency towards a superior outcome in patients receiving combined modality treatment was observed. At 60 months, 91% of patients receiving combined modality treatment and 87% of patients receiving chemotherapy alone were still in CR (after 94% of patients in both arms had initially achieved CR). Freedom from progression and OS rates were 86% and 97%, respectively, for patients treated with chemotherapy plus radiotherapy compared to 81% and 90%, respectively, for patients who received chemotherapy alone [19].

In the EORTC/GELA H9F study for patients with early favorable HL, all patients received six cycles of EBVP chemotherapy. Patients with CR/CRu were then randomized between 36 Gy IF-RT, 20 Gy IF-RT and no RT. The trial could not be completed according to plan since the no RT arm had to be closed prematurely due to an excessive rate of events [14].

In contrast, an analysis from Dana-Farber Cancer Institute including 71 patients with limited disease who were treated with six cycles of ABVD without consolidating radiotherapy revealed promising results. With a median follow-up of at least 60 months, only six patients relapsed. All of them could be successfully salvaged with second-line therapy and no patient died [20]. However, these data have to be interpreted with caution since they were not obtained in the course of a randomized clinical trial and a selection bias cannot be excluded due to the single-center character of the analysis.

In summary, the data available to date indicate that omission of radiotherapy after an appropriate chemotherapy might only be possible in carefully selected patients. To identify and possibly further reduce toxicity in these patients is currently one of the most relevant questions. Since response assessment based on CT scans alone does not seem adequate to distinguish between those patients who may be sufficiently treated with chemotherapy alone and those who require additional radiotherapy or even more intensive treatment, ongoing trials focus on the predictive value and possible stratification based on the results of interim fluoro-deoxyglucose positron emission tomography (FDG-PET).

Response adapted therapy based on FDG-PET

As indicated by Danish and Italian groups, early interim FDG-PET might be a good predictor for treatment failure in HL patients [21-22]. Furthermore, the results of the GHSG HD15 trial for patients with advanced HL indicate that FDG-PET is a valuable tool for the decision whether patients with residual lymphoma after chemotherapy should be irradiated or not. Patients with residual lymphoma larger than 2.5 cm had PET scans. Patients with negative PET were not irradiated, patients with positive PET were irradiated. The negative prognostic value (NPV) defined as the portion of patients without progression, relapse or radiotherapy within 12 months was 94% [23].

Based on these findings, various ongoing trials evaluate whether treatment of patients with early-stage HL might be stratified on the basis of the result of an interim PET scan.

In the EORTC/GELA H10 trial, the treatment in the standard arm consists of three cycles of ABVD chemotherapy for patients with favorable risk profile and four cycles of ABVD chemotherapy for patients with unfavorable risk profile. Chemotherapy is followed by involved-node RT (IN-RT) which means a reduction of the radiation fields compared to the standard IF-RT technique [24]. In the experimental study arms, treatment is stratified on the basis of the result of a PET scan performed after the second chemotherapy cycle. Patients with negative PET receive two or three additional cycles of ABVD depending on their risk profile. Patients with positive PET receive an intensified treatment consisting of two cycles of BEACOPPescalated followed by IN-RT.

In the GHSG HD16 trial for patients with early favorable HL, patients receive two cycles of ABVD chemotherapy. Then, PET scan is performed in all patients. In the experimental arm, those patients with positive PET additionally receive 30 Gy IF-RT, those with negative PET do not. In the standard arm, all patients receive 30 Gy IF-RT subsequent to chemotherapy irrespective of the PET result.

In a large British trial which has already started recruitment in 2003, patients with a negative PET after three cycles of ABVD chemotherapy are randomized between either no further treatment or IF-RT. Patients with positive PET receive a fourth cycle of ABVD chemotherapy followed by IF-RT [25].

Conclusions

Introduction of combined modality approaches has led to cure rates beyond 90% in patients with early-stage HL. Since these cure rates can hardly be further improved, current trials aim at evaluating whether a response adapted stratification of treatment based on the risk profile of the individual patient is possible and practicable. At the moment, FDG-PET is considered the most promising tool to distinguish between those patients who might receive a reduced treatment without worsening the prognosis and those patients who might benefit from an intensified treatment. However, final results from large randomized trials addressing this issue are pending. Therefore, a brief chemotherapy followed by IF-RT remains the standard treatment for patients with early-stage HL.

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Advanced Stages

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The upfront chemotherapy regimen to induce complete response in young patients with advanced Hodgkin remains a matter of debate.

ABVD chemotherapy is currently widely used as standard treatment of Hodgkin lymphoma (HL) as well in USA as in Europe, but the escalated BEACOPP (BEACOPPesc) regimen developed by the German Hodgkin study group[1] (GHSG), which delivers more drugs at a higher dose intensity appears to improve outcome. BEACOPPesc provides a 10-years failure free and overall survival of 82% and 86% respectively, and two recently published trials demonstrated that this regimen improves the probability of 3y-PFS by more than 15% when compared to ABVD in advanced HL2,3.

Despite a related increased toxicity, upfront use of BEACOPPesc appears to be critical to improve outcome as demonstrated by the german HD14 trial showing a significantly better PFS for patients with early unfavorable HL when treated by 2 cycles of-BEACOPPesc followed by 2 cycles of ABVD, compared to 4 cycles of ABVD[4].

The better efficiency of BEACOPPesc against lymphoma is associated with a marked and frequent but manageable immediate hematologic toxicity and a higher risk of secondary myelodysplasia or acute myeloid leukemia. Inversely, the long term results of the HD9 trial show that the whole incidence of second cancer is not different in patients receiving BEACOPPescfrom those treated by COPP/ABV1.

The gonadal toxicity which is a real concern in young women, and increases with the number of cycles delivered and the age of patients is quite higher when using the BEACOPPesc regimen. Moreover the efficiency of protective therapy as GnRH agonist to prevent ovarian failure is still debated 6,7.

So, this toxicity is worth consideration, and encourages us to identify:

- Early responding patients after BEACOPPesc-treatment, able to benefit from a strategy of dose intensity decrease after upfront BEACOPPesc as well in term of treatment safety as in term of cure rate.

- Patients requiring to maintain during the whole treatment a higher dose intensity than that provides by the ABVD regimen

[18]-fluorodeoxyglucose-positron emission tomography (PET) was shown to improve primary staging and response assessment after completion of the first line treatment in HL[8], and was recently implemented to standardized response criteria for malignant lymphoma[9].

An increasing interest in using PET earlier during HL treatment is currently emerging, to better predict response to treatment and drive the consolidation therapy. PET performed after 2 courses of chemotherapy (PET2) was shown to predict patients outcome in term of progression free survival [10,11] and reaches a negative predictive value of 98% in BEACOPP treated patients[12]. With upfrontBEACOPPesc regimen, about 60% patients will reach a negative PET2[12]. So, PET2 allows to identify a population of early responding patients suitable for receiving a ABVD conventional dose chemotherapy after 2 cycles of upfront BEACOPPesc.

However, early PET positivity criteria are a specific issue in order to identify the right population of patients which might benefit to a risk adapted strategy. Early PET positivity criteria, based on a visual 5-point scale have been recently approved in the first international workshop on interim PET held in Deauville13, and have been tested with a good reproducibility in a multicentric trial setting14. These criteria improved by using a SUVmax analysis of the reference organ, will be implemented in the new GELA trial AHL 2011 which was designed to test in patients with Ann Arbor stage III, IV or high risk IIB according to the GHSG criteria1, a treatment strategy driven by PET after 2 cycles of BEACOPPesc, delivering 4 cycles of ABVD for PET2 negative patients and 4 cycles of BEACOPPesc for PET2 positive patients, and compared to a treatment no monitored by early PET.

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Hodgkin Lymphoma: Relapse and New Drugs

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Abstract

Although to date most patients with Hodgkin Lymphoma (HL) can be cured, current treatment is associated with acute and long-term complications as infertility, cardiovascular damage and secondary malignancies. Autologous peripheral blood stem cell transplantation (PBSCT) has been established for patients with a first relapse due to superior disease control as compared to conventional chemotherapy. However, for patients in second or higher relapse, no standard therapy exists and, in general, the ultimate goal of curing the patient cannot be followed any longer. Therefore, novel effective therapies are urgently needed for patients relapsing after high dose chemotherapy.

Currently emerging promising approaches include drugs targeting cell surface structures by monoclonal antibodies (moAbs) and immunotoxins, as well

as small molecules targeting intracellular proteins. Here we summarize the biological basis and early clinical data on emerging drugs for HL, that are expected to change the treatment in both relapsed and first-line HL patients.

Introduction

Currently about 80-90% of all adult patients with a first diagnosis of Hodgkin Lymphoma (HL) can be cured with radiochemotherapy[1-4]. Moreover, about half of all patients in first relapse achieve long-term remission with high dose chemotherapy and autologous stem cell transplantation[5]. However, long term survival in patients relapsing after high dose chemotherapy is poor and novel therapeutics for these patients are needed[6]. Moreover, for surviving patients, current treatment is associated with considerable acute- and long-term toxicity. In particular cardiovascular damage, pulmonary toxicity and secondary malignancies affect the patients[7]. Less life-threatening long-term effects as permanent infertility, psychosocial effects and chronic fatigue might affect virtually all Hodgkin-survivors and reduce their quality of life years and decades after treatment[8].

The search for novel, equally effective but less toxic therapies remains a great challenge due to the unique biological and clinical characteristics of the disease. First, only 1-2% of the cells in Hodgkin Lymphoma biopsies consist of malignant Reed-Sternberg-cells and the vast majority encompasses reactive bystander cells and connective tissue[9]. Therefore, *in vitro* testing of novel agents must rely on experiments that are based on Hodgkin-cell cultures, which consist of 100% HL cells and might not reflect the complex *in vivo* tumor biology. The same applies for xenotransplantation-mouse models of HL, in which cultured HL cells are implanted into immunocompromised (mostly SCID-) mice, which do not reflect the complex interplay of HL cells with the bystander cells that are present in human HL[10].

Second, due to the scarcity of malignant cells within the tumors, the isolation and characterization of Hodgkin-cells has only been successful in the past years[11-13]. Unlike in other hematological entities, the discovery of characteristic molecular features, as bcr-abl in chronic myeloid leukemia, that might permit direct targeting the causative principal of the disease, has not yet been successful in HL[14].

Finally, in spite of considerable efforts, the search for clinical and biological prognostic or risk scores that help identifying patients at high risk for primary refractory disease or relapse has been not very successful so far[15-18]. In this article, we will describe the standard treatment of relapsed HL patients from high-dose chemotherapy in first relapse to new drugs being investigated in multiple relapsed patients.

Treatment of relapsed HL

First relapse

Today, high dose chemotherapy (HDCT) followed by APBSCT is the standard therapy for patients with relapsed or refractory HL. The most compelling evidence for the superiority of HDCT compared with conventional-dose salvage therapy in relapsed HL is based on two randomized trials. The first trial, performed by the British National Lymphoma Investigation (BNLI), compared two to three cycles mini-BEAM (BCNU, etoposide, cytosine-arabinoside and melphalan) with BEAM and APBSCT[19].The largest randomized multicenter trial was performed by the German Hodgkin Lymphoma Study Group/European Group for Blood and Marrow Transplantation (GHSG/EBMT) to determine the benefit of HDCT in relapsed HL (HD-R1)[20]. Patients with relapse after polychemotherapy were randomly assigned to either four cycles of conventional chemotherapy (Dexa-BEAM) or two cycles of Dexa-BEAM followed by BEAM-HDCT and APBSCT. The final analysis of 144 evaluable patients revealed that patients with chemo-sensitive disease had a superior outcome as measured by freedom from treatment failure (FFTF) at three years (55% versus 34%) when treated with HDCT compared with the conventional treatment group. Therefore, two cycles of conventional salvage chemotherapy followed by BEAM is considered standard treatment for these patients by the GHSG and most other groups in this field, though a survival benefit has never been shown in these trials.

Salvage therapy in HL

Several studies have been performed with conventional salvage regimens before the administration of HDCT[21,22]. Although response rate (RR) and toxicity profile of salvage chemotherapy are different, detailed analyses comparing various regimens are difficult due to the generally small number of patients and the heterogeneous patient population, i.e. patients with primary progressive and relapsed disease. No randomized trial exists comparing the

effectiveness of different conventional salvage chemotherapies. Due to the lack of randomized studies, the selection of conventional salvage therapy should be based on the potential to induce high response rates with low toxicities allowing the majority of patients to proceed to the final myeloablative regimen.

The most important variables affecting outcome in HDCT studies are time to relapse (late relapse > early relapse > progressive disease), clinical stage at relapse, anemia at relapse, chemosensitivity to conventional salvage chemotherapy and the remission status before HDCT (complete response > partial response > stable disease)[22-27] .

Recent clinical studies demonstrated a clear relationship between chemotherapy dose intensity and tumor response in HL[28]. There are two principal ways to enhance dose intensity. Doses of cytotoxic drugs can be intensified by increasing the individual drug dose, or shortening the interval between treatments, or both. The use of granulocyte colony-stimulating factor (G-CSF) for interval shortening has made this approach feasible. The introduction of accelerated chemotherapy regimens by interval shortening with growth factor support has shown promising results in first-line chemotherapy regimens with HL and Non-Hodgkin lymphoma. Consequently, a time-intensified DHAP (dexamethasone, cisplatinum and high-dose cytarabine) regimen was evaluated as salvage therapy in 102 relapsed or refractory HL patients. Two cycles of DHAP given in short intervals were very effective inducing a CR rate of 21% and an overall response rate (ORR= CR+PR) of 89% while the therapy was well-tolerated with hematological WHO grade 3 and 4 toxicities occurring in only 48% of all courses. Peripheral stem cell harvest was successful in 96% of all patients[29.] This study demonstrated that a brief tumor-reducing program with DHAP supported with G-CSF is a very effective and well-tolerated approach before HDCT in patients with relapsed and refractory HL. As a direct consequence, time-intensified DHAP was implemented into the prospectively randomized HD-R2 study that followed HD-R1.

Besides time-intensification, dose-intensification has also been evaluated to improve responses in relapsed or refractory HL. In recent years, sequential HDCT has been investigated in the treatment of solid tumors, hematologic and lymphoproliferative disorders. Initial results from phase I/II studies indicated that this treatment modality can be safe and effective. Following initial cytoreduction, few non-cross-resistant agents are given at short intervals in accordance with the Norton-Simon hypothesis[30]. In general, APBSCT and the use of growth factors allow the application of the putatively most effective drugs at the highest possible dose at intervals of 1-3 weeks. Sequential HDCT thereby enables the highest possible dosing over a minimum period of time. Since HL is a chemo-sensitive disease, sequential HDCT was evaluated to improve the treatment results of patients with relapsed or refractory HL. In a GHSG phase II pilot study, patients received an initial cytoreduction with time-intensified DHAP and responding patients received sequential HDCT consisting of high-dose cyclophosphamide, high-dose methotrexate plus vincristine and high-dose etoposide followed by BEAM and APBSCT. At 100 days after APBSCT this regimen showed a good CR rate of 72% and after a median follow-up of 30 months an OS of 78%. Remarkably, patients with early and late relapse had similar outcome suggesting that one of the most important prognostic factors in these patients might be overcome with further dose intensification[31]. As a result of this study, the GHSG in cooperation with the European Organization for Research and Treatment of Cancer (EORTC) developed the large intergroup HD-R2 trial in which relapsed HL patients responding to two cycles of DHAP were randomized to receive either BEAM followed by APBSCT or sequential HDCT followed by BEAM and APBSCT.

Sequential single agent high-dose chemotherapy: Final Analysis of the HD-R2 trial

In the intensified experimental arm the mean duration of therapy was significantly higher; furthermore grade 4 world health organization (WHO) toxicities and protocol violations were significantly more frequent. Mortality was nearly identical in both arms (standard vs. intensified 20% vs. 18%) and there was no difference regarding FFTF, PFS and OS. The respective 3-year-rates of the standard vs. intensified arm were FFTF: 71% vs. 65%, PFS: 72 vs. 67% and OS: 87% vs. 80%. Patients with Ann-Arbor stage IV, early or multiple relapse or anemia had a significantly higher risk for another relapse. In conclusion, further dose intensification with sequential HDCT does not improve the results. Therefore, two cycles of DHAP followed by BEAM and APBSCT remains the GHSG standard treatment for patients with relapsed HL.

Treatment of refractory and multiple relapsed HL

About half of these primary progressive or relapsed patients can be successfully salvaged with intensi-

fied high dose chemotherapy combined with autologous stem-cell transplantation[32]. The remaining refractory patients are currently treated with palliative regimens or experimental approaches within clinical trials and generally have very poor overall survival[33]. Patients who experience a second relapse after APBSCT have an estimated overall survival of only three years[34]. Considering the young median age of around 35 years of HL patients, the loss of life expectancy in these patients is high. In the past decade, allogeneic stem cell transplantation for poor prognosis HL patients has become an increasingly used approach. However, no prospectively controlled data on this intervention exist and its use cannot be recommended outside clinical trials. A register analysis from the EBMT, presented at the International Symposium on Hodgkin Lymphoma 2010, reported no survival benefit of transplanted patients as compared to a palliative care strategy. Therefore, in general, single agent chemotherapy should be applied in this palliative situation.

New drugs

Monoclonal antibodies

Since some naked antibodies have been tested in HL without convincing results (e.g. MDX-060, SGN-30), current developments include bispecific antibodies and antibody-drug immunoconjugates. The following section summarizes available data according to the targeted antigen.

CD30

Early studies suggested that anti CD30 antibodies induce apoptosis in cultured HL cells, activate antibody-dependent cellular cytotoxicity (ADCC) and inhibit tumor growth in xenograft models of HL35,[35,36]. However clinical trials with unconjugated monoclonal anti CD30 antibodies were disappointing and showed only moderate activity of the constructs MDX-060 and SGN-30.

MDX-060 was tested in two phase I/II dose escalation trials in 72 patients with relapsed an refractory HL without reaching the maximal tolerable dose (MTD) with only moderate activity and responses in four patients: two complete (CR) and two partial remissions (PR)[37].

SGN-30 was tested in 38 relapsed and refractory patients in a single- und multi-dose phase I/II study without dose limiting toxicities (DLT) without clinical responses and stable disease (SD) in four patients[38]. The low clinical activity of unconjugated anti CD30 antibodies was attributed to binding of soluble CD30 (sCD30), low target affinity of the tested constructs and low affinity for effector-cell Fc Receptors. To enhance target- and effector-cell affinity, two modified anti CD30 antibodies, MDX-1401 and XmAb2513, have been analyzed in vitro with promising results and are currently being tested in phase I/II studies in the USA[39].

Several immunotoxins, consisting of an antigen binding domain and a toxin, have previously been tested in relapsed and refractory HL patients with some activity including a Ricin-A-anti-CD25-, a Ricin-A-anti CD30, a pseudomonas-exotoxin-anti-CD25 and a Saporin-anti CD30-construct[40,41,42]. However, tolerability was limited in these constructs, as the immunoconjugates induced vascular-leak-syndromes in some patients due to toxin effects on non-malignant tissues. SGN-35 is a novel antibody-drug immunoconjugate, which might overcome the limitations of previous constructs by combining an anti CD30 binding domain with the toxin Monomethylauristatin E (MMAE) which is toxic only upon internalization into the target cell[43].

Following a phase I pilot study that showed good tolerability with an overall response rate (ORR) of 54%, SGN-35 is currently evaluated in patients with relapsed CD 30 positive lymphomas. Preliminary data suggest high ORR and comparably low toxicity of the compound[44]. A phase II study published at the ASH-meeting 2010 showed an objective overall response rate of 86% including 53% complete remissions. No other drug has achieved comparable results so far.

CD20

The chimeric anti CD20 antibody rituximab in standard dose (375 mg/m^2 once weekly four times) was tested in a phase II study in 21 patients with relapsed or refractory LPHL without significant adverse events and an ORR of 94% (8 CRs, 6 PRs)[45]. Similar results were reported from an American study in relapsed and refractory LPHL (CR 41%, CR unconfirmed 5% und PR 54%)[46].

In a phase II study in 22 patients with relapsed or refractory classical HL (cHL), the investigators could achieve responses in six patients with six weekly doses of rituximab (375 mg/m^2). In another study, rituximab was combined with gemcitabine with high response rates (48% ORR), although no

control group was included in this study[47]. Interestingly, in both studies patients responded irrespective of CD 20 expression on H-RS (Hodgkin Reed-Sternberg) cells suggesting an indirect effect of rituximab in HL. Rituximab in combination with chemotherapy is currently being evaluated in several randomized clinical trials in LPHL and cHL including the large HD18 trial of the GHSG.

Bispecific constructs

Bispecific constructs simultaneously bind the target cell and an effector cell and specifically activate the anti-tumor immunity. The constructs tested thus far utilized natural killer cells (NK-cells) or monocytes as effector cells. One murine anti-CD30-anti-CD16 construct was tested with good tolerability and some activity alone or in combination with Interleukin-2 (ORR 13% and 25%, respectively)[48,49]. Similar effects were measured with an anti-CD30-anti-CD64 construct. Fourteen relapsed and refractory HL patients treated in this phase I/II study responded to the bispecific antibody without reaching the MTD[50]. Although these two bispecific antibodies have not been developed further clinically, recent experiments using two different novel anti-CD30-IL2-fusion proteins have suggested preclinical in vitro and in vivo activity of these constructs that should be further evaluated in clinical trials[51].

IMIDs

The thalidomide-derivate lenalidomide (Revlimid) belongs to the group of immunomodulatory drugs (IMIDs) and induces apoptosis in malignant cells, exerts anti-angiogenic effects, and activates NK-cell and T-cell mediated anti-tumor immunity[52]. Lenalidomide has been approved for the treatment of Multiple Myeloma and the myelodysplastic syndrome with 5q-syndrome. Lenalidomide has been administered in off-label use and in two ongoing phase II clinical trials in relapsed and refractory HL. Preliminary reports suggest excellent tolerability and responses in up to 33% of the patients[53-55]. As a consequence of these promising results, a phase I/II trial combining lenalidomide with AVD chemotherapy has recently been initiated in elderly HL patients by the German Hodgkin Study Group.

HDAC-Inhibitors/Deacetylase-Inhibitors

Alteration of oncogenes and tumor-suppressor genes by posttranscriptional acetylation and histone modification is a crucial mechanism of cancerogenesis and has been implicated in the loss of B-cell phenotype and cell survival in HRS cells [14,56,57]. In non-malignant cells, there is a balance between histone acetylation and deacetylation mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. In contrast, posttranscriptional hyperacetylation in malignant cells leads to silencing of tumor suppressor genes and aberrant regulation of non-histone proteins including transcription factors and anti-apoptotic proteins. To date, four groups of 18 different HDACs are known, of which group I and II are considered the clinically most relevant[58]. HDACs can be inhibited by several either isotype-selective HDAC inhibitors (inhibition of class I HDACs) or pan-HDAC inhibitors (Inhibition of class I and II) that have shown preclinical activity in HL[57,59]. Several currently recruiting trials are evaluating the safety and efficacy of HDAC inhibitors in HL. Preliminary reports suggest some clinical activity with ORR up to 40%, however, significant adverse effects as fatigue, cytopenia and pericardial effusions have been noted[60,61].

mTOR-inhibitors

The PI3K/AKT1/mTOR pathway is constitutionally activated in H-RS cells through CD30-, CD40-, RTK- and RANK-signaling and inhibition of AKT1/mTOR by various inhibitors cause cell cycle arrest and apoptosis in H-RS cells[62-65]. On this basis, 19 patients with relapsed HL were treated with a fixed dose of the oral mTOR inhibitor everolimus (10mg daily) in a recently published phase II study. Treatment was continued until unacceptable toxicity or disease progression occurred. The investigators reported an impressive ORR of 47% with eight patients achieving a PR and one patient achieving a CR. Notably, four patients remained in remission for at least 12 months[66]. Based on preclinical data that suggest a highly synergistic effect of combining mTOR inhibitors with HDAC inhibitors, a phase I study of everolimus combined with the HDAC inhibitor panobinostat in patients with relapsed lymphomas has been initiated[45].

Conclusions

Although current treatment for HL is effective, there are considerable late toxicities raising concerns even decades after treatment. Moreover, treatment for patients who relapse is insufficient and there is still no curative treatment for patients

who relapse after high-dose chemotherapy and autologous stem-cell support.

Although early in vitro findings on monoclonal antibodies for the therapy of HL have been promising, results from first clinical trials have been disappointing. However, since monoclonal antibodies have relatively little effect as single agents, they might prove to be useful in combination with chemotherapy (e.g. GHSG HD18 study). Recent results on the use of immunotoxins suggest that the severe side effects of earlier constructs can be avoided by using selective toxins. Antibody-drug immunoconjugates as SGN-35 might soon be an established therapeutic option for multiple relapsed HL or could even be implemented into the first line therapy. With increasing knowledge on the molecular pathogenesis of HL there are several novel compounds as mTOR-inhibitors, IMIDs, HSP90-inhibitors and HDAC-inhibitors that have shown to be tolerable and have clinically relevant activity in HL. Future studies should aim for implementing relatively non-toxic experimental drugs into the first line therapy in order to maintain or even increase the high cure rates and to decrease the toxicity of the current treatment for HL patients.

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Myelodysplastic Syndromes

Recent years have seen considerable developments in our understanding of the molecuar basis and pathophysiology of MDS, which are likely to lead to refined classification systems. The interest in these studies has been further enhanced by the availability of drugs that are now approved for the treatment of MDS. This session will cover some of the molecular basis and classifications of MDS, and will review current therapy for MDS with non-transplant and transplant strategies. New data indicate that the clonal karyotype may have more profound effects on outcome, both with transplant and non-transplant therapy, than the marrow myeloblast count. Insights at the molecular level, showing chromosomal instability including uniparental disomy even in patients without cytogenetic abnormalities as determined by conventional methodology are likely to identify additional, more narrowly defined subgroups of patients, and may influence the selection of therapy. Novel chemotherapeutic approaches with single agents or combinations, as well as vaccines and other immunotherapies are yielding some promising results. Hematopoietic cell transplantation, currently the only modality with proven curative potential, has undergone major changes in the form of reduced/low intensity conditioning regimens and graft manipulation, allowing to carry out transplants, at least in subpopulations of patients, even in the seventh or eighth decade of life. Thus, this session should update the audience on the state of the art of diagnosis, classification, pathophysiology, and therapy of MDS.

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Old and New Diagnostic Approaches to MDS

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Since decades, the diagnosis of myelodysplastic syndromes (MDS) is based on cytomorphological features as investigated by smears and histopathology. Several techniques have to be applied in parallel: MGG staining, myeloperoxidase reaction, non-specific esterase, and iron staining. In addition, PAS is recommended in some cases [1]. With respect to histopathology, several further aspects including also immunohistology staining using CD34 and other markers is useful.

The detection of blasts in MDS is based on the peripheral blood and the bone marrow in parallel and a backbone for classification systems such as FAB, IPSS or the new and recent WHO classification[2,3,4].

Due to several well-known aspects, the evaluation of blast percentages and even more the grading of dysgranulopoiesis, dyserythropoiesis or dysmegakaryopoiesis (for MDS at least 10% of cells have to be dysplastic to be called “dysplasia”) these methods have problems with respect to sensitivity and specificity. This is also not better using histomorphology, which for example has difficulties to detect ring sideroblasts.

It is therefore unquestionable that the diagnosis of MDS should be done by experienced pathologists and/or hematologists. Even if so, the sensitivity and specificity are far away from 100% and in many cases of suspected or early MDS another biopsy should be recommended 3 months later after all other reasons have been excluded.

In addition to cytomorphology and histopathology, chromosome banding analysis, accompanied by FISH, has a major important impact for the diagnosis and especially for prognostication in MDS. This is at least true, since the IPSS was published[3]. It is recommended that in all suspicious cases of MDS

or AML, a bone-marrow biopsy including heparin syringe is done to perform chromosome banding analysis. As new drugs have been developed over the last years, especially 5q- should be investigated. If this is not possible by chromosome banding analysis, FISH on interphase cells may help to circumvent this missing information. International guidelines have been published to organize chromosome banding analysis for MDS and give some hints, how to handle cases with suboptimal chromosome banding quality or no bone marrow taken[5]. It has to be stated that the investigation of peripheral blood alone for cytogenetics normally is not recommended because it is not possible to harvest metaphases if in the peripheral blood only non-dividing cells are present.

Since some years, immunophenotyping (flow cytometry) is also used in MDS: 1. to count the blasts and compare these results to morphology; 2. to investigate dysplasia on the different cell lineages by specific aberrant expressions of antibodies. In the last years, several papers recommended these approaches, give some guidelines[6] and will be expanded in the near future using up to 10 colours in parallel.

More and more molecular studies are introduced for the diagnosis of MDS as well as for prognostication and even for minimal residual disease screening, for example after transplantation. Several markers such as *RUNX1*, *NRAS*, *MLL*-PTD, *FLT3*, even *NPM1* have been published to be mutated in MDS. This is also true for new markers that have been found as key players in MDS and AML during the last 2 years such as *TET2, EZH2, ASXL1, CBL, P53, JAK2, IDH1, IDH2* and *DNMT3A*. Even if this list of genes is not compete, it clearly demonstrates that there's a lot of work to be done to test all of these genes in patients with MDS, to better demonstrate their incidence, their diagnostic and prognostic importance. Several studies are ongoing and have been published recently to investigate these genes for patients with especially early MDS or to better demonstrate the risk of transformation into AML as today has been described by the IPSS.

Even gene-expression profiling can help to discriminate high-risk and low-risk MDS patients and can provide prognostic information that is independent of other markers that are included in the IPSS[7].

In conclusion, the diagnosis of MDS is still based on cytomorphology, histopathology and cytogenetics by chromosome banding analysis, accompanied by FISH. Newer techniques can also be applied such as immunophenotyping or molecular methods investigating several genes of interest. The next few years will demonstrate how important this comprehensive scenario for the diagnosis of MDS will be and they will also clearly show how targeted treatment approaches can be used for subentities. As the inclusion of such new diagnostic tools will change the treatment strategies in MDS, we are today entering a fascinating era from diagnosis to treatment in MDS patients.

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Current non-Transplant Treatment Approaches for Patients with Myelodysplastic Syndromes (MDS)

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Abstract

The term myelodysplastic syndromes (MDS) summarizes a range of different stem-cell disorders, which are clinically characterized by ineffective hematopoiesis and peripheral cytopenia. The heterogeneity is reflected not only by the variety of hematological manifestations, but also by the great differences in survival and incidences of acute myeloid leukemia between individual patients. Whereas some patients succumb to complications of bone marrow failure or leukemia development within a few months of diagnosis, others show a relatively stable course and may survive for many years. Therefore, the time point and choice of treatment should be based on a reliable risk stratification. Because MDS are a disease of the elderly population, there are potential risks from intensive treatment approaches. In fact, new treatments such as immunomodulatory and epigenetic agents are becoming increasingly available and already have improved patient outcome.

Introduction

The International Prognostic Scoring System (IPSS) is still the most widely accepted tool for estimating the prognosis of untreated patients with MDS (Greenberg *et al*, 1997). Patients with IPSS Low or INT-1 are usually defined as "low-risk" MDS, and subject to therapy aiming at relieve of anemia or cytopenia and improve quality of life. Recent epidemiological data indicate that the presence of red blood cell transfusion need is associated with a poorer prognosis, irrespective of other risk factors (Malcovati *et al*, 2005). These patients are eligible for receiving iron chelation therapy in order to prevent

toxicity from severe iron overload. Several other therapeutic modalities for patients with MDS have been developed over the past few years. Immunomodulatory drugs like lenalidomide are a valuable option especially in patients with a deletion on the long arm of chromosome 5 (del5q). In contrast, in patients with advanced disease (e.g. IPSS INT-2/ High), drugs which might alter the disease course are needed. For example, azacitidine treatment prolongs overall survival compared to conventional treatment approaches (Fenaux *et al*, 2009). Still, with the rare exception of patients who achieve long lasting remissions with induction chemotherapy, allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only modality with proven curative potential (Deeg, 2005). This short review will focus on the current developments in the treatment modalities of patients with MDS.

Erythopoetin-stimulating agents (ESA)

Treatment with ESA as single therapy may induce erythroid responses in around of 25% of unselected patients with low-risk MDS, and the addition of G-CSF may increase this response rate especially in patients with RARS (Park *et al*, 2008;Hellstrom-Lindberg, 2003). Therefore, ESA± addition of G-CSF is considered a first line treatment for patients with MDS and anemia, provided they show pretreatment variables predicting for a response to treatment (Hellstrom-Lindberg *et al*, 2003). These include a low (<500 U/l) endogenous EPO-level as well as low transfusion burden. When selecting patients according to this model, response rate can be easily predicted thus omitting unnecessary treatment to patients. The median duration of a response to ESA +/- G-CSF is around 24 months and this should be used as a comparison, when evaluating the effect of new treatments for the anemia of MDS. Although a plenty of trials including phase III studies have been performed with ESAs and the fact that they are widely used and accepted in the medical community, still, no specific ESA is currently licensed for the treatment of MDS. In fact, prospective trials are currently in preparation including combination studies with new compounds in order to further improve responses.

Immunomodulatory drugs

The classification by the World Health Organization (WHO) allows distinction between pure refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) and RA / RARS with multi-lineage dysplasia. Moreover, it transfers patients with an isolated deletion of 5q and <5% blasts, into a separate category. This definition has proven extremely valuable, since the genetic defect(s) of low-risk MDS patients with del(5q) may constitute a target for biological therapy. In fact, lenalidomide, one of the new immunomodulating oral drugs (IMIDS) is a thalidomide structural analogue, and has been shown in several clinical trials to induce major erythroid responses in about two thirds of patients with low-risk MDS and del(5q) including cytogenetic responses to treatment (List *et al*, 2006). Still, lenalidomide is not licensed in the EU due to some concerns of induction of disease progression by the drug itself, which does not seem to be drug-related but a result of the great clinical heterogeneity of del(5q) MDS. Retrospective data further do not suggest that the intrinsic rate of AML progression of about 20% might be increased by lenalidomide in del(5q) MDS (Germing *et al*, 2009). Therefore, lenalidomide is at present investigated in a series of follow-up studies to establish its role in MDS with del(5q).

Further, a large phase II study, MDS-002 for patients with non-del(5q)- low-risk MDS, has been demonstrated activity including induction of transfusion independence in almost one third of patients with a median duration of response of 43 weeks (Raza *et al*, 2008), which is considerable lower than in the MDS del(5q) group. There is an ongoing phase III trial in transfusion dependent non-(del5q) MDS with the aim to establish the drug as standard of care in this indication. To conclude, lenalidomide is a remarkably effective drug especially for a biologically relatively well defined subset of MDS patients, and will play an important role in the future management of MDS.

Other drugs which target dysregulated immune responses in MDS include ATG (Sloand *et al*, 2008) and the anti-CD52 antibody Campath. The latter has recently shown impressive response rates in a well-defined subgroup of MDS, which included cytogenetic remissions as well (Sloand *et al*, 2010). Further studies need to establish the role of immunosuppressive therapy in the management of MDS.

Epigenetic treatment

In the treatment of patients with advanced MDS, it has become increasingly clear that intensive treatment strategies are not ideal for the elderly patient population suffering from significant comorbidities. Additionally, a significant proportion of those patients will also have adverse karyotypic abnormalities that have a negative impact on the ability to

achieve complete remission with intensive treatment strategies. Previously, such patients would have been treated with low-dose chemotherapy, including cytarabine, melphalan and others, or with supportive care only. Now, two compounds (azacitidine and decitabine) belonging to the group of DNA-methyl transferase inhibitors have entered the clinic. One main mechanism of action of both drugs is epigenetic. Epigenetic changes are not mutations or deletions, but rather reductions or increases of the expression of certain functionally normal genes. This is usually regulated in two ways. In promoter regions of genes, cytosine residues are regularly bound to guanine bases through phosphorylation. The region is referred to as CpG island. Genes are "silenced" by the methylation of cytosine residues in the promoter regions of genes. The second way of reducing gene expression is by deacetylation of lysine residues in histone proteins. The DNA is wrapped around those histones, and only if the histones are acetylated can the DNA be read. Methylated promoters recruit histone deacetylases (HDAC) within transcriptional inhibitory complexes and further reduce gene expression. Hypermethylation of certain tumor-suppressor genes has been shown especially in advanced MDS, which makes a targeted epigenetic therapy desirable. Indeed, azacitidine and decitabine bind the DNA methyltransferases (DNMT) in an irreversible way. This leads to functional depletion of DNMTs and to a reversal of hypermethylation after several cell divisions.

A controlled, randomized, international, prospective, multicenter, phase III study of azacitidine was performed in Europe (Fenaux *et al*, 2009). 5-Azacitidine was administered at 75 mg/m^2 per day for 7 consecutive days every month. The control arm treatment included best supportive care only, low-dose cytarabine, or conventional AML induction chemotherapy. 358 patients, median age 69 years, with intermediate-2 or high-risk MDS according to IPSS were randomized. After a median follow-up of 21.1 months, median overall survival was 24.5 months for the azacitidine group versus 15 months for patients in the conventional care groups (p=0.0001). A subgroup analysis was performed on the three different conventional care regimens: 105 patients had received best supportive care, 49 received low-dose cytarabine, and 25 received intensive chemotherapy. Azacitidine showed a similar prolongation of the median overall survival in all three subgroups. This prolongation was statistically significant for the comparison to best supportive care (9.6 months, p= 0.0045) and low-dose cytarabine (9.2 months, p= 0.0006). The patient numbers were too small in the comparison to intensive chemotherapy to show an effect. Overall, the study lead to the approval of azacitidine in MDS in the EU.

Decitabine has also been shown to be an active drug in high-risk MDS with response rates almost comparable to that of azacitidine. However, it failed to show an improvement in overall survival compared to supportive care only in a randomized trial (Wijermans *et al*, 2008). There might be several reasons for this observation including the different patient characteristics (older age, more advanced disease) and the lower number of cycles administered to the patients compared to the azacitidine trial. Currently, the drug has not been licensed by the EMEA. Therefore, in the EU azacitidine has become the new standard of care in the treatment of advanced MDS. There are ongoing trials comparing both drugs directly or investigating a combination with HDAC-inhibitors in order to improve response rates.

Conclusions

With the availability of disease-specific drugs the therapeutic armamentarium for our patients suffering from MDS will hopefully further increase. This will result in a need for clinical and molecular markers in order to better predict response to treatment. Therefore, eligible patients should enter clinical trials in order to improve our understanding of the heterogeneous disease complex called "MDS".

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Current State of Hematopoietic Stem Cell Transplantation for MDS

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Introduction

Myelodysplastic syndrome (MDS) comprises a spectrum of clonal disorders of hematopoiesis. Typically, patients present with anemia or other cytopenias, but prognosis varies. About one-third of patients will progress to acute myeloid leukemia (AML). The remaining patients show progressive peripheral blood cytopenias and may succumb to intervening infections or hemorrhage.

Treatment decisions will depend upon disease presentation, patient age and condition. The only currently available treatment modality with proven curative potential is hematopoietic cell transplantation (HCT); long term survival ranges from 25%-70%[1,2]. However, there is a lack of controlled trials, and there is significant selection bias based on age, comorbid condition and possibly other factors.The fact that the median age at the time of diagnosis is in the early 70s prevented many of these patients from being considered for HCT until quite recently. The progressive modification of conditioning regimens to prepare patients for HCT over the past decade now allows to offer HCT to a growing number of older patients. The more recent inclusion of haploidentical donors and the use of cord blood has overcome some of the limitations of donor availability. However, even with these approaches, not all patients are transplant candidates.

Who should be considered for allogeneic HCT?

Age has been a major factor when deciding about allogeneic HCT, and younger patients are likely to be considered for HCT sooner and more liberally. A recent report on 2728 patients with MDS showed that 42% of those less than 50 years of age underwent HCT, but only 8% of older patients[3].

The International Prognostic Scoring System (IPSS) serves as a guide for decision making regarding HCT. A retrospective registry-based analysis by Cutler et al. suggested that patients in risk categories high or intermediate-2 who had an HLA matched sibling donor had the best prognosis if transplanted early in the course[4]. A more conservative approach appeared to be advantageous in patients in categories intermediate-1 or low. However, patient age and factors such as marrow fibrosis or transfusion dependence[4,5] and additional factors also affect prognosis[5,6]. Patient age, time from diagnosis to HCT , year of transplant, disease stage, source of stem cells, donor type, conditioning intensity, and the WHO Prognostic Scoring System (WPSS) were shown to provide an independent prognostic criterion for overall survival (OS) and relapse[7]. In one report on 89 MDS patients transplanted from 2002 to 2008, the 3-year OS was 79%, 49% and 27%, respectively, for patients with WPSS low-intermediate, high, and very high-risk categories, respectively[8].

In patients less than 18 years of age, relapse-free survival (RFS) of 65%, 48% and 28%, respectively, has been reported for refractory cytopenias with mulltilineage dysplasia (RCMD), RAEB and RAEB-t[9], consistent with the pattern seen in older patients. The timing of HCT remains controversial[10]. In a series of 374 patients with low-risk MDS (median age 39 years), the 4-year OS was 52%[11], without a significant difference between HLA-identical sibling and matched URD transplants; survival was superior and treatment-related mortality (TRM) was lower among patients transplanted early after diagnosis[11]. Similar data have been reported by the European Blood and Marrow Transplantation (EBMT) Group in an analysis of 692 patients with MDS. The OS and relapse rates were 47% and 34% for good risk, 40% and 35% for intermediate risk, and 31% and 57% for high-risk cytogenetics, respectively[12].

The use of flow cytometric scoring has shown a correlation between the severity of flow-cytometric aberrancies and the probability of relapse after HSCT[13].

Age and medical co-morbidities

Several recent studies have shown that older age per se is not a contra-indication to HSCT[14]. TRM rates were similar in patients 50-60 years old and in those older than 60 years (4-year estimates: 36% *versus* 39%). A similar analysis was preseented using CIBMTR data[15]. The HCT-specific co-morbidity

index (HCT-CI) has been useful in stratifying patients for different conditioning regimens of various intensities[16-20]. An additional recently identified factor that appears to be associated with inferior OS after HCT is iron overload, related to infections and organ toxicity[21-28].

Pre-transplant and post-HCT therapy

Numerous studies have examined the impact of induction chemotherapy prior to allogeneic HCT on HCT outcome. The role is not clear[29-32]. The question pertains not only to classic induction chemotherapy, but also hypomethylating agents[33,34]. Nevertheless, hypomethylating agents may be useful in stabilizing the disease without adding TRM. While controversial, the best time point for HCT might be when patients have achieved "best response"[35]. The DNA methyltransferase inhibitors may also have a role after HCT to prevent relapse in high-risk patients or to treat early relapse[36-38]. Preemptive donor lymphocyte infusion (DLI) may also improve transplant outcomes in high-risk MDS by decreasing relapse rates[39-41].

Alternative donor transplants

HLA matched related donors are available in only 25% to 30% of patients, and URDs are identified for less than 10% to maybe 60% of patients, dependent upon patient ethnicity. Recent studies show that the use of cord blood or, possibly, HLA haploidentical donors are successful in a considerable proportion of patients, and these stem cell sources are availble for the vast majoriy of patients[42-51].

Bone marrow versus peripheral blood grafts

The results of various studies indicate a superior HCT outcome, particularly in high-risk patients, when peripheral blood progenitor cells are used as a source of stem cells[52,53]. The use of PBPC has been associated with faster engraftment, lower TRM, increased chronic GVHD rates, and lower relapse rates[54]. However, the results of a randomized study of URDs are still pending.

High intensity versus reduced intensity conditioning

Controversy surrounds the choice of conditioning regimens. Basically all published studies contain a bias in regards to patient selection for one as compared to another regimen. Generally, older individuals or patients with co-morbid conditions have been prepared with lower intensity regimens, while younger patients and otherwise healthy individuals have typically received high-dose conditioning. A randomized trial comparing RIC with high-dose conditioning is currently getting underway in the USA.

In view of the fact that relapse has remained a major post-HCT problem in high-risk patients, the current approach generally is to give the highest dose intensity that a patient is expected to tolerate.

Outlook

Immunologic and pharmacologic manipulations after HCT may reduce relapse rates. The growing pool of URDs, and the use of alternative stem cell sources (cord blood and HLA haploidentical donors) will expand the use of allogeneic HCT for MDS, and it is likely that an increasing number of patients with MDS will be transplanted.

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Infections

Welcome to the Session on Infections. Infections are major obstacles in our efforts to cure patients with leukemia lymphoma and myeloma. In this session we will give update overviews on viral, fungal and bacterial infections in these patients. We are privileged to have Prof. Catherine Cordonnier and Prof. Per Ljungman with us; both are very well known worldwide as experts and leaders in these fields. Prof. Per Ljungman, from Karolinska University Hospital, Stockholm, Sweden, will talk about: Viruses – The invisible enemies. Prof. Catherine Cordonnier from Henri Mondor University Hospital, Créteil, France, will talk about: Fungi – The good, the bad and the ugly. I will talk about: Bacteria - The threat of superbugs.

Enjoy the session!

Dan Engelhard, MD

Per Ljungman, MD

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Work address: Hematology Center, Karolinska University Hospital, SE-14186 Stockholm

A. Professional preparation

M.D (Karolinska Institutet, Stockholm 1975)
Ph.D (Virology, Karolinska Institutet, Stockholm 1985).
Postdoc and fellow in Infectious Diseases, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA 1986-87.
Board certified in Internal Medicine (1985) and Hematology (1988), Sweden.

B. Appointments

Adjunct professor of Hematology (2000-2009), Guest professor of Hematology (2010-), Karolinska Institutet, Stockholm, Sweden

C. Current positions

Director, Dept. of Hematology, Karolinska University Hospital, Stockholm, Sweden (2004-)

D. Scientific activities

Tutorships:

PhD students Main tutor (5) and assistant tutor (4) for graduated PhD students at Karolinska Institutet

Ongoing tutorships Main tutor for three current PhD students

Other Visiting Professor, Dept. of Haematology, University College London, London, UK (1998-2004)
Visiting Professor, University of Amsterdam, the Netherlands, 2006
Director, Dept of Hematology, Huddinge University Hospital 1998-2004

E. International activities

Elected positions

Board member and chairman Infectious Diseases Working Party, European Group for Blood and Marrow Transplantation (EBMT) 1992-1998
Chairman, Registry Subcommitte, EBMT 1998-2004
Secretary, European Group for Bone Marrow Transplantation (EBMT) 2004-2010
Council member, International Immunocompromised Host Society 2000-2004
Vice president, International Immunocompromised Host Society 2004-2006
President elect, International Immunocompromised Host Society 2006-2008
President, International Immunocompromised Host Society 2008-2010
Past President, International Immunocompromised Host Society 2010-
Swedish representative, JACIE 2005-
Scientific advisor, Swedish Medical Products Agency, 2000-
Alternate member, European Medicines Agency Committee on Advanced Therapy (CAT) 2009-

Congress planning activities

Member Program Committee ICAAC 2003-2008
General Secretary, 18th Meeting of the European Group for Blood and Marrow Transplantation, Stockholm 1992.
President 5th International Cytomegalovirus Conference Stockholm 1995
Member scientific committee, 3d, 4th, 6th, 7th, 8th , 9th, 10th, 13th International Cytomegalovirus conferences.
General Secretary, 14th meeting International Society of Hematology, European and African Division, Stockholm 1997
Chairman, Local Scientific committee, 10th European Congress of Microbiology and Infectious Diseases (ECCMID). Stockholm 2000.
President 2nd World Conference on Transplant Infectious Diseases, Stockholm 2000
Member, Organizing committee, European Hematology Association Meeting, Stockholm, 2005.
Chair, scientific committee, EBMT Göteborg 2009

Other activities

Chair, Workpackage 15, supportive care, European Leukemia Net (EU Network of Excellence) 2003-2010
Chairman, committee on vaccinations, Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective 2007-2009
Chairman, writing group on Infectious Society of America guidelines for vaccination of stem cell transplant recipients, 2008-2011.
Invited lectures (partial list): American Society for Hematology (educational program), Infectious Diseases Society of America (IDSA), International Society for Infectious Diseases, European Hematology Association, European Conference for Clinical Microbiology and Infectious Diseases (ECCMID), EBMT, International Immunocompromised Host Society, International Herpesvirus Workshop, International Society for Hematology, Japanese Society for Blood and Marrow Transplantation, Spanish Society for Hematology, Belgian Society for Hematology, British Society for Hematology, Turkish Society for Hematology, South African Society for Hematology and Oncology, Harvard, University of Washington, CDC Atlanta, Georgia Medical College, Wayne State University, MD Anderson Cancer Center, University of Tübingen, Free University of Amsterdam, University of Florens, Charité,

F. Editorships
Co-editor – Transplant infections from Lippincott-Raven Publishers 1998, 2003, 2010
Section Editor – Clinical Bone Marrow and Stem Cell Transplantation, Cambridge publications 2003
Co-Editor, Bone Marrow Transplantation, 2005-
Member Editorial Boards for Transplant Infectious Disease, Haematologica, Antiviral research, JID.
G. Publications
Author of >290 peer reviewed papers in international journals. In addition, the author of several reviews and book chapters.
H. Clinical Trial activities
Swedish and international PI for several prospective clinical trials.
Member of several advisory boards for drugs in development
Chair and member of several DSMB for clinical trials.
Chair Clinical Trials Center, Huddinge University Hospital 2002-2004
Deputy Chair, Clinical Trials Center, Karolinska University Hospital 2004-2006

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Education

University Paris 12 Créteil, France.

Current academic position

Professor in Hematology, University Paris 12.

Current position

Hematology Department, Head, Director of the allogeneic stem cell transplant program.
Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris and Université Paris 12, Créteil, 94000 France

Last ICH-GCP training

February 5th, 2010

Principal areas of interest

Acute leukaemia, Stem cell transplant, Infectious complications in hematologic diseases.

Teaching experience

Teaching Hematology at the Université Paris XII since 1981.
Teaching Hematology, Stem cell transplant, and Infections in Onco-Hematology in International Training Courses.

Ongoing or recent other activities

Chairperson of the Infectious Diseases Working Party of the EBMT (1998-2004)
Member of the Advisory Scientific Committee of ESCMID (European Society of Clinical Microbiology and Infectious Diseases): 2004-2007
Chairperson of the European Conference on Infections in Leukemia (2005-)
Member of the Editorial board of *Bone Marrow Transplantation*
Participation in the Vaccination working group, and cochair of the "Rare infections" working group of the CDC initiative for guidelines in the prophylaxis of infections in HCT.

Ten recent publications

Considering pharmacodynamics and pharmacokinetics of antibacterials for optimizing the management of febrile neutropenia. O Lortholary, A Lefort, M Tod, AM Chomat, C Cordonnier. *Lancet Infectious Diseases*, 2008 ; 8 (10) ; 612-20.

Galactomannan antigenemia serum levels depends on neutrophil counts in haematological patients with invasive aspergillosis. C Cordonnier, F Botterel , R Ben Amor, et al. *Clinical Microbiology and Infection*, 2009 Jan;15(1):81-6.

Empiric versus pre-emptive antifungal therapy for high-risk febrile neutropenia: The PREVERT trial. C Cordonnier, C Pautas, S Maury, et al. *Clin Infect Dis* 2009, 48, 1042-1051.

Regionally limited or rare infections : prevention after hematopoietic cell transplantation. J Gea-Banacloche, H Masur, C Arns da Cuhna, T Chiller, L Kirchoff, P Shaw, M Tomblyn, C Cordonnier *Bone Marrow Transplant* 2009,44 :489-94.

The epidemiology of *S pneumoniae* infections in hematology and stem cell transplant patients: Are these strains covered by the available anti-pneumococcal vaccines in France? K Debbache, E Varon, Y Hicheri, P Legrand, JL Donay, P Ribaud, C Cordonnier *Clinical Microbiology and Infection* 2009, 15: 865-8.

Randomised Study of Early Versus Late Immunisation with Pneumococcal Conjugate Vaccine after Allogeneic Stem Cell Transplantation. C Cordonnier, M Labopin,V Chesnel et al. *Clin Infect Dis* 2009 ; 48 : 1392-401.

Immune Response to the 23-Valent Polysaccharide Pneumococcal Vaccine after the 7-Valent Conjugate Vaccine in Allogeneic Stem Cell Transplant Recipients: Results from the EBMT IDWP01 Trial C Cordonnier, M Labopin,V Chesnel et al. *Vaccine*, 2010 : 28 (15) : 2730-34.

A retrospective series of gut aspergillosis in hematology patients. E Kazan, JMaertens, R Herbrecht, M Weisser, B Gachot, A Vekhoff, D Caillot, E Raffoux, T Fagot, O Reman, Francoise Isnard , A Thiebaut, S Bretagne, C Cordonnier *Clin Microbiol Infect 2010,* Epub ahead of print

Updated guidelines for managing fungal diseases in hematology patients. Y. Hicheri, A. Toma, S. Maury, C. Pautas, H. Mallek-Kaci, C. Cordonnier *Expert Review on Anti-infective Therapy*, 2010 Sep;8(9):1049-60.

Voriconazole for Secondary Prophylaxis of Invasive Fungal Infection in Allogeneic Stem Cell Transplant Recipients: Results of the VOSIFI Study. C Cordonnier, M Rovira, J Maertens, et al. *Haematologica,* 2010 Jul 15. [Epub ahead of print].

Fungal Diseases in Hematology Patients: The Good, The Bad, and The Ugly

Catherine Cordonnier

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Two decades ago, fungal disease was seen as an additional fatality in the course of hematological diseases. It is now an increasing complication, but with a better understanding of risk factors, new options for early diagnosis, and an antifungal armamentarium which, taken altogether, allows to cure a significant number of patients. Among the most common fungi encountered in this setting, there is a good, a bad and an ugly. The good was – but is likely no anymore – candida, since during a long time, yeasts infections have been considered to be at better prognosis than the mold infections. The bad is aspergillus with its poor prognosis. The ugly is zygomycosis, which may be extremely and quickly invasive, which is difficult to early recognize due to the lack of specific indirect marker, and for which the list of active antifungals is limited.

Many risk factors, such as the duration and depth of neutropenia, or steroid administration, are common for yeasts and mold infections. However, each has specific risk factors, such as central venous line for candidemia, or environment for aspergillus infection[1]. Recent guidelines, both from the Northamerican, and European side, help us in the therapeutic options[2-5]. However, a lot remains to be done so that the impact of fungal disease on the course of hematological diseases could be reduced.

Candidemia And Other Invasive Candidiasis

Candidemia and other invasive candidiasis become less and less frequent in the hematology ward, as illustrated by the more recent prospective trials on candidemia, where most of the patients are recruited in the ICU rather than in the hematology ward[6-8]. However, a significant number of patients still develop candidemia in the course of hematologic malignancies or stem cell transplantation (SCT). The epidemiology of candida infections in hematology and cancer centers progressively changed over time, with a shift to less *Candida albicans*, and consequently less fluconazole-susceptible strains. However, despite this shift observed in many centers, fluconazole is the only antifungal which was shown to provide a long-term survival benefit in allogeneic stem cell transplantation[9]. Blood cultures are poorly sensitive and rarely early positive in candidemia, even in severe clinical presentations. The use of mannan and antimannans has been recently reviewed, but most of the data come from the ICU area, with still few experience in hematology. First line treatment, either with candins or liposomal amphotericin B, should be re-adapted according to the identification of the candida and its susceptibility pattern, as soon and often as possible. In candidemia, there is a consensus to continue antifungal treatment for at least 14 days after the last positive blood culture, as far as there is no deep localization which could deserve longer therapy[2].

Aspergillosis

Aspergillosis is nowadays the most common fungal disease in the hematology ward, mainly in acute myeloid leukemia patients, and recipients of allogeneic SCT[10-11]. However, the recent data of the US through Transnet show a center effect with various incidences according to the type of SCT, also to the center[12]. Many factors, including geographic and environmental factors , but also genetic predisposition[13] may impact on the natural incidence of aspergillosis. Therefore, we may expect that the benefit of primary prophylaxis such as posaconazole[14,15] or voriconazole[16] may have a different practical impact according to the local epidemiology: important in centers with a high incidence, debatable in other ones.

The prognosis of aspergillus infection has been considerably improved during the last decade. However, measuring the efficacy and survival 3 months after the diagnosis of aspergillus infection may be not enough to really assess the impact of such an event in the course of leukemia or transplant. We have recently shown that even though the patient had an initial favorable outcome after aspergillosis, this event indirectly impacts the long-term outcome by changing the doses or timing of chemotherapy[17]. It may also lead to changing a my-

eloablative regimen to a reduced intensity one in a transplant project, and this may also impact the final outcome. Efforts to determine the best strategy or combination of strategies, among antifungal prophylaxis, preemptive or empirical treatment, should be pursued to avoid overt disease[18-20].

Zygomycosis

In Europe, zygomycosis is the second cause of mold disease in hematology patients. Although it remains rare when compared to aspergillosis, the incidence has been regularly growing over the last 20 years[10, 21]. The disease mostly affects acute myeloid leukemia patients or allogeneic SCT, although the increasing number of successive therapeutic lines in lymphoproliferative disorders create deep immunodepression sometimes close to the one observed after SCT. The prevalent localization of zygomycosis is the lung in 35 to 55% of the cases, followed by sinusitis, and in the more severe cases, a possible extension from sinuses to the bones and the brain. The lung presentation of zygomycosis is extremely close to the one of aspergillosis, but the galactomannan test is here negative[22]. Endoscopic bronchoscopy and mainly lung or sinus biopsies should be promptly done since the disease can progress very quickly to deep extension. As this is a very rare disease, there is sofar no prospective study helping us to choose the best therapeutic options for zygomycosis. However, from retrospective studies, and in vitro spectrum of the different antifungals, there is a general consensus to consider that liposomal amphotericin B is probably the best option, followed by posaconazole[21]. However, in many cases, antifungals and surgical removal of the fungal burden, as any way to improve the immune status of the patient, should be combined, and surgery has often to be performed early in case of extensive sinusitis in order to avoid unreversible deep extension.

The increasing number of SCT performed worldwide, due to an increasing number of alternative donors and cord-blood transplant, the routine practice of reduced intensity conditioning leading for transplanting older patients, the availability of new immunesuppressive drugs are many factors explaining an increasing concern about fungal disease in hematology. Efforts, and prospective trials raising important questions about the management of such complications should be encouraged.

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Dan Engelhard, MD.

Prof. Dan Engelhard heads the Department of Pediatrics and the Pediatric Infectious Diseases & AIDS at the Hadassah-Hebrew University Hospital in Ein Kerem, Jerusalem, where he also holds the Clara & Seymour Smoller Chair in Pediatrics. Prof. Engelhard is an expert in pediatrics and infectious diseases and his main interests are infections in the immuno-compromised host. He has been active in a variety of international societies and in preparation of international guidelines for preventions and management of infections in leukemia patients and recipients of haematopoietic stem cell transplantation.

The Threat of Superbugs

Dan Engelhard

Hadassah University Hospital, Jerusalem, Israel

Bacterial pathogens are a major threat to patients with malignancies especially those hospitalized with neutropenia following chemotherapy or haematopoietic stem cell transplantation (HSCT), and to patients with prolonged hospitalization, especially those with co-morbidities such as graft-vs.-host disease (GVHD).

Since the critical role of bacterial pathogens in the outcome of the patients was recognized 50 years ago, an empiric antimicrobial therapy for febrile neutropenia became a standard approach, dramatically improving the outcome of bacteremic patients during the neutropenic period.

With the extensive use of prophylactic antibiotics, empiric antibiotic therapy and antibiotic treatment for documented infections, increasing resistance to antimicrobial agents has developed over the years. The frequency of extended-spectrum beta-lactamase (ESBL) producers in enterobacteriaceae isolated from blood cultures of patients with malignant diseases and those following HSCT has been steadily rising, from 2 percent in the early 1990s to 25 to over 40 percent of all enterobacteriacea today[1-6].

ESBLs are beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side-chain. These cephalosporins include cefotaxime, ceftriaxone and ceftazidime, as well as the oxyimino-monobactam aztreonam. Carbapenems are, therefore, the treatment of choice for serious infections due to ESBL-producing organisms.

Use of carbapenems has, however, led to the emergence of carbapenem-resistant bacteria, the so-called 'superbugs', such as *Klebsiella pneumoniae* carbapenemase (KPC)-producing organisms and the emerging and spreading New Delhi metallo-be-

ta-lactamase (NDM-1)-producing *Escherichia coli*[7]. Significantly increased mortality associated with infections with carbapenem-resistant pathogens has been reported[8-10].

Pseudomonas aeruginosa is another significant pathogen that is frequently resistant to antibiotics: 25 to 72 percent of isolates is reported to be resistant to quinolones, up to 50 percent is resistant to third-generation cephalosporines, up to 30 percent to piperacillin-tazobactam and 8 to 44 percent are resistant to carbapenem[1,6,11-13]. Twenty-five to 60 percent of *Pseudomonas aeruginosa* isolates are multi-drug resistant (MDR) — that is, they are resistant to three or more classes of anti-pseudomonas drugs (4, 6, 13-15).

Increased mortality associated with infection due to MDR *Pseudomonas aeruginosa* has been reported[13]. Another extremely problematic carbapenem-resistant gram-negative rod is *Stenotrophomonas maltophilia*[16]. Treatment options for the carbapenem-resistant gram-negative rods include colistin and tigecycline.

Increasing resistance to antibiotics is ongoing process in gram-positive bacteria, as well. Ampicillin resistance in enterococci is one example[6, 17]. There is also increasing resistance to vancomycin among enterococci[6,17-19]. Five to 50 percent of HSCT patients are colonized with vancomycin-resistant enterococci (VRE), usually *E. faecium*, many of them developing infection from this pathogen[20-25]. VRE bloodstream infection serves as a marker of severely ill patients with poor prognoses, as it is associated with high mortality rate[22].

Knowledge of local resistance patterns is essential for providing the best and most appropriate empirical antibiotic treatment. Strenuous efforts should also be made to control the burgeoning emergence of resistance to antibiotics.

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Indolent Lymphomas

Dear colleagues,

I would like to welcome you to this session on low grade lymphoma We are most fortunate that my inability to understand simple instructions from the organisers has led to our being able to welcome not 2 but 3 exceptional speakers to discuss the latest advances in low grade lymphoma.

Before you hear from them I will give an overview of current therapy , we will then hear from Andreas Rosenwald who will present the latest data on the molecular biology of low grade lymphoma , then Ron Levy will discuss how we can use these advances to develop new therapies , and finally Anas Younes will present data of which new agents are currently entering clinical practice .

This promises to be a very exciting and stimulating session which will give you the opportunity to ask questions and discuss the topic with leaders in this field

Robert Marcus, MD

Andreas Rosenwald, MD

Position Title: Professor of Pathology

Institution and Location	DEGREE	Year	FIELD OF STUDY
College of Medicine, University of Luebeck, Germany	M.D.	1995	Medicine
Postdoctoral Training, Laboratory of L.M. Staudt, National Cancer Institute, NIH, Bethesda, MD		1999-2003	Lymphoma Research

A. Personal Statement

I am highly motivated to be a member of the working group on the upcoming WHO-ICD Revision project for hematological malignancies. I am a fully trained hematopathologist and chairman of the Institute of Pathology, University of Würzburg, Germany. I have been elected as one of altogether five reference pathologists for hematopathology in Germany. My institution constitutes one of Germany's largest reference centers for malignant lymphomas with more than 7000 lymph node specimens being sent to our department annually. I serve on national diagnostic reference pathology panels in all major types of malignant lymphomas including indolent and aggressive B-cell lymphomas as well as T-cell lymphomas. I have also been part of the reference panel of the Leukemia and Lymphoma Molecular Profiling Project (LLMPP) since 2007, where more than 2000 lymphoma specimens were reviewed by an international panel of expert hematopathologists at the NIH.

Scientifically, my major interest is in the molecular and genetic characterization of malignant lymphomas. I have administered many scientific projects in the past (including staffing, research protections, budget) and, for many years, I am principal investigator in national, European and international research networks in malignant lymphomas. These include, for example, the German Network Project 'Molecular Mechanisms in Malignant Lymphomas', the European Mantle Cell Lymphoma Consortium and the NIH-funded LLMPP. I first-authored highly-ranked papers in which diagnostic and prognostic gene expression signatures were established for various types of B-cell lymphomas.

In summary, I have a track record of successful and productive research projects in lymphomas and, most importantly, a long-standing expertise in the diagnosis of all types of malignant lymphomas and other hematological malignancies.

B. Positions and Honors

Positions and Employment

1996-1999 Residency Training in Pathology/Hematopathology, University of Würzburg, Germany

2003-2009 Principal Investigator, Junior Research Group, Institute of Pathology/Interdisciplinary Center for Clinical Research, University of Würzburg, Germany,

2003-2009 Staff Pathologist, College of Medicine, Department of Pathology, University of Würzburg, Germany.

2009-present Professor of Pathology, Chairman, Institute of Pathology, University of Würzburg, Germany

Other Experience and Professional Memberships

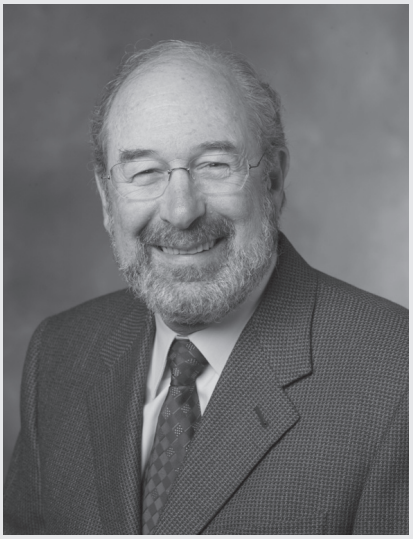
2009-present Elected Member of the International Lymphoma Study Group (ILSG)

2009-present Board of Directors, Comprehensive Cancer Center (CCC), University of Würzburg, Germany

Honors and Awards

1998 Young Investigators' Award (European Association for Haematopathology)

2004 Vincenz-Czerny Award (German Society for Hematology and Oncology)



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Academic History

1963	Harvard University, A.B.
1968	Stanford University, M.D.
Post-Doctoral And Residency Training	
1968-1970	Internship and Residency in Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts
1970-1972	Clinical Associate, Immunology Branch, National Cancer Institute
1972-1973	Fellow, Department of Medicine, Division of Oncology, Stanford University Medical Center, Stanford, California
1973-1975	Fellow of the Helen Hay Whitney Foundation, Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, Israel

Certification And Licenses

1970	Commonwealth of Massachusetts
1973	Board Certification, Internal Medicine
1975	State of California Medical License #G021994
1979	Board Certification, Medical Oncology

Employment History

1970-1972	Clinical Associate, Immunology Branch, National Cancer Institute, Bethesda, Maryland
1975-1981	Assistant Professor of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, California
1981-1987	Associate Professor of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, California
1987-Present	Professor of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, California
1987-Present	Robert K. Summy and Helen K. Summy Professor, Stanford University School of Medicine, Stanford, California
1987-Present	Frank and Else Schilling American Cancer Society Clinical Research Professor
1993-Present	Chief of the Division of Oncology, Stanford University School of Medicine, Stanford, California

Post-Degree Honors and Awards

1977-1982	Investigator, Howard Hughes Medical Institute
1979	Member, American Society of Clinical Investigation
1982	Armand Hammer Award for Cancer Research
1983	Ciba-Geigy/Drew Award in Biomedical Research
1987	Association of American Physicians
1987	American Cancer Society Clinical Research Professor
1989	Dr. Josef Steiner Prize for Cancer Research
1997	Joseph H. Burchenal Clinical Cancer Research Award, American

Association for Cancer Research

1999	Karnofsky Award, American Society of Clinical Oncology
1999	Charles F. Kettering Prize, General Motors Cancer Research Foundation
1999	Centeon Award, 6th International Conference on Bispecific Antibodies
2000	C. Chester Stock Award, Memorial Sloan-Kettering Cancer Center
2000	Medal of Honor, American Cancer Society
2000	Key to the Cure Award, Cure for Lymphoma Foundation
2001	Evelyn Hoffman Memorial Award, Lymphoma Research Foundation of America
2003	Jeffrey A. Gottlieb Memorial Award, M.D. Anderson Cancer Center
2004	Donald Ware Waddell Award, Arizona Cancer Center
2004	J.E. Wallace Sterling Award, Stanford Medical Alumni Association
2004	Discovery Health Channel Medical Honoree, DAR Constitution Hall Washington DC
2005	Damashek Prize, American Society of Hematology
2006	iSBTc Richard V. Smalley Memorial Lectureship Award
2007	Member, Institute of Medicine of the National Academies
2007	di Villiers International Achievement Award, Leukemia and Lymphoma Society
2008	Member, National Academy of Science
2009	King Faisal International Prize, The King Faisal Foundation

Professional Review Activities

1988-1992	Chairman, American Cancer Society Immunology Study Section
1989-1993	Chairman, Board of Scientific Counselors, Division of Cancer Treatment, National Institute of Health
1992-1996	Program Committee and Block Chairman for Tumor Immunology, American Association of Immunology
1992-1996 and	General Motors Cancer Research Foundation Awards Assembly
2001	American Association of Medical Schools Task Force on Financial Conflicts of Interest in Clinical Research

2001	Dorothy P. Landon - American Association for Cancer Research Translational Cancer Research Prize Committee
2002	Chairman, Joseph H. Burchinal Award Committee, American Association of Cancer Research
2002-2005	Margaret Early Trust
2002-2005	G&P Charitable Foundation Award
2002-2005	The V Foundation Award
2002-2007	Damon Runyon Clinical Investigators Award
2003-2007	Member Research Council, American Cancer Society
2004-2007	Board of Directors, American Association for Cancer Research
1994-Present	Scientific Advisory Board, Fred Hutchinson Cancer Research Center
2001-Present	Conflict of Interest Committee for Stanford University School of Medicine
2002-Present	Board of Directors, Damon Runyon Cancer Research Fund
2007-Present	Chairman, Rachleff Research Award, Damon Runyon Research Fund

Research Grant Committees

Margaret Early Trust
Lymphoma Research Foundation

Scientific Advisory Boards

Agensys, Santa Monica, CA
Cell Genesis, Foster City, CA
Five Prime, South San Francisco, CA
InNexus, Scottsdale, AZ
Angelica
Micromet, Bethesda, MD
Macrogenics, Bethesda, MD

Society Memberships

American College of Physicians
American Association for Cancer Research
American Society of Clinical Oncology
American Association of Immunology
American Federation for Clinical Research
American Society of Clinical Investigation
American Society of Hematology
Western Society of Medicine
Association of American Physicians
Academy of Cancer Immunology

Major Research Interests

Immunology, Cancer Biology, Medical Oncology

Visiting Professorships

1994	Woodward Visiting Professor, Memorial Sloan Kettering Cancer Center, NY
1995	Morton Mason Lecture, University of Texas Southwestern
1996	University of Minnesota Cancer Center
1999	University of Nebraska Cancer Center
2007	William J. Harrington Visiting Professor, University of Miami

Invited Lectureships (last 3 years)

January 2007	Keystone Symposia Scientific Advisory Board, Immunological Intervention in Human Disease, Big Sky, Montana
February 2007	FDA/NCI Sponsored Workshop, Bring Therapeutic Cancer Vaccines and Immunotherapies Through Development to Licensure, Bethesda, Maryland
March 2007	Follicular Lymphoma, Vaccines, North Berwick, Scotland
October 2007	Hematology Society of Australia and New Zealand Annual Scientific Meeting, Lymphoma Vaccines & Lymphoma Vaccines: tricks of the trade, Gold Coast, Australia
October 2008	Nordic Lymphoma Meeting, Vaccine strategies against lymphomas – how far have we reached and prospects for the future, Helsinki, Finland.
November 2008	Leukaemia Research Fund, Grantholders Day and Annual Guest Lecture, Immunotherapy of lymphoma; from the passive to the active, London, England.
November 2008	The Leukemia & Lymphoma Society, Stohlman Scholar Scientific Symposium 2008, Using the Immune system to treat Lymphoma, Kansas City, Missouri
March 2009	The King Faisal Foundation, King Faisal Specialist Hospital and Research Center, Using the Immune system to treat Lymphoma, Riyadh, Saudi Arabia
March 2010	14th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myelomas, Whistler, BC, Canada
June 2010	Federation of Clinical Immunology Societies, FOCIS 10th Anniversary Session, Boston MA
August 2010	14th International Congress of Immunology: Antibody therapy of cancer. Targeting the tumor and the host immune system. Kobe, Japan
February 2011	Keystone Symposium, Antibodies as Drugs. Keystone, Colorado

Follicular Lymphoma-Pathogenesis, Diagnosis and Therapy

Ronald Levy

Stanford University, California, United States of America

Follicular lymphoma is an indolent disease with a long natural history but currently not curable.

It is almost associated with a chromosomal translocation that brings the BCL2 gene next to the immunoglobulin promoter/enhancer, resulting in deregulated and over expression of the BCL2 gene/protein. Immunostaining of biopsy specimens shows high expression of the BCL2 protein within the neoplastic follicles, a feature that distinguishes FL follicles from normal germinal centers. There are very good clinical prognostic scoring systems for FL, including the FLIPI.

The management of FL has two opposing paradigms: aggressive strategies assume the possibility of cure and use dose-intensive therapies, gentler strategies assume that the disease is not ultimately curable and attempt to manage as a chronic disease.

At the time of diagnosis it is important to review the pathology to distinguish grades I,II, IIIa from grade IIIb. The latter should be managed as DLBCL with adriamycin combinations in an attempt to cure.

It is also important to stage the patient carefully because stage I disease may be curable with local radiotherapy. This is the only role for PET scans in managing FL.

For low grade, advanced stage disease, the typical initial approach to management is to watch and wait. Multiple attempts to challenge this policy have failed to show a survival advantage of initial therapy, including the recent results presented by Ardeshna at the 2010 ASH meeting.

When initial therapy is indicated Rituxan containing regimens have proven superior to those without. Indeed, initial therapy with Rituxan alone may be sufficient.

When the disease becomes more aggressive, Bendamustine-Rituxan has proven to be superior to CHOP-Rituxan, according to the results presented by Rummel at the 2009 ASH meeting. These results have not yet been published but they have already changed the standard of care in the U.S. At the time of first remission Rituxan maintenance therapy has shown an advantage in progression-free survival over no maintenance according to the results of the PRIMA trial presented at the 2010 ASCO meeting. Although Rituxan maintenance may become a standard of care in some countries, the final proof of the value of this maintenance therapy must await an analysis of overall survival. It is still possible that Rituxan maintenance will result in the disease becoming resistant to this drug at the time of eventual relapse and it is possible that an overall survival benefit may ultimately favor the group that did not receive maintenance. Many new agents are being tested in FL, including monoclonal antibodies, vaccines, and small molecules. New pathogenic mutations are being discovered. The future will certainly include changes in therapy for this disease and we should all be prepared to ultimately approach this disease as curable.

Anas Younes, M.D.

PRESENT TITLE AND AFFILIATION
Primary Appointment
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Director, Clinical and Translational Reserach Program, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TXDual/Joint/Adjunct Appointment
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Degree-Granting Education
The University of Damascus School of Medicine, Damascus, Syria, MD, 1983, Medicine
Postgraduate Training
Guest Researcher, Endocrine and Reproductive Research Branch (ERRB), NICHD, National Institutes of Health, Bethesda, MD, Dr. Kevin Catt, 7/1984–6/1985
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Board Certification
American Board of Internal Medicine, 124872, 9/1989
American Board of Medical Oncology, 124872, 11/1991, Recertification Date: 2012
Licensures
Active
Texas Medical Board, TX, J1817, 9/1989–2/2011
Department of Public Safety, TX, 20081285, 11/2008–11/2009
Drug Enforcement Administration, TX, BY170000346, 5/2009–5/2012
Inactive
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Assistant Professor, Division of Cancer Medicine, U.T. M.D. Anderson Cancer Center, Houston, TX, 1992–1997
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Faculty Member, Department of Immunology, Graduate School of Biomedical Sciences (GSBS), The University of Texas-Houston Health Science Center, Houston, TX, 1998–2009
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Team Leader, Lymphoma and Myeloma Drug Development Program, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, 2003–present
Team Leader, Hodgkin Lymphoma & T-Cell Lymphoma Program, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, 2004–present
Director, Clinical and Translational Reserach Program, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, 2005–present
Other Appointments/Responsibilities
Member, SAB, International Symposium on Hodgkin Lymphoma, Cologne, Germany, 2007–present
Member (Adhoc), NCI SEP Study Section, Bethesda, MD, 2007–present
Member, Lymphoma Committe, Southwest Oncology Group, San Antonio, TX, 10/2008–present
Member, EAB, Rochester/Tuscon Lymphoma SPORE, Rochester, NY, 2009–present
Member, NCI Subcommittee, H Study Section, Bethesda, MD, 2009
EAB Member, Metabolism Branch, NCI, Bethesda, MD, 2009
Member (Scientific Advisory Board), Lymphoma Research Foundation, New York, NY, 3/2009–present
Member, National Cancer Institute/Lymphoma Steering Committee, Bethesda, MD, 12/2009–present
IAB Member, M. D. Anderson Cancer Center Head and Neck SPORE, Houston, TX, 1/2010–present

Endowed Positions
N/A
Consultantships
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Military or Other Governmental Service
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Institutional Committee Activities
Medical Records Subcommittee, Member, 1/1991–1/1994
Institution Review Board (IRB), Member, 1/1992–1/1994
Physician Advisor for Utilization Review, Member, 1/1994–1/1998
M.D. Anderson Presidential Search Committee, Member, 1/1996
Quality Improvement Subcommittee, Member, 1/1997
Medication Use Task Force, Chairman, 1/1998–1/1999
Pharmacy and Therapeutics Committee, Chairman, 1/1998–1/2002
Credentials Committee of the Medical Staff, Alternate Member, 1/1999–1/2002
Advisory Committee of the Grants & Contracts Database, Member, 1/1999–present
Research Funding Oversight Committee, Institutional Research Grant Program, Member, 1/2000–present
Order Set Project, Member, 1/2000
Clinical and Translational Research Center (CTRC) Steering Committee, Member, 1/2001–1/2004
Medical Oncology Fellowship Selection Committee, Member, 2002–2007
Executive Committee of the Medical Staff (ECMS), Vice Chair, 1/2002–present
M. D. Anderson Faculty Achievement Award Selection Committee, Member, 1/2002
Fellowship Supervisory Committee, Member, 2003–2005
Clinical Research Review Committee, Member (alternate), 1/2003–1/2004
Institution Review Board (IRB), Member (alternate), 1/2003–1/2004
Executive Committee of the Medical Staff (ECMS), Chairman, 1/2003–1/2006
MDACC Quality Council, Member, 1/2003–present
MDACC Bylaws Working Group, Member, 1/2004–1/2006
M.D. Anderson Bylaws Committee, Chairman, 2006–present
AYA Program, Co-director, 2007–present
Phase II Committee, Member, 2007–present
Clinical Faculty Review Committee, Member, 9/2008–8/2011
Council of Committee Chairs, Chairman, 9/2008–present
MDACC SWOG Executive Committee, Member, 2009–present
Clinical Faculty Review Committee, Member, 9/2009–2/2010

HONORS AND AWARDS
Clinical Scholars Award for Biomedical Research, Sloan-Kettering Institute, 1991–1992
Dana Research Fellow, Sloan-Kettering Institute, 1991–1992
Clinical Oncology Career Development Award, American Cancer Society, 1996–1999
Faculty Excellence Award, M.D. Anderson Cancer Center, 1996–1999

Novel Targeted Therapies for Follicular Lymphoma

Anas Younes

MD Anderson Cancer Center, Texas, United States of America

An improved understanding of the molecular biology of cancer cell growth and survival and the role of the microenvironment in supporting the survival of cancer cells, including lymphoma cells, has led to the identification of a number of potential therapeutic targets.

Monoclonal antibodies

In1997 the FDA approved the first unconjugated (naked) mAb—rituximab—for the treatment of relapsed $CD20^+$ B-cell lymphoma. Several naked mAbs have since been developed to target other surface antigens and receptors, but with limited success. To date, three naked mAbs (rituximab, ofatumumab, and alemtuzumab) and two radioimmuno mAbs (ibritumomab tiuxetan and ^{131}I-tositumomab) have been approved by the FDA for the treatment of B-cell lymphoid malignancies, and all but one of these target CD20 antigen. Despite that clinical success and the relative simplicity of this approach, theTo-date, CD20 antigen remained unchallenged as a target for mAb therapy for more than a decade. Other anti-CD20 naked mAbs, including GA101, veltuzumab, and ocrelizumab are in clinical development; however, it remains to be seen how these new mAbs will perform in the clinical setting compared with rituximab. Importantly, despite the dense expression of CD20 by a variety of B-cell lymphomas, many patients do not respond to anti-CD20 antibodies, indicating that CD20 expression alone is not sufficient to predict response to therapy. Thus, the benefits of newer mAbs are likely to be marginal unless they address specific mechanisms of resistance to anti-CD20 antibodies.

Two antibody-drug conjugates (ADCs) are currently being explored in follicular lymphoma targeting CD22 and CD19. Unlike CD20, both CD22 and CD19 are internalized, and therefore, are more suitable for ADC strategies. Inotuzumab ozogamicin (CMC–544) is a humanized anti-CD22 antibody conjugated to calicheamicin, a potent antitumor antibiotic that binds to DNA. In a phase I study, inotuzumab ozogamicin was administered intravenously every 4 weeks in patients with relapsed B-cell lymphoma. The maximum tolerated dose was 1.8 mg/m^2, and the dose-limiting toxic effects (DLTs) were thrombocytopenia, neutropenia, and hepatic toxicity. Compared with the naked anti-CD22 antibody epratuzumab, inotuzumab ozogamicin demonstrated an improved single-agent clinical activity, with ORRs of 68% in follicular lymphoma and 15% in DLBCL. In a follow-up study, inotuzumab ozogamicin was combined with rituximab in patients with relapsed follicular lymphoma or DLBCL. This novel antibody combination produced an ORR of 84% in 38 patients with follicular lymphoma, with a median progression-free survival (PFS) of 23.6 months. Patients with DLBCL (n = 40) had an ORR of 80%, with a median PFS of 15.1 months. The ORR was only 20% in 25 patients with rituximab-refractory lymphoma, which was associated with a short median PFS (2 months).

SAR3419 is a humanized IgG1 mAb to CD19 that is conjugated through a disulfide link to the maytansinoid derivative DM4, a potent tubulin inhibitor that binds to the vinca site. Results from a multidose phase I study of SAR3419 in patients with relapsed $CD19^+$ B-cell non-Hodgkin lymphoma were reported in 2009. Patients received SAR3419 by intravenous infusions every 21 days for up to six doses. Unlike inotuzumab ozogamicin, SAR3419 had no substantial hepatic or hematopoietic toxic effects; by contrast, the DLT of SAR3419 was reversible severe blurred vision, which was associated with microcystic epithelial corneal changes. Of 25 evaluable patients, 17 (68%) demonstrated reduction in their tumor measurements, and of those patients, two achieved partial response and three achieved a complete response. Furthermore, seven (53%) of 13 patients with rituximab-refractory disease demonstrated reduction in their tumor measurements. Thus, the lack of profound hematologic toxic effects and the ability to induce responses in rituximab-refractory patients may provide an opportunity for combining SAR3419 with other active regimens for the treatment of B-cell lymphoma. Of note, although preclinical data have demonstrated the superiority of SAR3419 compared with the CD19 antibody, no comparative clinical data are available for patients with relapsed lymphoma using an anti-CD19 antibody.

Small molecules targeting oncogenic pathways

Advances in tumor biology have led to the identification of a variety of intracellular oncogenic pathways as potential targets for cancer therapy. These pathways can be targeted with small molecules that can selectively inhibit specific signaling molecules known to be activated in lymphoma, many of which are not 'driver' targets but contribute to the survival of lymphoma cells.

PI3K/Akt/mTOR pathway inhibitors. The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway is dysfunctional in cancer, making it an important target for drug development. Oncogenic activation of the PI3K pathway is associated with gain-of-function mutations in the PI3K p110α or p85α isoforms and/or with the loss-of-function of the *PTEN*. In lymphoid malignancies, PI3K pathway activation is rarely associated with these mutations; rather, it is linked to constitutive B-cell receptor (BCR) activation and/or to exposure to survival factors present in the microenvironment, such as CD30, CD40, BAFF, and RANK. First-generation mTOR inhibitors were soluble rapamycin derivatives (rapalogues), two of which have been approved by the FDA for the treatment of renal cell carcinoma: temsirolimus (CCI–779) and everolimus (RAD001). The exact anticancer mechanisms of mTOR inhibitors remain unclear, but likely mechanisms include induction of autophagy, anti-angiogenesis, immunoregulation, and inhibition of protein translation of critical cell survival proteins. Thus, because mTOR inhibitors primarily induce cell-cycle arrest and autophagy, it is likely that clinical responses to mTOR inhibitors are augmented *in vivo* by modulation of the microenvironment and angiogenesis. Temsirolimus (CCI-779) demonstrated broad activity in a variety of lymphoma subtypes, including a 50% response rate in patients with relapsed follicular lymphoma. More recently, CAL–101, a potent oral selective inhibitor of the PI3K isoform p110δ, produced a 56% response rate in a phase I trial, especially in patients with relapsed indolent lymphoma and MCL. These data, together with results achieved using mTOR inhibitors, confirm that targeting the PI3K/Akt/mTOR pathway is a promising strategy for the treatment of lymphoma.

Immunomodulatory drugs. Lenalidomide is a derivative of thalidomide and is an immunomodulatory agent. Lenalidomide's mechanism of action is not completely understood, but it involves a direct antiproliferative effect, modulation of the tumor microenvironment, inhibition of angiogenesis, and enhancement of immune cell function. Several phase II studies have demonstrated promising clinical activity of lenalidomide in a variety of lymphoma subtypes when it was administered orally at 25 mg daily for 3 weeks in 4-week cycles. For example, the ORRs were 27%, 28%, 42%, and 45%, respectively, in patients with relapsed follicular lymphoma, DLBCL, MCL, and TCL. Importantly, responses were seen in patients who had failed to respond to their previous regimen, including rituximab-refractory patients. Lenalidomide primary toxicity was myelosuppression, which required dose reductions or interruptions in almost 50% of patients. This toxic profile suggests that combining lenalidomide with conventional chemotherapy regimens might be difficult and that alternative approaches should be investigated, including administration of lenalidomide as maintenance after chemotherapy or in combination with other biologic agents that have minimal hematologic toxic effects, such as rituximab.

BCR signaling inhibitors. Studies have demonstrated that in subsets of B-cell lymphomas, augmented BCR signaling may promote their survival.[83] This finding has led to the development of small molecules that inhibit Syk and **Bruton's tyrosine kinase** (that are involved in B-cell receptor signaling.[83–85] In a phase II study, fostamatinib demonstrated clinical activity in a variety of B-cell malignancies; the highest ORR, 55%, was observed in patients with relapsed SLL or CLL. A large phase II study of fostamatinib is currently enrolling patients to further confirm the agent's activity in patients with CLL. Similarly, a phase-I study of the **Bruton's tyrosine kinase** small-molecule inhibitor PCI32765 demonstrated clinical activity in a variety of B-cell lymphoid malignancies

JAK and STAT pathway inhibitors. The Janus kinase (JAK) signal transducers and activators of transcription (STAT) pathway has an important role in the proliferation and pathogenesis of hematologic malignancies. Somatic activating-point mutations in *JAK2* have been reported in most myeloproliferative disorders but are rarely described in Hodgkin lymphoma and non-Hodgkin lymphoma. JAK2 activation has been reported to be associated with mutation of the suppressor of cytokine signaling-1 gene in Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. On the basis that activated STAT3 and STAT5 signalling promotes the growth and survival of a variety of lymphomas, the novel oral JAK2 small-molecule inhibitor SB1518 was evaluated in patients with relapsed Hodgkin lymphoma and non-Hodgkin lymphoma in a phase I study. Clinical responses were observed in patients with relapsed MCL, follicular lymphoma, SLL, and Hodgkin lymphoma. A phase II clinical trial will soon be conducted to confirm this promising clinical activity.

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Kings College Hospital
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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

Introduction and Current Therapy for Follicular Lymphoma

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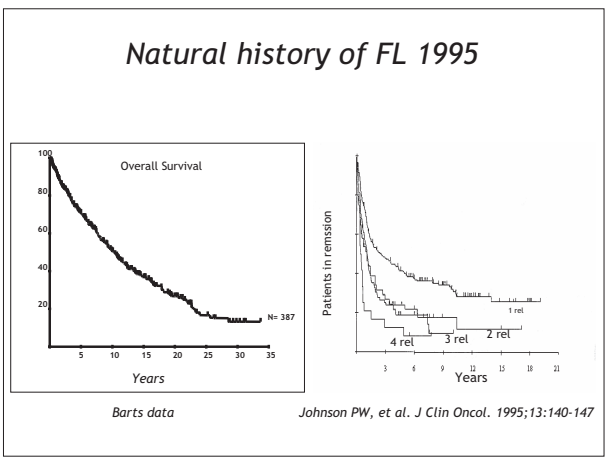
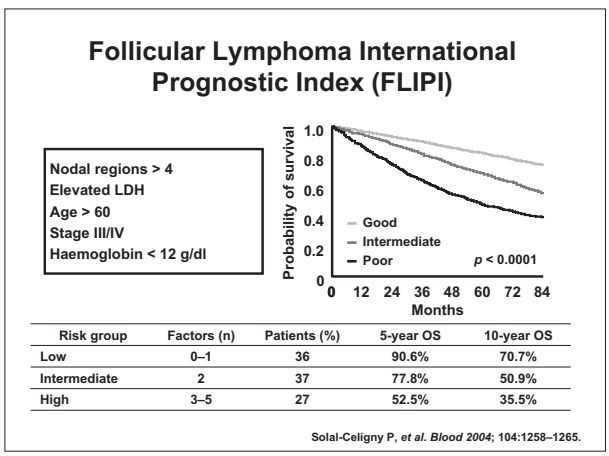




FLIP 1 and FLIP 2 – Prognostic Groups in Follicular NHL

	FLIPI			FLIPI2		
Variables	Age, stage, Hb, LDH, nodal areas			Age, Hb, BM, β2M, nodal size		
Risk groups	Low (0-1)	Intermediate (2)	High (≥ 3)	Low (0-1)	Intermediate (2)	High (≥ 3)
%	36	37	27	20	53	27
5-yr OS	91	78	52	98	88	77

Solal-Celigny P, *et al. Blood 2004*; 104:1258–1265.
Federico M, et al. *J Clin Oncol*. 2009. 20;27(27):4555-62.

Criteria for commencing therapy in FL

BNLI

- Life threatening organ involvement
- "B" symptoms
- Bone marrow failure
- Rapidly progressive disease over any 3–6 month period

GELF

- Bulky disease : nodal/ extranodal mass > 7cm
- B symptoms
- Raised B2-microglobulin /LDH
- Involvement of 3 nodal sites (>3 cm)
- Splenic enlargement
- Compression syndrome
- Pleural/peritoneal effusion

Watch and wait in Follicular Lymphoma

		n	% Not Treated	TTT (months)	% ORR CR	OS (yrs)
Portlock [1]	ww	44	43	31	NA	10.1
Horning [2]	ww	83	38 *	36	NA	11
O'Brien[3]	ww	56	21	33	NA	6.3
Young [4]	ww	44	17#	34	NA/43	Both 83 % (4yrs)
	PromaceMopp/ TNI	60	--	--	NA/78	
Brice [5]	ww	66	20	24	70	78 % (5yrs)
	Prmust/IF	127	--	--	78/70	70/84 %
Ardeshna [6]	ww	151	19 (at 10yrs)	31.2	76/27	6.7
	Chloramb	158	--	--	90/63	5.9

* Including 23% Spont. remissions

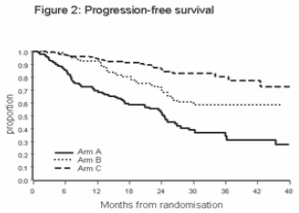
1 Portlock et al. Ann Intern Med 1979
2 Horning et al. N.Engl.J.Med 1984
3 O'Brien et al. Q J Med 1991
4 Young et al. Semin Hematol.1988
5 Brice et al. J Clin Oncol 1997
6 Ardeshna et al. Lancet 2003

Intergroup randomised "Watch and Wait" trial in asymptomatic FL

462 patients FL Asymptomatic Non bulk No critical organ failure → Randomisation

- ARM-C: 186 -Watch and Wait
- ARM-B: 84- Rituximab, 4 weeks standard course
- ARM-A: 192 - Rituximab, 4 weeks standard course followed by maintenance 1 dose every 2 months for 2 years

PFS – W and W vs R vs R+R



Conclusions

- TTNT and PFS prolonged in patients receiving Rituximab
- Impact of R + R uncertain
- No OS data
- Will early R given to asymptomatic patients have any impact on natural history of the disease (cf MGUS , early stage CLL)
- Will early R have any impact on the total duration of remission achievable with R based therapies at the time of subsequent recurrence ?

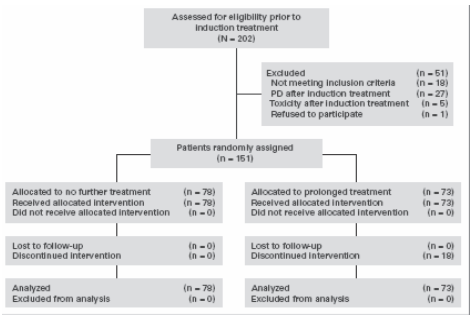
Published Ahead of Print on August 9, 2010 as 10.1200/JCO.2010.28.4786
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.28.4786

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Long-Term Follow-Up of Patients With Follicular Lymphoma Receiving Single-Agent Rituximab at Two Different Schedules in Trial SAKK 35/98

Giovanni Martinelli, Shu-Fang Hsu Schmitz, Urs Utiger, Thomas Cerny, Urs Hess, Simona Bassi, Emmie Okkinga, Roger Stupp, Rolf Stahel, Marc Heizmann, Daniel Vorobiof, Andreas Lohri, Pierre-Yves Dietrich, Emanuele Zucca, and Michele Ghielmini

Martinelli et al JCO 2010



Martinelli et al JCO 2010

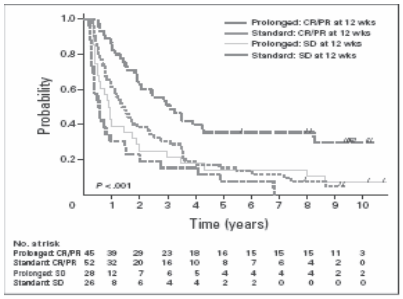
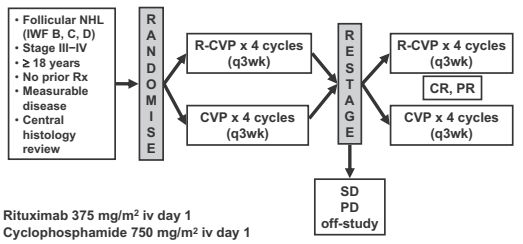


Fig 2. Event-free survival by treatment arm according to response to the induction treatment (complete response [CR]/partial response [PR] or stable disease [SD]).

Single agent R after Martinelli

- No FLIP scores – how many patients needed treatment all ?- < 33% raised LDH , <50% 5cm masses
- Entry criteria : a diagnosis of FL (!!)
- Mixture of treated and untreated patients
- Best outcome : previously untreated patients responding to R induction (self fulfilling prophecy ?) only 38 patients in this group

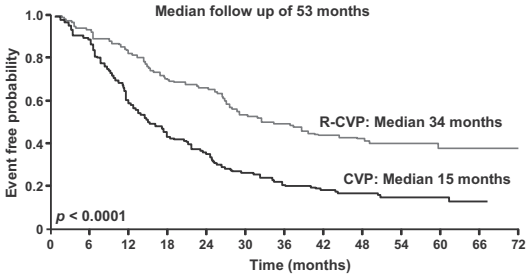
R-CVP versus CVP study design



Rituximab 375 mg/m² iv day 1
Cyclophosphamide 750 mg/m² iv day 1
Vincristine 1.4 mg/m² iv day 1
Prednisone 40 mg/m² po days 1–5

Marcus R, *et al* Blood 2005; 105:1417–1423.

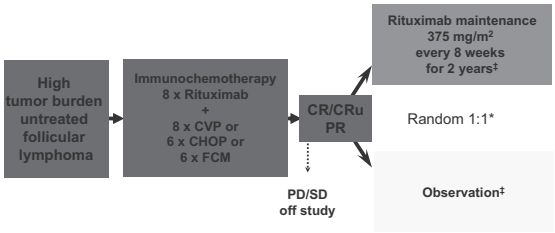
Rituximab-based induction therapy significantly improves time to progression



First line FL: R-Chemo Phase III trials

FLIPI (LR/IR/HR)	Regimen	Phase	Pts	ORR %	CR%	Duration	Ref
14 / 41 / 45	R-CHOP	III	428	96	17	TTF: 2y 85%	Hiddemann , Blood 04
- / 42 / 46	R-CHOP R-Benda	III	540	91.3	30	PFS: 46.7m PFS: n.r.	Rummel, ASH 09*
7 / 37 / 56	R-MCP->IFN	III	201	92	50	PFS: n.r. -4y 71%	Herold, JCO 07
19 / 41 / 40	R-CVP	III	331	81	41	TTP: 34 mo	Marcus, Blood 05
19 / 35 / 46	R-CHVP+IFN	III	358	85	34	PFS: n.r. -5y 53%	Salles, Blood 08

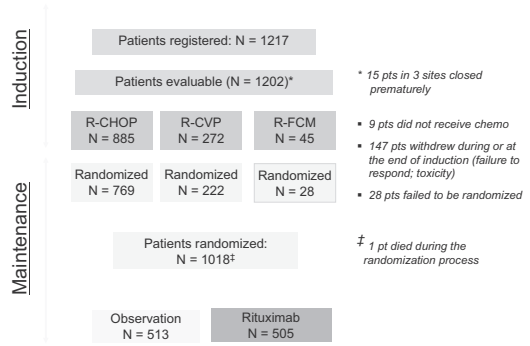
PRIMA: study design and results *Salles et al ASCO 2010*



* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up

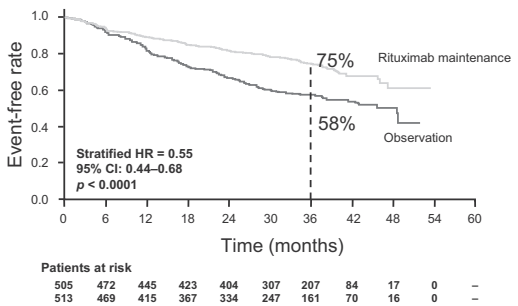
Salles GA, et al. *ASCO Meeting Abstracts.* 2010;28:8004

Patient disposition



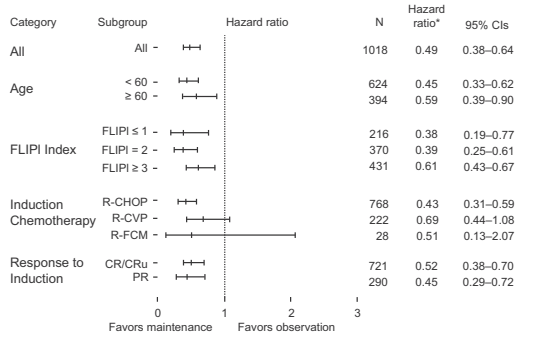
Salles GA, et al. *ASCO Meeting Abstracts.* 2010;28:8004.

ASH 2010 -Primary endpoint (PFS): 36 months' follow-up after randomisation



GA Salles *et al.* ASH 2010, Abstract 1788

Benefits of rituximab maintenance seen in all major sub-groups evaluated



* Non-stratified analysis

Salles GA, et al. *ASCO Meeting Abstracts.* 2010;28:8004.

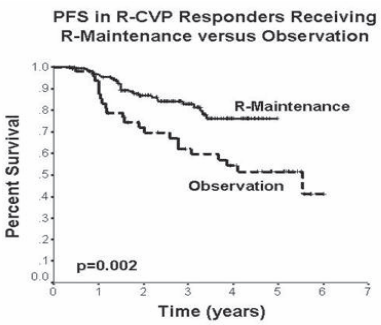
Conclusions (PRIMA)

- R maintenance increases PFS in all subgroups
- OS benefit not established
- PET negativity post induction strong determinant of PFS
- Most patients will still relapse eventually – projected median PFS 60 months
- What next ?

Unselected patients treated with R-CVP+ R *BCCA experience 2004- ASH#1803*

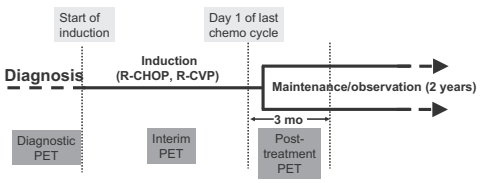
- 252 patients with advanced stage FL median age 60
- FLIP 0-1 – 27%, 2 – 29% 3-5 45%
- ORR 86% , CR/Cru 44%
- 59 patients observed (pre 2006) 167 – R maintenance
- 3 year PFS 83% vs 62%
- OS ND
- Conclusion : 2006 decision vindicated PFS improved in patients receiving R maintenance

BCCA R maintenance data in FL

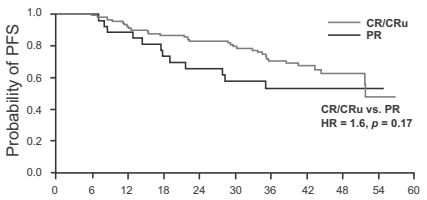


Role of PET in FL (*after Trotman et al with permission)*

- PRIMA database interrogated
- Investigators surveyed to identify PET-CTs
- Single-modality PET scans excluded
- Positive or negative scan: PET(+/–) defined by local investigator
- Primary endpoint: progression-free survival from PRIMA registration

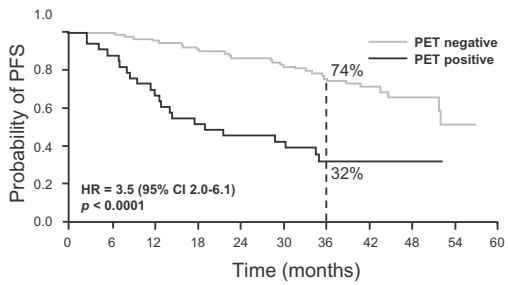


Progression-free survival (from study registration) Conventional response assessment



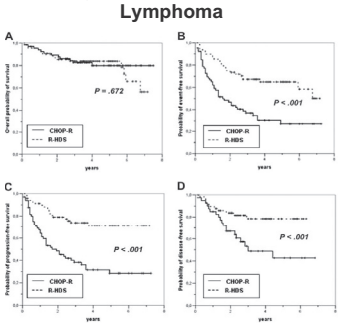
	No. of subjects	Event	Censored	Median PFS (months)
CR/CRu	89	35% (31)	65% (58)	52
PR	27	44% (12)	56% (15)	NR

Progression-free survival (from study registration) Post-treatment PET-CT based assessment



	No. of subjects	Event	Censored	Median PFS (months)
PET negative	91	31% (28)	69% (63)	NR
PET positive	33	67% (22)	33% (11)	19

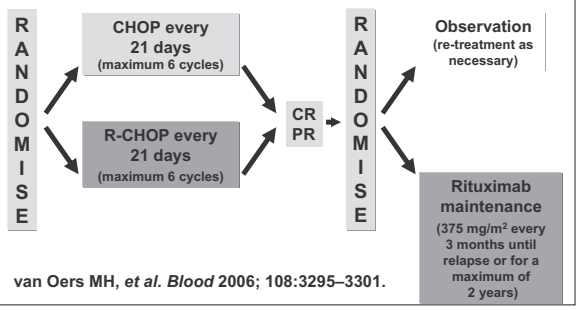
PBSCT versus R-chemotherapy in 134 previously untreated patients with Follicular Lymphoma



Ladetto, M. et al. *Blood.* 2008;111:4004-4013

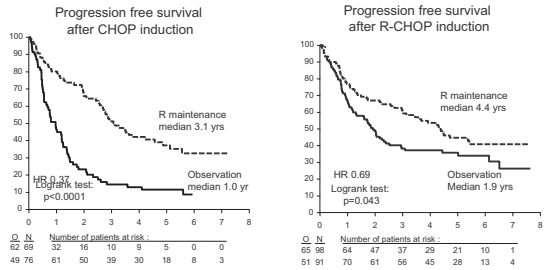
EORTC 20981

Rituximab maintenance in relapsed/resistant follicular non-Hodgkin's lymphoma



van Oers MH, *et al. Blood* 2006; 108:3295–3301.

EORTC 20981



van Oers MH, et al. *J Clin Oncol.*. 2010;28(17):2853-8.

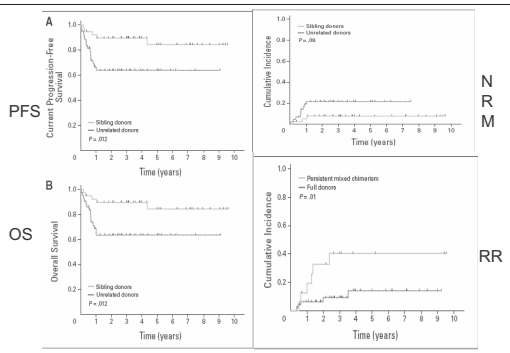
T-Cell–Depleted Reduced-Intensity Transplantation Followed by Donor Leukocyte Infusions to Promote Graft-Versus-Lymphoma Activity Results in Excellent Long-Term Survival in Patients With Multiply Relapsed Follicular Lymphoma

Kirsty J. Thomson, Emma C. Morris, Don Milligan, Anne N. Parker, Ann E. Hunter, Gordon Cook, Adrian J.C. Bloor, Fiona Clark, Majid Kazmi, David C. Linch, Ronjon Chakraverty, Karl S. Peggs, and Stephen Mackinnon

Published Ahead of Print on July 6, 2010 as 10.1200/JCO.2009.26.9100
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.26.9100

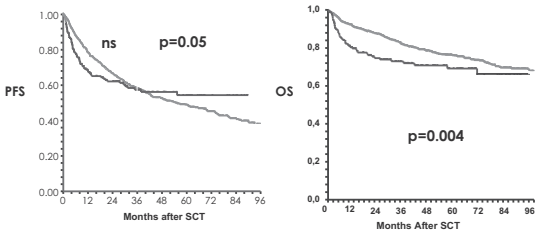
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Thomson KJ, et al. *J Clin Oncol.* 2010 Aug 10;28(23):3695-700.



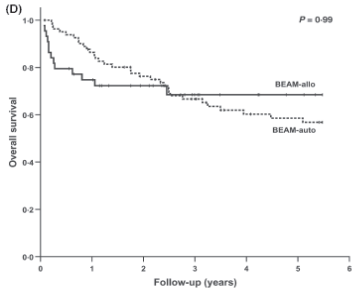
Thomson KJ, et al. *J Clin Oncol.* 2010 Aug 10;28(23):3695-700.

Allo vs Auto PBSCT FL Robinson et al ASH 2008



Robinson SP, et al. *Blood (ASH Annual Meeting Abstracts)*. 2008;**112**:458.

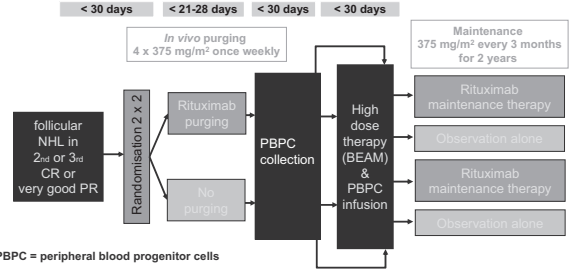
Outcome of BEAM-autologous and BEAM-alemtuzumab allogeneic transplantation in relapsed advanced stage follicular lymphoma



W Ingram et al , Brit J Haem 2008

EBMT- LYM1: Trial summary

Accrual Oct 1999–Apr 2006



PBPC = peripheral blood progenitor cells

B-cell depletion by rituximab and/or no treatment is established at randomisation in a 2x2 design

Pettengell R, et al. *ASCO Meeting Abstracts.* 2010;28:8005.

EBMT-LYM-1: Entry criteria

Inclusion criteria

- Relapsed follicular NHL, rituximab naive
- 1 or 2 prior chemotherapy regimens
- CD20 positive
- CR or good PR following re-induction of chemotherapy
- Good performance status
- Pathological material for review and PCR

Exclusion criteria

- Histological transformation
- Previous transplant
- Extensive prior radiotherapy

Pettengell R, et al. *ASCO Meeting Abstracts.* 2010;28:8005.

EBMT LYM-1 – ASH Update 2010

	R Purging +R	R Maintenance	R Purging	No R
Pt number	69	69	72	70
Median PFS	NR@ 6.4 y	7.23 y	4.03 y	3.34 y
5y PFS	*62.9 %*	*56 %*	*46 %*	*37.6 %*
5y OS	79.5 %	80.5 %	84.8 %	78.4 %

Lenalidomide Plus Rituximab for Untreated Indolent B-Cell NHL: Study Design

Drug	Dose	Administration	
Rituximab	375 mg/m^2	IV	Day 1
Lenalidomide	20 mg/day*	Oral	Days 1-21

- **28-day cycle, with delay for toxicity or cytopenia**
- **Restaging was performed after cycles 3 and 6**
- **Lenalidomide increased to 25 mg/day after 3 cycles if SD**

IV=intravenous; SD=stable disease; SLL=small lymphocytic lymphoma.
*SLL patients received 10 mg/day cycle 1, 15 mg/day cycle 2, 20 mg/day on cycle 3.
Fowler et al. Abstract and poster presented at: 2010 Annual ASCO Meeting; June 4-8, 2010; Chicago, IL. Abstract 8036

Lenalidomide Plus Rituximab for Untreated Indolent B-Cell NHL: Responses

Histology	N	NE, n	SD, n	PR, n	CR/CRu, n	% ORR (%CR/CRu) Eval (n=45)	ITT (n=48)
Follicular	30	1	1	3	25	97 (86)	93 (83)
SLL	5	-	1	2	2	80 (40)	80 (40)
Marginal	13	2	3	2	6	73 (55)	62 (46)
Total	48	3	5	7	33	89 (73)	83 (69)

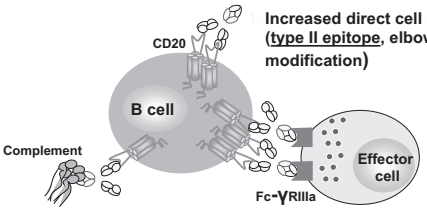
Molecular response

PCR results*	Screening	S/P Cycle 3	S/P Cycle 6
BCL-2 positive	11	3	1
BCL-2 negative	18	26	28
Total % conversion	-	8/11 (73%)	10/11 (91%)

NE=not evaluable; CRu=unconfirmed complete response; PCR=polymerase chain reaction; ITT=intention-to-treat.
BM and peripheral blood were tested at baseline, cycle 3, and cycle 6.
Fowler et al. Abstract and poster presented at: 2010 Annual ASCO Meeting; June 4-8, 2010; Chicago, IL. Abstract 8036.

GA101 induces high ADCC and cell death

Mechanisms of action of GA101 (a type II antibody) versus type I antibodies (e.g., rituximab, 2H7)



Increased direct cell death (type II epitope, elbow-hinge modification)

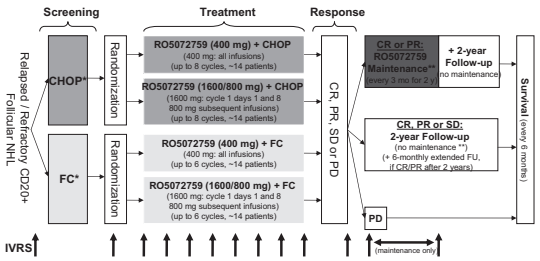
3. **Lower CDC activity unlike rituximab (type I epitope) due to recognition of type II epitope**

Increased ADCC via increased affinity to the 'ADCC receptor' Fc-γRIIIA

GA-101 in refractory LG NHL – *ASH 2010 Salles et al*

	LD Cohort (400mg)	HD Cohort (1600/800mg)	All
Number	18	22	40
Sex (M/F)	12/6	13/9	25/15
Follicular histology (n)	14	20	34
Median age	51 (42-79)	61.5 (44-76)	60.5 yrs (42-79)
Median prior treatments	3 (1-8)	3 (1-11)	3 (1-11)
Previous rituximab (n)	18	21	39
Rituximab refractory	12	10	22
Prior stem cell transplant	6	8	14
Response Data			
EOR	3 (17%)	12 (55%)	15 (38%)
EOR in refractory patients	1 (8%)	5 (50%)	6 (27%)
Median PFS)	6 months [1.1-16.9+]	11.3 months [1.8-14.2+]	

BO21000 Study Design



* As determined by investigator
** As determined by investigator and confirmed by Sponsor
CR = Complete Response
PR = Partial Response
SD = Stable Disease
PD = Progessive Disease

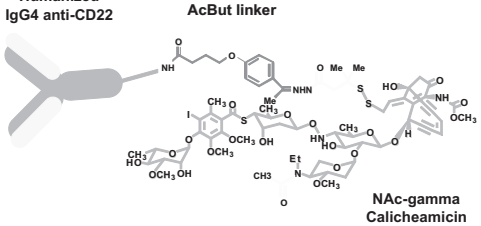
Total: approx. 56 eligible patients

CD22-Targeted Chemotherapy, CMC-544

Inotuzumab Ozogamicin

Humanized IgG4 anti-CD22

AcBut linker



NAc-gamma Calicheamicin DMH

CMC-544 2010 update *#430 Goy et al*

- **43 patients with refractory/relapsed LG NHL (35 FL)**
- **Median age 62 , 43% > 4 regimens**
- **FLIPI 59% 3-5**
- **ORR 53% CR 19%**
- **PFS : 59% @6/12**
- **26% discontinued due to AE's/SAE's (myeloid , LFTs)**
- **Conclusions : Further studies warranted**

Conclusions

- *R-Chemo-R standard of care in patients who require therapy*
- *Patients relapsing early likely to benefit from PBSCT ? Allo /? Auto*
- *Patients relapsing late to receive same/similar Rx again*
- *Older patients may receive novel agents ? Bendamustine ? New Abs or "boosted" Ab*
- *Most patients especially in high FLIP groups will still have their lives substantially shortened by this disease*

Chronic Myeloid Leukemia

Dear colleagues,

I would like to extend a warm welcome to this session on chronic myeloid leukemia, which will cover a topical set of issues relating to the practical management of patients with CML. Fueled by the spectacular success of imatinib as front-line therapy for CML, we are becoming increasingly ambitious in our treatment goals. The availability of new drugs, more sensitive diagnostic tests and an improved understanding of mechanisms of treatment failure are enabling us to even consider cure as a long-term goal.

In the beginning of this session, I will review the current data on TKI-based therapy of CML, with a focus on the newer second generation kinase inhibitors. Ali Turhan will make a convincing case for the profound value of molecular studies in the everyday clinical management of patients, and Ahmet Elmaacly will discuss the current – and possibly future- role of SCT in treatment of CML.

We can anticipate that this will be an interesting and thought-provoking session, which should stimulate a lively discussion and give ample opportunity to ask questions to the expert members oft he faculty.

Oliver Ottmann, MD

Current Treatment: Rise of the Second Generation TKIs

Oliver Ottmann

Universitatsklinik Frankfurt, Medizinische Klinik III, Frankfurt, Germany

Approximately 13 years after the ABL tyrosine kinase inhibitor imatinib first entered clinical testing, young colleagues in hematology are starting to be unfamiliar with the dismal outcome of CML patients in what is now referred to as the „pre-imatinib" era. The 8 year update of the pivotal IRIS trial, in which imatinib was randomized against what was then standard therapy for CML, interferon-alpha plus cytarabine, illustrates the spectacular impact of imatinib on outcome: with intention to treat analysis, estimated overall survival was 85% after 8 years, and 93% when only CML-related CML deaths were considered. The annual rate of events peaked during the first three years and then consistently declined overall and event-free survival of newly diagnosed chronic phase CML patients. Notably, progression to accelerated or blast phase disease became an exceedingly rare event after the 3rd or 4th year of treatment.

Despite the success of imatinib treatment, a number of issues have become apparent which indicate room for improvement. An analysis of patient disposition in the IRIS trial revealed that nearly 40% of patients did not have an acceptable outcome and discontinued study treatment, due to failure to achieve a complete cytogenetic response (CCyR), loss of a CCyR or safety and tolerability issues. Those patients who discontinued imatinib did poorly, with a 50% survival probability 5 years after stopping imatinib. Thus, it appaers there is a significant subset of patients who could benefit from improved therapy.

Achievement of a complete cytogenetic response has long been considered the best surrogate marker for excellent long-term event-free survival and continues to be a robust indicator of success as determined by a lack of progression. Across a variety of studies, including IRIS, TOPS, ENESTnd, DASISION, and SPIRIT, the CCyR rates after 12 months ranged from 58% to 72%. With the continuous improvement and wider availability of molecular analysis of minimal residual disease by RT-PCR, the focus has shifted to evaluation of these more sensitive techniques as potentially superior predictive tests. Major molecular response, defined as 0.1% BCR-ABL by International Scale, has a firm place in the response classification of the ELN recommendations, and even more stringent criteria of complete molecular response or undetectable bcr-abl transcripts have become relevant in the discussion of potential cure. These cyto- and molecular-genetic analyses facilitated more precise assessment of the efficacy of the newer second generation TKI such as nilotinib and dasatinib.

In order to improve treatment results in patients with more advanced stages of CML or those in chronic phase who had failed imatinib, several second generation TKi were developed by rational drug design. Whereas nilotinib is a chemical modificationof the imatinib molecule, dasatinb and bosutinib are dual ABL and SRC family kinase inhibitors. Phase 2 studies demonstrated that these compounds were generally well tolerated, with somewhat distinct toxicity profiles. As no randomized comparisons between these agents are available, precluding a direct comparison. Based on generally small, single-arm studies, all three of these agents showed significant activity in second line treatment of imatinib resistant CML-CP, with complete hematologic response rates ranging from approximately 70% to 90% and CCyR rates of 40% to 50%.

Mutations in the tyrosine kinase domain (TKD) of bcr-abl are present in a substantial proportion of patients resistant to imatinib. Identification of the presence and type of mutation have an impact on treatment decisions when deciding on which TKI to utilize for salvage therapy. Thus, the T315I gatekeeper mutations confers absolute resistance to nilotinib, dasatinib and bosutinib, while the so-called P-loop mutations are variably susceptible to these agents. However, the probability of inducing a CCyR in a patients harboring a P-loop mutations by using nilotinib are minimal, while dasatinib displays little inhibitory activity against cells harboring the F317L or V299L mutation. Thus, mutational testing is recommended in all patients who develop resistance to a TKI, based on rising levels of bcr-abl transcripts.

After nilotinib, dasatinib and bosutinib were shown to have substantial anti-leukemic efficacy

as second-line agents in CML patients failing imatinib, it was a rational decision to introduce these novel drugs into the front-line setting. Two large, randomized trials comparing either dasatinib or nilotinib with standard dose imatinib led to the regulatory approval of these drugs for the front-line treatment of CML. The ENESTnd Study was a 3-arm clinical trial comparing nilotinib at doses of 300 mg and 400mg twice daily with imatinib (400 mg daily), while the DASISION trial compared 100 mg dasatinib with the same standard dose of imatinib.The primary endpoints in these two studies were major molecular response at 12 months and confirmed CCyR by 12 months, respectively. Thus, direct comparisons between these studies need tob e viewed critically. Nevertheless, both studies demonstrated significant superiority of the 2nd generation TKI over imatinib in terms of CCyR and MMR rates at or by the 1 year timepoint. Notably, the response kinetics were also far more rapid with nilotinib and dasatinib than with imatinib, One of the most striking findings was the profound reduction of the number of patients progressing to accelerated or blast phase on treatment: in the ENESTnd trial, 4.2% of imatinib-treated patients progressed during the first 24 months, in contrast to 0.7% and 1.1% with 300 mg BID and 400 mg BID, respectively. It should be noted that to date, these superior results have not yet resulted in an improvement of overall survival. Tolerability was good, discontinuation rates due to adverse events ranged from 8% to 11% in these two trials. Comparable results were obtained in a randomized trial of bosutinib 500 mg/day versus imatinib 400 mg/day, although in this trial the primary endpoint (CCyR at 12 months) was not statistically significantly different.

Considering the rapidity with which deep molecular responses are achieved with these second generation TKI, the issue of discontinuation of TKI is receiving considerable attention. Two studies with reasonably long follow-up have been reported, the french STIM study and an australian study. A complete molecular response of at least two years duration was prerequisite for stopping the TKI in both studies. Approximately 60% of patients lost their CMR, almost all within 6 months of discontinuation. Most of the remaining patients retained their CMR for up to 2 years. It is encouraging to note that all patients who lost their molecular or even cytogenetic response remained sensitive to imatinib re-challenge. Extensive molecular studies using both RT-PCR for detection of bcr-abl transcripts and PCR to identify patient specific BCR-ABL DNA surprisingly revealed the presence of BCR-ABL DNA even in patients who mainteined their molecular response as assessed by RT-PCR. Clearly, therefore, any attempts at discontinuing TKI treatment should be restricted to clinical trials with close monitoring of the patients.

The aforementioned results highlight the most important remaining issues in first-line CML treatment: the inability to eradicate leukemic stem cells with the available TKI and the resistance to TKI conferred by the T315I gatekeeper mutations. The latter problem is being addressed by novel agents including the 3rd generation TKI ponatinib, allosteric inhibitors and stem cell transplantation. Exploitation of signaling pathways that are involved in self-renewal of leukemic stem cells (e.g. the hedgehog pathway) and can be inhibited by pharmacologic agents, e.g. smoothened antagonists, hold considerable promise in eliminating those cells capable of causing leukemic recurrence. While the results of studies testing these compounds are awaited, the option of allogeneic SCT in those patients who fail TKI therapy should not be forgotton.

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Titles

M.D. 1978 (University of Paris)
Ph.D 1990 (University of British Columbia, Vancouver, Canada)
Associate Professor of Hematology 1991 (University of Paris V)
Professor of Hematology (2005)(University of Poitiers)

Education

1972-1978: **Medical School** (Faculté de Médecine Broussais-Hôtel-Dieu, Université Pierre et Marie Curie, Paris, France).
1978-1984: Internal Medicine Residency, Paris University Hospitals
1984-1986: Medical Oncology Fellowship (J.H. Goldie) Cancer Control Agency of British Columbia et Vancouver General Hospital, Vancouver, Canada
1986-1991: **Ph.D and post-doctoral fellowship**: **(C.J. Eaves)** (University of British Columbia and the Terry Fox Laboratory, B.C Cancer Research Centre, Vancouver, Canada)

Clinical Appointments

1991- 1995: Clinical Assistant Professor of Hematology, **(B. Varet)** Hôpital Necker, Paris, France
1995-2005: Scientific Director -Cell Therapy Unit, Institut Gustave Roussy, Villejuif, France
1995-2005: Staff Member and Consultant Hematologist- Department of Medical Oncology, Division of Hematology, Institut Gustave Roussy , Villejuif, France.
2005-Present: Consultant Hematologist, Institut Gustave Roussy, Villejuif, France
2005- Present: Head, Division of Laboratory Hematology and Oncology University of Poitiers, Hospital Jean Bernard

Research Appointments

1991-1995 Team Leader in Hematology, CNRS URA 1461, Hopital Necker, Paris, France
1995-2005 Team Leader INSERM U362, Institut Gustave Roussy, Villejuif, France
2005-2008: Research Director, EA3805 – "Leukemic and therapeutic Stem cells" University of Poitiers
2008-Present: Co-Director, INSERMU935- University Paris Sud 11/ University of Poitiers

Licences and Diplomas

ECFMG (USA); VQUE (USA)
Doctor of Medicine (University Pierre Marie-Curie Paris VI , France)
Nephrology Subspecialty Qualification (Paris, France)
Medical Oncology Qualification (Univ. British Columbia, Vancouver, Canada)
Doctor of Philosophy (PhD) (Univ. British Columbia, Vancouver, Canada)
Hematology Subspeciality Qualification (University Paris V, France)
Habilitation for Directing Research (University Paris V, France)

Memberships

American Society of Hematology /Société Française d'Hématologie

Research Interests

Chronic myelogenous leukemia (CML) therapy
CML stem cells: Self-renewal and persistance of leukemic stem cells,
CML models
Hematopoietic potential of adult and embryonic stem cells
Cell Therapy, Regenerative medicine, Stem cell plasticity

Ahmet H. Elmaağaçlı, M.D.

Date of Birth: September 1, 1961
Birthplace: Kayseri/Turkey
Domestic Status: Married

Education

Elementary School	1967-1971
High-School (College)	1971-1980
Education in Chemistry	
University of Siegen/Germany	1980-1981
Medical Education	
University of Tübingen Medical School	1981-1985
	1986-1988
Education in Molecular Biology	
Arizona State University /Tempe, Arizona	1985-1986

Professional Experience:

Fellow in Internal Medicine	
Medical Dept. Herzzentrum Berlin	1/89-6/89
Dept. of Internal Medicine (Tumour Research)Essen	6/89-6/91
Military Hospital Burdur/Turkey	8/91-12/91
Dept. of Hematology Aachen	1/92-12/92
Training in Molecular Biology Essen	
Institute of Molecular Biology/Essen	12/92-5/93
Dept. of Bone Marrow Transplantation Essen	5/93
Licensure in Internal Medicine	2/98
Licensure in Hematology/Oncology	8/01

Current Position
Assistant Medical Director at Dept. of Bone Marrow Transplantation and Assistant Professor for Internal Medicine at the University of Essen Medical School
Head of the molecular genetic laboratory at the Dept. of BMT
Head of the outpatient-service of the Dept. of BMT

Research Experience
Numerous grants in experimental and clinical bone marrow transplantation.

Current Research Topics
Clinical blood and marrow transplantation
Minimal residual disease
Chimerism studies
Impact of single nucleotide gene polymorphism on transplant
Short interference RNA and leukemic relapse
HCMV and leukemic relapse in AML

Society Memberships
American Society of Hematology
German Society of Internal Medicine
European Bone Marrow Transplantation Cooperative Group
Turkish Society of Hematology

Clinical Studies
Extracorporal Photopheresis for treatment of chronic GVHD
Single nucleotide polymorphism and transplantation
CD34+ enriched PBSCT for CML
HCMV and leukemic relapse in AML

Stem Cell Transplant in Imatinib Era: Any Sign for Revival?

Ahmet Elmaağaçlı

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The BCR-ABL specific tyrosine kinase inhibitor (TKI) Imatinib is highly effective in the treatment of patients with chronic myeloid leukemia (CML) and has displaced Interferon alpha and allogeneic hematopoietic stem cell transplantation (HSCT) as primary therapies for patients with CML in first chronic phase (CP) in the recent years[1]. Although the majority of patients with CML in 1. CP benefits substantially from the use of TKI, some patients fail to respond or lose their initial response to treatment with TKI. These patients show a significant worse survival and progression-free survival (PFS) as reported by a study of Marin and co-worker. According to the published recommendations of the European Leukemia Net (ELN) in 2006, the assessment of response to TKI at 3, 6, 12 and 18 months helps to identify patients responding poorly to TKI[2]. Marin and co-worker reported that patients with CML in 1.CP not responding to imatinib and therefore classified as "failure" at each time of evaluation, show a significant worse rate of survival, PFS, and cytogenetic response than other patients. They found that based on the assessment at 12 months, patients with failure to imatinib had a 5-year survival rate of only 87.1% versus 95.1% ($p<0.02$), a PFS rate of 76% versus 90% ($p<0.002$) and a complete cytogenetic response rate of 26.7% versus 94.1% as compared to patients responding to imatinib ($p<0.001$), respectively. Further, they reported similar worse outcome for patients meeting the criteria of "suboptimal response" at 6 months (less than partial cytogenetic response with percentage of Philadelphia positive chromosome >35%) and 12 months (less than complete cytogenetic response), whereas responders to imatinib treatment had a 5-year PFS of 100%[2].

Although second-generation tyrosine kinase inhibitors are more effective in chronic phase of chronic myeloid leukemia (CML) inducing higher rates of response than imatinib, some patients also fail to respond, which is associated with a similar worse outcome as described for imatinib[3-6]. These non-responders often have a mutation at the BCR-ABL tyrosine kinase domain site or a clonal evolution, which is defined as the presence of a variety of additional, nonrandom chromosomal abnormalities beside the Philadelphia chromosome[7]. Clonal evolution occurs in approximately 30% of patients in acceleration phase (AP) and in about 80% patients in blastic phase. It represents also a criterion for AP and is generally associated with a poor prognosis. The most commonly reported clonal evolutions include double Philadelphia chromosome, chromosome 17 abnormalities, and trisomy 8[7].

Although TKI have revolutionized the management of chronic phase CML, their impact on the management of advanced phases of CML remain unsatisfactory. Treatment of advanced phases of CML has always been challenging and the induction of long-termed responses remains a rare event. Even when responses are obtained with the TKIs, they are short, particularly in patients with a blastic phase (BP) of CML.

Allogeneic stem cell transplantation (HSCT) represents a second-line therapy option for patients with CML in chronic phase after treatment with TKIs. But allogeneic HSCT is still associated with a high rate of transplant-related mortality (TRM) and morbidity reported from earlier published data mainly in the 1990's[8]. However, here we show that allogeneic HSCT for patients with CML has improved markedly in the last decade due to recent innovations in the detection and treatment of life-threatening complications after transplant and further, by optimizing the donor selection for unrelated donors using high-resolution testing for the histocompatibility antigen loci (HLA) A, -B, -C, -DR1, -DQ1[8]. Moreover, the risk of allogeneic HSCT for each patient can be assessed prior to transplant by the pretransplant EBMT score as described first by Gratwohl and coworkers[9]. This pretransplant EBMT score consists of the following five pretransplant variables: donor type, disease stage, age of recipient, gender combination of recipient and donor and time of diagnosis to transplant. Each of these variables covers two to three categories with a score of 0 to 2. The summation of the scores reflects the estimated probability of survival after transplant which is classified between score 0-1 (best category) and score 5-7 with the worst outcome of transplant.

In the following I report about the outcome of 252 patients who received an allogeneic transplant for CML after myeloablative conditioning from 1997 to 2007 at the University Hospital of Essen. We could clearly show that the OS of patients transplanted for CML in 1.CP correlated very well with the allocated EBMT score. Thus, we found an estimated 5-year OS

of 97%, 84%, 76% and 58% for patients with EBMT scores of 0-1 (n=30 patients), 2 (n=84 patients), 3 (n=70 patients), 4 (n=30 patients) respectively.

Further, we could show that patients transplanted with highly enriched CD34+ stem cells from HLA-identical sibling donors without any post transplant immunosuppression for CML in 1.CP had not only an improved OS but also a low incidence of acute graft-versus-host disease (GVHD) of only 30.1%. Hereby, GVHD occurred mainly after application of programmed donor-lymphocyte infusions (DLI). All patients received a myeloablative conditioning regimen including a total body irradiation regimen in most cases.

Patients transplanted in more advanced disease phases of CML (beyond 1. CP) had a reduced estimated OS of only 43.1% (n=61) as evaluated recently. From these patients 55.7% (n=34) were transplanted in second or third chronic phase, 23% (N=14) in acceleration and 21.3% (n=13) in a manifest blast crisis of CML. The 5-year estimation for overall survival declined with increasing EBMT pretransplant risk score as expected. Patients with advanced disease phase of CML had an overall survival of 55%, 45.5% and 15.4 %, respectively. Acute GVHD occurred in 51.8% of all patients, whereas a hematological relapse occurred in 18% 22% and 71.5%, respectively. The major cause of treatment failure was relapse after transplant as expected.

Improved outcome after transplant was recently also reported for CML patients in 1. CP by Saussele and co-worker who performed a matched-pair analysis with 53 patients receiving an allogeneic transplant for CML in 1. CP and 106 patients treated with imatinib[10]. Thereby they matched one transplanted patient to two patients who received a therapy with imatinib. They found no statistical differences in the outcome of both groups with an OS rate of more than 90% for each group after four years of observation. This retrospective analysis performed by the German CML study group demonstrates best the improved results of transplant.

For CML patients the results of allogeneic transplant further improved in the recent years and transplantation remains especially for patients with low pretransplant EBMT scores a highly effective second-line alternative therapy option after treatment failure of TKI[8,11].

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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 review treatment indications and current therapeutic options 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 evidence for the efficacy of allogeneic and autologous stem cell transplantation in CLL and its potential to change the natural history of the disease, and discuss indications and timing of transplantation.

Peter Dreger, MD.

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Personal Data

Born: 05/25/45 – Manresa (Barcelona, Spain)
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Medical Residency: Hospital Clínic, Barcelona (1969-1973)
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Hospital Position: Professor of Medicine. CLL and Lymphoma Program. Hospital Clínic. University of Barcelona. Chairman, European Research Initiative on CLL
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Research & Other Activities

Chronic lymphoproliferative disorders and lymphomas: Analyses of their biologic and clinic heterogeneityy. Molecular pathology, apoptotis mechanisms; prognostic models, experimental therapies.
Coordinator: Programa d' Hematología i Oncología – Institut de Reçerca Biomèdica August Pi i Sunyer (IDIBAPS)
Coordinator of PETHEMA trials on CLL and lymphomas
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Founding member of the *International Workshop on CLL*
Founding member od the European Research Initiative for CLL (ERIC)
Member of the Intenational Extranodal Lymphomas Study Group
Member of the Lymphoma Working Party of the EBMT
Chairman of CLL Studies of the IBMTR/ABMTR
Member of the WHO Committe (Chronic Lymphoid Leukemias)
Member of the WHO Clinical Advisory Committe for the Classification of Hematological Malignancies.
Member of the NCI Program on Leukemia and Lymphoma Molecular Profiling Project
Professor of the European School of Hematology
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Member of the Editorial Board

Leukemia and Lymphoma (UK), Medicina Clínica (Spain), Leukemia Research (UK), Annals Hematology (Germany), European Journal Hematology (Sweden), Molecular Biology & Cytokines (Germany), Hematology & Cell Therapy (France), Haematologica (Italy/Spain), Journal of Clinical Oncology (USA). Clinical Lymphoma (USA), European Journal of Haematology (Denmark), Clinical Lymphoma (USA), Young and Adolescent Clínical Oncology (USA), Advances in Hematology (USA)

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Societies and Scientific Associations

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President CATALAN SOCIETY OF HEMATOLOGY (1991-1995)
Treasurer EUROPEAN HEMATOLOGY ASSOCIATION
President MEETING OF THE EUROPEAN HEMATOLOGY ASSOCIATION (Barcelona, 1999)
President EUROPEAN HEMATOLOGY ASSOCIATION (since 2000)
Corresponding Member – ROYAL ACADEMY OF MEDICINE OF BARCELONA (since 2004)
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ANEP, FISS, Leukemia Research Found (U.K.), Instituto Italiano di Oncologia (Italy), Agencia Europea del Medicamento (Londres, U.K.) along with reviewer for many Medicine, Hematology and Oncology journals, including New England Journal of Medicine, Blood, Journal Clinical Oncology, Nature, The Lancet, Oncology and others.

Invitations to national and International Meetings: more than 150
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Recent Awards

Dade-Grifols (1975 y 1987)
Schering-Plough (1989 y 1991)
Ernest Schering (1999, 2001 y 2002)
Medaille de la Ville de Paris (1997)
Lección Antonio Raichs (Sociedad Española de Hematología) (1999)
Fundación Lilly Biomedicina Clínica (2002)
Emiram Eldor Lecture (University of Tel Aviv) (2003)
Generalitat de Catalunya. Distinció per a la Promoció de la Recerca Universitària (2004)
Royal College of Pathologists (Londres) Honorary Fellowship (2005)
Premio Severo Ochoa (2005)
Premio a la Calidad en el Sistema Nacional de Salud Ministerio de Sanidad y Consumo (2007)
IV Premio Nacional de Oncología Fundación Echevarne (2007)
Life Time Award European Society of Medical Oncology, 2008
Ben Gurion Medal (Israel) (2008)
Medalla Rai/Binet (2009)
Doctor Honoris Causa University of Athens (Greece) (2010)
Life Time Jean Bernard Award. European Hematology Association (EHA) 2010

Advisory Boards

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Tentative Topics are Standard Treatment and Indications

Emili Montserrat

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Treatment of patients with chronic lymphocytic leukemia (CLL) has experienced important progress in the last decade. However, treatment of patients with CLL is only indicated in case of active or progressive disease (e.g., general symptoms, lymphadenopathy or organomegaly increasing in size, anemia or thrombocytopenia due to bone marrow infiltration, autoimmune cytopenia not responding to conventional therapy, hypogammaglobulinemia plus infections, rapid blood lymphocyte doubling time).

In patients requiring therapy, recently published randomized trials demonstrate that the combination of fludarabine, cyclophosphamide, and rituximab (FCR) is the treatment of choice for both previously untreated and treated patients. Importantly, in patients with no prior therapy FCR not only produces both a significantly higher response rate and a longer progression-free survival but also a longer overall survival.

However, in spite of this progress, there is still a lot of room for improvement and many questions to be solved. For example, (1) there is an important proportion of patients in which due to comorbidity or advanced age FCR can not be safely given; (2) patients with 17p deletions or mutations do not respond to FCR; (3) patients failing to FCR have very poor prognosis (median survival, 2-3 years), and (4) CLL continues being incurable. Several genetic lesions predict response to current therapy. Thus, patients with 17p deletion in more than 20% of leukemic cells by FISH analysis do not respond to current chemotherapy. Likewise, those patients with 11q deletion respond much better to FCR than to other therapies. Although patients with 17p abnormalities (TP53 deletion or mutation) can respond to alemtuzumab plus corticosteroids, the proportion of responders is low and the progression-free and overall survival short.

Many new monoclonal antibodies (MoAbs), antileukemic agents and immunomodulators are being actively investigated and hopefully should improve current treatment results. Among new MoAbs, Ofatumumab, GA-101 and Veltuzumab are new anti-CD20 agents that have already demonstrated good clinical activity and are now investigated in randomized clinical trials.

Bendamustine is an antileukemic agent that has shown important activity in indolent lymphoid neoplasms, including CLL. Lenalidomide is an immunomodulatory agent widely investigated in many hematologic malignancies, including CLL, with positive results. Different phase II and phase III trials investigating these agents in combination are underway. Other newer agents include small molecular pharmaceuticals (SMIPs), such as TRU-016 which targets CD37, Bcl-2 antagonists including ABT-26 and Obatoclax, BCR-2 signal inhibitors (e.g., PI3K, PCI-32765 and CAL-101), and many other compounds.

Other areas which deserve investigation are the role of maintenance therapy (e.g., MoAbs, lenalidomide), as well as the use of minimal residual disease (an important surrogate for prolonged survival) as treatment endpoint.

Finally, allogeneic stem cell transplantation, which is the only treatment modality overcoming the impact of poor prognostic markers and resistance to therapy, should be considered in any single patient with TP53 deletions or mutations, as well as in patients failing to chemoimmunotherapy. Since results obtained with allogeneic stem cell transplantation are better in non-heavily pre-treated patients and when the disease is not totally refractory, this procedure should not be postponed in patients actually resistant to FCR, in whom further chemotherapy would only deteriorate their general clinical condition. Although reduced-intensity conditioning regimens have decreased transplant-related mortality, this continues being high (15-20%). Because of this, efforts are being made to improve the safety of transplants and to design novel forms of cellular therapy (e.g. manipulated autologous T cells).

In conclusion, in the last decade progress in the therapy of CLL has been quite impressive but many patients can not be treated with the most effective forms of therapy and cure remains elusive. In the near future, international cooperative studies exploring multitargeted, disease-risk oriented therapies should make possible further progress in the treatment of this disease.

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Eva Kimby is Associate Professor of Haematology at the Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden. Her main research interests are indolent lymphoma, CLL and the applications of immunotherapy. Dr Kimby was elected Chairman of the Group for Indolent Lymphomas within the Nordic Lymphoma Group in 1997 and Chairman of the Swedish CLL Group in 2004. She is a member of several national and international scientific societies and is a working member of the European Group for Blood and Marrow Transplantation CLL Subcommittee and the International Workshops on Waldenström's Macroglobulinemia and Vice-Chairman of the European Research Initiative on CLL (ERIC). Dr Kimby has an advisory role on the Scientific Board of the European Mantle Cell Lymphoma Network and is a reviewer for Haematologica, Blood, Leukemia and Journal of Clinical Oncology. She is actively involved as a key investigator in several haematology trial groups, is the Principal Investigator for two large Nordic rituximab +/- interferon trials and a co-investigator in several CLL studies. She has published more than 100 papers and several reviews in peer-reviewed international journals.

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Education and Professional Experience

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1974-1978	Resident in Medicine, Danderyd Hospital, Sweden.
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1980-1986	Registrar of Medicine (Hematology), Danderyd Hospital
1984	Resident in immunology SBL, Stockholm
1984-1989	Research Fellow in Hematology, Danderyd Hospital
1989	**Doctor of Medicine (Ph.D.) Thesis, Karolinska Institute**
1989-1992	Senior Registrar of Hematology, Danderyd Hospital
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1992-1994	Assistant Professor of Medicine, Division of Hematology, Danderyd Hospital.
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Medical Licensures

Fully qualified physician 1974
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Specialist in Internal Medicine 1981
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Doctor of Medicine (Ph.D.),Thesis Karolinska Institutet, Stockholm,1989
Several courses on GCP 1998-2008 and the new EU directive 2009

Membership of scientific societies

Swedish Society of Medical Sciences
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Swedish Society of Internal Medicine
Swedish Society of Oncology
The Nordic lymphoma group
European Hematology Association
The American Society of Hematology
The European Society of Medical Oncology
European Group for Blood and Marrow Transplantation

Major Interests

Chronic Lymphocytic Leukemia, T- and NK-cells. Non-Hodgkin-Lymphomas,focus on follicular lymphoma and Waldenstroms macroglobulinemia, Immunology, Monoclonal antibodies, Clinical trials , Microenvironment, FISH.

Medical trials:
Principal investigator: The Nordic Mabthera phase II trial in low-grade lymphomas 1998-99, Phase III trial in indolent lymphomas; Mabthera +/- IFN 2002- 2008 within The Nordic Lymphoma group 2002-.
Swedish PI in several CLL, FL and Waldenstrom trials.
Member the CLL trialists Collaboratve Group,Oxford.
Collaborator in International trials in Waldenströms macroglobulinemia.
Coinvestigator in the Stockholm alemtuzumab studies and in several international trials in CLL and lymphoma.
Principal investigator together with professor Emanuele Zucca in collaborative SAKK-NLG trials
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Organizational posts:
Chairman NLG subcommittee on Indolent Lymphoma since 1997.
Chairman Nordic Society of Haematology 2000-2001.
Chairman for program continuous medical education, Swedish Society of Hematology 1994-97.
Chairman Swedish CLLL group 2004 2010.
Vice chairman ERIC, European LeukemiaNetwork since 2007.
Working member of Swedish Lymphoma Group since 1997, vicechair since 2007.
Member coordinating group for Nordic lymphoma Group (NLG)
Member subcommittee EBMT CLL and Lymphoma Working Parties since1997.
Member Medical Advisory Board Waldenströms macroglobulinemia since 2001.
Member Advisory Board European Network Mantle cell lymphoma since 2003. Member Lunenburg Lymphoma Biomarker Consortium since 2005.
Member of the IWMF Scientific Advisory Committee since 2009
Teaching: Pre- and postgraduate courses at the Karolinska Institute. Postgraduate courses: Swedish and Nordic Society of Haematology and Swedish society of Oncology. USA CME courses 2005 and 2008. Book chapters in Swedish and English educational literature.
Lecturer at several international educational meetings on CLL and lymphoma; ESH International course on monoclonal antibodies, Paris 2003, Nordic Hematology meeting 2001, 2003, 2005 and 2007, 2010. Baltic Hematology meeting 2001, 2004, 2006, 2009 and 2010, Panhellenic Hematology meeting 2004 and 2006, St Petersburg, Pavlov University 2003, international meeting in Bajkal lake 2007, Moscow 2010, St Petersburg 2008 and 2010, Moldavia 2009.
Faculty member and lecturer LyNE meeting Dublin 2006, Barcelona 2007.
Organizer and lecturer: International course on lymphoma "Center of Excellence", Karolinska University Hospital 2004, 2005, 2006, 2008 and 2009, Södersjukhuset 2007.
Co-organizer and lecturer of ESH-EHA tutorial course in Talinn 2009, Nordic lymphoma group annual meeting 2007 and 2010.
Educational material and books
Author and co author of several chapters in Swedish and International books.
Chapter in Clinical New biological prognostic markers in CLL by Ghia et al, published by Wolters Kluwer Health, Italy 2010.
Invited chairman/lecturer international lymphoma-CLL meetings:
CLL session EHA Lyon 2003, EHA Hamburg 2006, EHA Wienna 2007, EHA Copenhagen 2008, ISH Uruguay 2008, EHA Berlin 2009, EBMT Gothenburg 2009, iwCLL Barcelona October 2009, HEMO 2010 Brazil
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The Joint Annual Meetings of the German, Austrian and Swiss Societies of Hematology and Oncology, Munich 2007, Mannheim 2009. ESMO-ECCO Berlin 2009. The German CLL group 2008. Invited lecturer Brasilian society of Hematology 2010.
Lectures on Waldenstroms macroglobulinemia EHA 2008, IWMF Stockholm 2008, Boston 2009, Venice 2010. Also chairman in several sessions in these meetings.
Co-chairman with professor Coiffier, international CME accredited meeting in Lisboa 2005, Barcelona 2006, Athens 2007, Paris 2008, Munich 2009 and France 2010.
Co-chairman with professor Franco Cavalli in the 10th International Conference on Malignant Lymphoma Lugano 2008. Invited lecturer Lugano 2011.
Panhellenic Hematology meeting Athens 2004, 2006, 2009. Lymphoma meeting Moscow 2010, St Petersburg 2008, and 2010.
International Lymphoma-myeloma meeting Turkey 2007, 2009 and 2011.
Review activity for international journals (JCO, Hematologica, Blood, Cancer Immunology and Immunotherapy. Leukemia & Lymphoma and others) and scientific meetings as EHA, IWCLL, Lugano.
Research activity: more than 120 original papers and several review articles published. Presentations of abstracts at International meetings; EHA, Lugano, IWCLL, ESMO and ASH.
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Supervisor: Victoria Hjalmar M.D., Ph.D. doctoral project on B-cell chronic lymphocytic leukemia (awarded a doctoral degree, Karolinska Institute 2001).
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Novel Perspectives for Resistant Disease

Eva Kimby

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In previously untreated patients with CLL several drugs alone or in combination have shown encouraging results. The situation is not as easy in relapsed and refractory patients, especially for patients resistant to fludarabine. Moreover, patients who relapse after fludarabine-based treatments have poor prognosis due to deteriorating immune functions and high infection rates.

Bendamustine, a drug that combines alkylating and purineanalog activities, has a proven activity in untreated patients randomized between chlorambucil and bendamustine. In heavily pretreated relapsed and refractory patients, this drug has shown high overall response rates and seems to be active in p53-deleted cases in *ex vivo* studies. New combinations of bendamustine with other drugs are currently under clinical investigation.

Monoclonal antibodies, as rituximab, down-modulate expression of antiapoptotic factors, making CLL cells more susceptible to chemotherapy. The combination fludarabine/cyclophosphamide/rituximab (FCR) was used in 177 previously treated CLL patients, with an overall response rate of 73%, with 25% complete responses. Fludarabine refractory patients had a good overall response rate of 58%, but with a low complete response (6%). The median follow-up of all patients was 28 months, and median time to progression for patients achieving complete response, nodular complete remission, and partial remission was 39, 33, and 15 months, respectively. The efficacy of FCR regimen was confirmed in a pivotal phase III randomized trial, REACH, including 552 patients with relapsed or refractory CLL. An improvement in median PFS was seen (30.6 vs 20.6 months; p = 0.0002) with a doubling of CR rates (24 vs 13%; p = 0.0007).

Deoxycoformycin (pentostatin) has also been used in combination with cyclophosphamide and rituximab for the treatment of relapsed or refractory CLL patients. In a series including 25% of patients refractory to fludarabine, the complete response rate was 25% and the overall response was 75%. The results suggested that deoxycoformycin is not cross-resistant with fludarabine.

Alemtuzumab (Campath-1H), a humanized anti-CD52 monoclonal antibody, was first approved for CLL patients with fludarabine refractory disease. In the pivotal study of alemtuzumab in refractory CLL (n= 93), the overall response rate was 33%, but only 2% of patients achieved complete response. The median time to progression for responders was 9.5 months, with an improvement in survival in responding patients. Alemtuzumab have activity also gainst chemotherapy resistant disease with the presence of 17 p deletions and/or p53 mutations. Overall, an impressive efficacy has been seen with clearing of the peripheral blood and bone marrow compartments of the disease, but with poor activity against bulky lymphadenopathy. In the treatment of relapsed or refractory disease, alemtuzumab in combination with fludarabine and rituximab have shown efficacy. In a series of patients including 40% of fludarabine-refractory cases an important number of overall responses (66%) and complete responses (24%) were seen.

Also other monoclonal antibodies have a potential activity in resistant CLL: new humanized anti-CD20 (veltuzumab, ofatumumab, GA-101), anti-CD22 (epratuzumab), anti-CD40 (HCD122), Lumiliximab (anti-CD23), and antiangiogenic antibodies (bevacizumab). Ofatumumab, a fully humanized anti-CD20 monoclonal antibody has shown an overall response rate of 51% for a double refractory (FA) group, refractory to both Fludara and alemtuzumab, and 44% for the BF-group (patients with bulky Fludara refractory disease). Two patients in the BF-ref group achieved complete remission.

Another glycoengineered CD20 antibody, GA101, a so called type II antibody, is differentiated from the type I CD20 antibodies rituximab and ofatumumab by superior overall activity in vitro and clinical studies are ongoing in CLL. Also TRU-016, a humanized anti-CD37 SMIP protein, is of interest in CLL. Preclinical studies have demonstrated that anti-CD37 SMIP protein mediates significantly greater direct killing of CLL cells than rituximab. TRU-016 also has greater Fc mediated cellular cytotoxicity of CLL cells than either alemtuzumab or rituximab. Early clinical trials have shown partial responses with single TRU-016 in CLL patients with prior therapies including those with del(17p13.1).

Steroids have since long been included in therapies against lymphoid malignancies.

The identification of genetic abnormalities in CLL associated with chemotherapy resistance had renewed the interest in steroid therapy as several effects of corticosteroids lead to induction of apoptosis in CLL cells. Glucocorticosteroids have been used in combination with other active CLL drugs in resistant CLL patients. Methylprednisolone at 1 g/m2 per day for five consecutive days (weeks 1, 5, 9, and 13) plus alemtuzumab 30 mg thrice weekly for 16 weeks was used in a clinical trial by the UK CLL cooperative group and clinical activity was seen in patients with deletion of p53; 30% complete response rate with negative minimal residual disease. Glucocorticosteroids have been combined also with rituximab. A high dose of methylprednisolone plus rituximab at 375 mg/m2 on days 1, 8, 15, 22 every four weeks, lead to an overall response from 78-93% with a 36% complete response. The treatment with high-dose methylprednisolone is associated with an increased rate of opportunistic infections, especially if combined with alemtuzumab.

CLL cells show an overexpression of the antiapoptotic protein BCL2, why anti-BCL2 molecules have been tested. Oblimersen, a DNA fragment binding to bcl2 mRNA target, leads to bcl2 mRNA destruction by the RNAse enzyme. A total of 241 patients were randomized to FC versus FC plus oblimersen. Stratification was made according to the number of prior therapies, refractoriness to fludarabine and response duration after the last therapy. In total, 58% of the patients were fludarabine-refractory. In the oblimersen arm, overall response rates (17 vs. 7%), complete response rates (9 vs. 3%), and response durations (> 31 vs. 20 months) were significantly higher, but without improvement in overall survival. In the fludarabine-sensitive subgroup, however, the combination of FC and oblimersen increased the overall survival significantly.

Another molecule that inhibits BCL2 is obatoclax, a pan-Bcl2antagonist that is able to activate the antiapoptotic proteins Bax and Bak and has *in vitro* activity against CLL cells. In a phase I trial obatoclax showed a modest single activity in heavily pretreated patients with advanced CLL. Also navitoclax (ABT-263), a novel, orally bioavailable, small molecule, binds with high affinity to Bcl-2, Bcl-xL, and Bcl-w, promoting apoptosis and h*as* demonstrated anti-tumor activity in patients with CLL. Thrombocytopenia was a dose-limiting toxicity.

Micro-environment seems to play a crucial role in the survival of CLL cells. T-cells and/or cytokines stimuli are important as is the the B-cell receptor and B-cell receptor induced signaling. Spleen tyrosine kinase (SYK) and other kinases initiates and amplifies the BCR signal. The CLL cells are thus effected by inhibiting SYK and other kinases as cyclin-dependent kinase (CDK). Fostamatinib disodium is a clinically available oral Syk inhibitor with an objective response in a small patient series with response in 6 of 11 chemotherapy resistant SLL/CLL patients (55%). Toxicities included diarrhea, fatigue, cytopenias, hypertension, and nausea.

Alvocidib (flavopiridol) is a synthetic flavone, a broad cyclin-dependent kinase(CDK) inhibitor that mediates apoptosis independent of p53 function. Flavopiridol affects mitochondria by downregulating the mitochondrial protein Mcl-1. Recent data suggest that flavopiridol mediates its cytotoxic effects via induction of mitochondrial permeability and changes in intracellular calcium. Single institution studies have shown that alvocidib has significant activity in patients with fludarabine-refractory CLL, including those with bulky lymphadenopathy or del(17p13.1). A recently published phase I trial reported partial responses in 40% of 51 relapsed CLL patients. In a multicenter, international phase 2 clinical trial of alvocidib the efficacy and safety among patients with fludarabine refractory CLL or prolymphocytic leukemia (B-PLL) arising from CLL, is evaluated. The early clinical responses to alvocidib at a preplanned interim analysis after approximately 40% of the planned 165 patients completed at least 2 cycles of therapy, showed a durable clinical activity in some fludarabine-refractory CLL patients, including those with bulky lymphadenopathy and adverse cytogenetics. Toxicity is a major problem for this drug, with several reports of tumor lysis syndrome and renal failure why careful monitoring is needed. Future directions for alvocidib include combinations and more trials to define the best doses and schedule of treatment.

The PI3K pathway is constitutively activated in CLL and dependent on PI3Kδ. CAL-101 is an isoform-selective inhibitor of PI3Kδ that inhibits PI3K signaling and induces apoptosis of CLL cells in vitro. CAL-101 is an oral small drug, that shows acceptable toxicity, and favorable clinical activity in heavily pretreated patients with CLL, including patients with refractory disease, bulky lymphadenopathy, and poor-prognosis cytogenetics. Important lymph node regression has been seen and prolonged duration of symptomatic tumor control.

The antitumoral effect of immunomodulators has been proved in hematologic malignancies. In CLL, both thalidomide and lenalidomide demonstrat-

ed to be active in clinical trials. The mechanisms by which these drugs induce cell death are not completely understood. Lenalidomide induces an increase of several cytokines (interleukins IL-6, IL-10, IL-2) and tumor necrosis factor receptor-1 levels and also seems to reverse the impaired immunologic synapse formation in *ex vivo* studies. In addition, lenalidomide enhances natural killer cell and monocyte-mediated, antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Lenalidomide may thus potentiate the clinical activity of rituximab.

Two phase II studies comprising a total of 99 patients have analyzed the role of lenalidomide in relapsed or refractory CLL patients. Lenalidomide was able to obtain overall response rates of 16-32% with a complete response of 7% in heavily pretreated CLL patients. The drug also appears to have clinical activity in patients with poor-risk prognostic factors. The overall response rate in refractory patients to fludarabine was 30%, and in patients with del(17p) or del(11q) it was 31%.

The optimal dosing of lenalidomide for CLL have not yet been established, doses ranging from 5-25 mg/day for 21 days of a 28-day cycle. Using 25 mg daily, particularly in patients with high lymphocyte counts, several adverse effects have been described as the tumor-flare syndrome. This is a painful lymph node enlargement at the onset of therapy due to a B-cell activation induced by the drug. Also cases of tumor-lysis syndrome have been described especially when CLL patients are treated with high doses of lenalidomide. The above phase II studies in patients with relapsed or refractory CLL used starting doses of 10 mg or 25 mg daily of lenalidomide with promising responses. A phase II/III study was initiated to assess lenalidomide in a dose of 10 mg/d vs 25 mg/d given continuously for 21 days of a 28-day cycle. However, four cases of serious tumor lysis syndrome (TLS) prompted an independent data monitoring committee to amend the protocol into a phase I trial.

In conclusion, there are several treatment options for patients with relapsed and refractory CLL. The disease-free interval after the last therapy, age/comorbidities, the number and type of previous treatments and the presence of risk factors are important to evaluate before therapy decision. Patients relapsing after a short disease-free interval and those truly refractory to alkylating agents or fludarabine alone can be salvaged using purine analogs, combined preferably with alkylating agents and monoclonal antibodies. For patients with del17p/TP53, alemtuzumab and high doses of glucocorticosteroids are active treatments.

In patients with comorbidities the ultimate goal should be the palliation of symptoms, while the treatment of choice for younger patients with CLL also includes allo transplantation.

Inclusion in clinical trials aimed to test the activity of new drugs or drug combinations is always an option.

Peter Dreger, MD

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.

Stem Cell Transplantation

Peter Dreger

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With an incidence rate of about 5 per 100.000, Chronic lymphocytic leukemia (CLL) is the most common lymphoid neoplasm in Europe [1]. Although the results of first-line therapy for CLL are becoming more and more effective, and the overall outcome has steadily improved over the last two decades, allogeneic stem cell transplantation (alloSCT) is increasingly used in CLL. With 354 transplants performed, CLL was the leading alloSCT indication among NHL registered with the EBMT in 2009, followed by TCL (211), FL (199), DLCL (171), and MCL (136) (EBMT, data on file).

In contrast to autografting, where stem cells are re-infused to compensate for the hematopoietic toxicity of single-hit high-dose therapy, alloSCT represents a fundamentally different biological principle, namely the ignition of a permanent immunotherapeutic process within the recipient: the graft-versus-lymphoma effect (GVL). Thus, three crucial questions need to be addressed for each indication in order to assess the potential benefit of alloSCT: 1. Is GVL effective? 2. Can it be translated into therapeutic benefit with acceptable toxicity? 3. Which indications do result from the individual efficacy / toxicity ratio?

Although not curable, CLL often has an indolent behaviour with good responsiveness to cytoreductive treatment or no need for treatment at all. However, about 20% of the patients in need for treatment show an aggressive course and die within few years from diagnosis despite early institution of intensive immunochemotherapy [2;3]. These so called "poor-risk" patients are characterized by preexisting or rapidly developing resistance to conventional chemotherapy, including modern purine analogue-antibody combination regimens [4;5].

Evidence for GVL activity in CLL

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 even if the alloSCT was performed with reduced-intensity conditioning (RIC) [6]. Furthermore, GVL activity in CLL is indicated by a reduced relapse risk in the presence of chronic graft-versus-host disease (GVHD) [7-9], and an increased relapse risk associated with the use of T-cell depletion (TCD) [10;11]. The most

Table 1. Results of prospective clinical trials on RIC alloSCT in CLL

	Dreger et al [16]	Sorror et al [28]	Brown et al [29]	Schetelig et al [30]	Delgado et al [31]
n	90	82	46	30	41
Proportion of alternative donors[a]	59%	37%	67%	57%	41%
4-year progression-free survival	42%[b]	39% (5y)	34% (2y)	58%	45% (27-62) (2y)
4-year overall survival	65%	50% (5y)	54% (2y)	69%	51% (33-69) (2y)
4-year non-relapse mortality	23%	23% (5y)	17% (2y)	15%	26% (14-46) (2y)
Follow-up (years)	3.8 (0.6-8.5)	5	1.7	3.7 (2.1-5.6)	1.3 (0-5.2)

[a] donors other than HLA-identical siblings
[b] event-free survival (counting graft rejection as event)

compelling proof of the GVL principle in CLL, however, comes from studies analyzing the kinetics of minimal residual disease (MRD) after RIC alloSCT, demonstrating that regularly achievement of MRD negativity is linked to immune intervention, such as tapering of immunosuppression or donor lymphocyte infusions (DLI; n=6) [12]. MRD negativity one year post transplant seems to be durable in >90% of patients and predictive for the absence of clinical relapse [12]. 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.

Efficacy and risk of alloSCT in poor-risk CLL

As summarized in **Table 1**, long-term progression-free survival (PFS) can be achieved in 30-60% of transplanted patients by RIC alloSCT. Where studied, patients with poor-risk CLL as defined by purine-analogue refractoriness or presence of deletion 17p- had a similar outcome to patients without poor-risk characteristics [11;13]. This seems to apply also for patients whose poor-risk is caused by TP53 mutations [14]. In a study assessing the value of alemtuzumab in fludarabine-refractory CLL, the only long-term survivors were those who had been consolidated with alloSCT [15]. In conclusion, (RIC) alloSCT seems to be effective in poor-risk CLL, thereby overcoming the adverse prognostic impact of purine analogue refractoriness and del 17p-. However, active or unresponsive disease at the time of alloSCT still remains an predictor of an unfavorable outcome [13;16].

Whereas non-relapse mortality (NRM) rates of up to 44% were reported in older registry analyses of myeloablative alloSCT for CLL [17;18], more recent data obtained with RIC uniformly show an NRM between 15-25% (**Table 1**). This advantage of RIC is even more remarkable as RIC cohorts are generally older and are characterized by higher comorbidity scores. It has to be stressed that in the era of RIC, where the direct toxic effect of the conditioning regimen is often moderate and NRM is essentially due to GVHD and its complications, non-relapse deaths mostly do not occur in the transplant phase but are distributed over the first 24 post-transplant months. For instance, the „early death“ rate as defined by mortality at day +100 post SCT was less than 3% in the German CLL3X trial [16]. This has to be taken into account when considering the risk of dying with and without transplant.

Indications of alloSCT in CLL

In 2007, the EBMT published a consensus on indications for alloSCT in CLL, stating that alloSCT is a reasonable treatment option for eligible patients with previously treated, poor-risk CLL. Criteria for “poor-risk CLL” according to this “EBMT Transplant Consensus” are purine analogue refractoriness, early relapse after purine analogue combination therapy, and CLL with del 17p- or TP53 lesions requiring treatment [19]. Although in the meantime novel treatment modalities and a huge body of additional scientific information have become available, no significant progress has been made in terms of improving the outcome of purine analogue-refractory CLL and 17p-deleted or TP53-mutated CLL [2;20;21]. Therefore poor-risk CLL remains poor-risk CLL as defined in the EBMT CLL Transplant Consensus, and alloSCT the only treatment with the potential of providing long-term disease control in this condition. In addition to disease risk, patient-related risk factors, such as age and comorbidity, have to be considered when the decision about alloSCT is made [22].

Role of autografting in CLL

Before the advent of purine analogs and antibodies, autologous stem cell transplantation (autoHSCT) has been considered an attractive treatment alternative for a selected group of patients. Pioneers in the field of autoHSCT for CLL were Gribben and coworkers from the Dana Faber Cancer Center [23]. An update published in 2005 showed that relapses continued to occur after 10 years of follow-up, translating into a 6-year PFS of 30% and a 6-year OS of 58% [10]. In the MRC pilot study, a large multicenter phase-II trial on autoHSCT as part of first-line CLL treatment, the 5-year OS and PFS rates were 78% and 52% [24]. An update of the GCLLSG CLL3 study, which had a similar design, showed a median OS of 10.5 years and a median PFS of 6.8 years after early autoHSCT [25]. The first and to date only phase III randomized trial was conducted by the EBMT [26]: patients in CR after first- or second-line treatment were randomized to consolidating autoHSCT or watchful waiting. Median EFS was 24 months in the observation group and 51 months in the autoHSCT group, translating into 5-year EFS of 24% and 42%, respectively. While autoHSCT almost doubled EFS and time to retreatment, there was no significant difference in OS (5-year OS 84% and 86%, respectively). In addition, several studies indicate that autoHSCT seems to fail to achieve durable MRD negativity [24;27], which means that autoHSCT cannot be considered as a curative treatment in CLL. Moreover, long-term follow-up observations have raised concerns about the increased incidence of therapy-related myeloid neoplasms (MDS and AML) after autoHSCT. In the Dana Faber and MRC series, a 5- and 8-year incidence-rate of 12% was observed [10]. With all these limitations, autoHSCT cannot be recommended as a standard approach in CLL in the year 2011.

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Aggressive Lymphomas

It is a great pleasure for me to welcome all of you to this session dedicated to Peripheral T Cell Lymphoma (PTCL). PTCL still remain a challenge for all of us. Clinically, most entities are aggressive diseases with overall poor response to classical treatments, and have a dismal prognosis. The diagnosis of PTCL is often difficult, as many cases comprise a reactive cellular infiltrate, which may mask the neoplastic cell population. Moreover, demonstration of T-cell clonality is not feasible by routine immunophenotyping. The complexity of the biology and pathophysiology of PTCLs has been only partly ellucidated. Research in this field has been compounded by the concurrent rarity and diversity of PTCLs, hampering the collection of homogeneous cohorts of patients, the heterogeneity of the pathological samples, the absence of cell lines representative of the major entities, and the lack of good animal models. In recent years, however, novel insights have been gained from genome-wide profiling analyses.

This session has been divided into four specific topics with the idea to cover at least some of the 'burning questions' which are still nowadays opened in the field of PTCL. In order to achieve that, we have tried to put together a group of worldwide recognized experts in the subject. The first talk on Pathology and Pathophysiology of PTCL will be covered by Prof. Philippe Gaulard (Hopital Henry Mondor, Creteil, France) from the Groupe d'Etude des Lymphomes des Adultes (GELA). The GELA Group and specifically Prof. Gaulard have been very active in the last years to try to give some insight in the biology of these diseases. In addition, there will be three more clinically oriented presentations. Prof. Dr. Norbert Schmitz (Asklepios Hospital St Georg, Hamburg, Germany) and one of the leaders of the German High-Grade non-Hodgkins Lymphoma Study Group (DSHNHL) will be presenting what is nowadays known about first line therapy in PTCL patients and options for the future, Prof. Francesco D'Amore (University Hospital Aarhus, Aarhus, Denmark) who is currently the chairman of the Danish Lymphoma Group and of the Working Group on T-cell lymphomas of the Nordic Lymphoma Group will present the role of new drugs in the treatment of this disease and finally, the role of intensive therapies i.e. autologous and allogeneic stem cell transplantation in the therapeutic landscape of PTCL will be discussed by myself.

It is our intention to try to cover as much as possible the major open questions in the PTCL field; some of them will be answered by the different speakers and I am sure that many others will still be the subject of future investigations.

Anna Sureda, MD

Philippe Gaulard, MD

Philippe Gaulard, M.D., is Professor of Anatomic Pathology at the Paris XII University School of Medicine in Créteil (France) and is the director of the research Unit at the INSERM focusing on the oncogenesis of lymphoid malignancies. He maintains an important practice of hematopathology comprising many consultation cases, and is the past medical director of the Pathology Institute of the GELA (Groupe d'Etude des Lymphomes de l'Adulte, a large multicentric consortium of hematologists and pathologists from France and several neighbouring European countries conducting clinical trials for the tratment of adult aggressive lymphomas). He is a member of the International Lymphoma Study Group and of the WHO 4th Lymphoma Classification Commitee. He is currently the president of the European Association for Haematopathology. He has authored more than 230 scientific publications. His current research interest include the molecular chracterization of lymphoma entities including primary mediastinal large B-cell lymphoma and neoplasms derived from mature T and NK cells.

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Dept of Pathology, Hôpital Henri Mondor, Créteil.
Married, 4 children
- 1973-1979: Medical studies
- 1979 – 1984: residency (Internat des Hôpitaux de Paris)
- 1985: training in Immunology (DEA, Institut Pasteur, Paris)
- 1983: certication in Pathology (Paris VI).
- 1992: "Diplôme d'Habilitation à Diriger les Recherches"
- 1992: Professor of Pathology

MAIN PRESENT OCCUPATIONS
- Professor of Pathology
- Director of the research group Equipe INSERM U955 "Immunology and Oncogenesis of Lymphoid Tumours"
- Chair of the Pathology Institute of the GELA (Groupe d'Etude des Lymphomes de l'Adulte).
- Member of the International Lymphoma Study Group (ILSG)
- President elect (2008 -) of the European Association of Haematopathology (EAHP)
- Member of the WHO 4th Lymphoma Classification Committee.

TEACHING ACTIVITIES
- Education of training pathologists, Master and PhD students
- Organization of post-graduate courses in France and abroad (lymphoma classification, immunohistochemistry, in situ hybridization, ..)
- Invited visiting professor at the Mayo Clinic (Rochester, December 2005)
- Regular invited lecturer in National and International congresses (IAP, EAHP, EHA, …);
- in 2008-09, invited lecturer at scientific meetings of the EAHP (2008), International Academy of Pathology (Athens, 2008), European Congress of Pathology (Florence 2009), South Californian Lymphoma Group (UCLA, California, 2009), T-cell lymphoma meetings (Washington, 2008, Bologna, 2009), EHA and educational meetings in Brussels, Greece, Mexico, Israel,…

EXPERT ACTIVITES
- Invited reviewer in Blood, J Clin Oncol, Int J Cancer, Am J Pathol, Oncogene, Clin Cancer Res, J Pathology, Leukemia, Haematologica, Br J Haematol, Annals of Oncology, …
- Referee of national (French ministries of Health and Research, ARC, DRC de Paris, INSERM, INCa, ANR, AERES..) and international (Cancer Research UK, Netherlands, Hong Kong,…) institutions
- Grants from ARC, Ligue contre le Cancer, INCa, DHOS, ministry of Health (PHRC), etc. Since 2007, financial supports from INCa and PHRC have been obtained for 640 KE.
- Invited contributor of several chapters for the Updated WHO classification (2008).
- In the last years, invitation to contribute for chapters and review articles (incl a review article for the ASH 2008 meeting in Hematology Am Soc Hematol Educ Program in 2008).

RESEARCH ACTIVITIES

With the aim to characterize new lymphoma entities on the basis of molecular findings, we have 1) identified $\gamma\delta$ T cell lymphomas, characterized the molecular signature of NK-cell lymphomas and identified the normal cell counterpart of angio-immunoblastic T-cell lymphoma; 2) contributed to the description of molecular alterations in Primary Mediastinal B-cell lymphoma, with a specific gene signature; 3) identified markers associated with outcome in diffiuse large B-cell lymphomas.
We have initiated the French bio-clinical network on T-cell lymphomas sponsored by PHRC and INCa.
In december 2009, 239 publications referenced in Medline.

Pathology and Pathophysiology of Peripheral T-cell Lymphomas

Philippe Gaulard[1], Laurence de Leval[2]

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Malignancies derived from mature (post-thymic) T cells and NK cells, collectively referred to as peripheral T-cell lymphomas (PTCLs), are a heterogeneous group of rare diseases usually manifesting clinical aggressiveness. They account for less than 15% of non-Hodgkin lymphomas in most countries but show important geographic variations, with an overall higher frequency in Asia and central/south America, especially of those induced by the human T-lymphotropic virus-1 (HTLV1) and by the Epstein-Barr virus (EBV).

Despite novel insights gained from molecular profiling studies and clinico-pathological analyses, the complexity of the biology and pathophysiology of PTCLs is only partly deciphered. The normal NK and T-cell lineages from which PTCLs derive constitute a complex system with numerous functional subsets involved in innate and adaptive immunity and the cellular origin of several entities remains poorly defined. With the notable exception of *Anaplastic Lymphoma kinase* (*ALK*) rearrangements in ALK-positive ALCL, few other recurrent translocations have been identified in PTCLs. In addition, most PTCLs have a broad range of cellular composition and several entities lack distinct immunophenotypic profiles. This implies that the diagnosis and classification of PTCLs is often difficult and that the clinical features and anatomic location of the disease are important in defining PTCL entities. Indeed, in the WHO classification, PTCLs are listed according to their presentation as disseminated/leukemic, predominantly extranodal or cutaneous, or predominantly nodal diseases (**Table 1)**. Finally, research in the field of PTCLs has been compounded by the concurrent rarity and diversity of PTCLs hampering the collection of homogeneous cohorts of patients, the heterogeneity of the pathological samples, the absence of cell lines representative of the major entities, and the lack of good animal models. In recent years, however, novel insights have been gained from genome-wide profiling analyses.

In western countries, the most common forms present as nodal tumors which currently include four entities : angioimmunoblastic T-cell lymphoma (AITL), ALK-positive anaplastic large cell lymphoma (ALCL), ALK-negative anaplastic large cell lymphoma and PTCL, not otherwise specified (PTCL, NOS). The diagnosis of AITL and ALK-positive ALCL relies on the identification of distinctive features whereas that of PTCL, NOS is based on the exclusion of any recognizable ("not otherwise specified") subtype of T-cell lymphoma.

Angioimmunoblastic T-cell lymphoma (AITL), likely the most common PTCL in several Western countries, is a systemic disease manifested by polyadenopathy, B symptoms, frequent skin rash, polyclonal hypergammaglobulinemia and various immunologic abnormalities. The disease has a dismal prognosis. The cellular derivation of AITL from the normal follicular helper T cell (T_{FH}) subset specialized in providing B-cell help, likely explains the prominent non-neoplastic component in AITL tissues and the clinical manifestations of the disease reflective of an immunological dysfunction. It also provides new diagnostic markers such as the CXCL13, PD1, ICOS, … useful for the diagnosis in routine practice and helpful to delineate AITL from PTCL, not otherwise specified (PTCL, NOS). ALK-positive anaplastic large cell lymphoma (ALCL), defined by ALK gene translocation on chromosome 2p23, is composed of CD30+ cytotoxic cells with peculiar ("hallmark") cytological appearance. The disease preferentially affects children and young adults and usually carries a good prognosis. Besides the most common t(2;5)(p23;q35), which fuses the ALK to the nucleophosmin gene (NPM) on chromosome 5, variant translocations have been reported. All translocations juxtapose the cytoplasmic catalytic domain of ALK to a partner protein, forming a chimeric fusion protein which induces constitutive ALK tyrosine kinase activation. In vitro and in vivo studies have demonstrated the oncogenic proprties of ALK that are mediated by interaction with downstream molecules that engage intracellular signalling pathways,

among which the JAK3-STAT3 pathway is of prime importance. ALK-negative ALCL, introduced in the 2008 WHO classification as a provisional entity, is defined as a large cell lymphoma with comparable morphology to ALK-positive ALCL, but lack of ALK expression. It is clinically less favorable and the oncogenic alterations are unknown. PTCL, not otherwise specified (PTCL, NOS), the most heterogeneous category of PTCL, is defined by default for cases not fulfilling the criteria for more «specific» entities. The disease is usually disseminated with a common nodal presentation although any site may be affected. The prognosis is poor (20-30% 5-year survival). PTCL, NOS are derived from activated CD4+ (or CD8+) T cells, are markedly heterogeneous, at the morphological and even molecular levels. Overlap between PTCL, NOS signature and AITL or ALCL signatures has been observed which may reflect the influence of non-neoplastic elements, or the existence of common tumor-associated pathways. Rare cases with a cytotoxic profile and a poorer outcome have been reported. Some of the later may show translocation involving the IRF4/MUM1 gene at 6p25, similarly to a subset of cutaneous ALCL. Importantly, overexpression of the PDGFRalpha has been observed in PTCL, NOS, a finding that might have therapeutic implications given the potential sensitivity of this tyrosine kinase to Imatinib.

Among the morphological variants that have been recognized, the *follicular variant* of PTCL, with a follicular growth pattern, is characterized by a T_{FH} phenotype and features of AITL in some cases - raising the question of a possible relationship to AITL – and an association with a recurrent chromosomal translocation t(5;9)(q33;q22) involving ITK and SYK tyrosine kinases. Interestingly, however, overexpression and activation of SYK appear to be a feature common to most PTCLs, which potentially represents a novel therapeutic target.

Most entities of extranodal T or NK cell lymphomas - with the notable exception of mycosis fungoides and Sezary syndrome - derive from cytotoxic cells, with peculiar tropism for specific anatomic localizations. Cytotoxic cells comprise different subsets of a/b, mostly CD8, or g/d T cells and NK cells which share a common thymic precursor, cytolytic properties and some regulatory functions, disclose structural homologies with expression of NK receptors (KIR,…), and may show similar distribution in some tissues.

Despite heterogeneity in their clinical presentation, several non-cutaneous extranodal T or NK cell lymphomas entities show common features: (1) the tumors often disclose a broad cytologic spectrum; (2) lymph node involvement is rare, whereas spread to other extranodal sites is common; (3) hemophagocytic syndrome is relatively frequent; (4) most of these tumors derive from cytotoxic lymphocytes; (5) the disease definition heavily depends upon clinical features; (6) the clinical evolution of these patients is usually aggressive and the present therapeutic strategies are limited; (7) antigen stimulation (such as EBV in extranodal NK/T-cell lymphoma, nasal-type, or gliadin in enteropathy-associated T-cell lymphoma), genetic background and/or context of immunosuppression may play important role in the pathogenesis of some entities.

In the recent 2008 WHO classification, the main changes refer to cutaneous PTCLs: (1) the term “subcutaneous panniculitis-like T-cell lymphomas” is restricted to those T-cell lymphomas involving the subcitis with panniculitis features and a derivation from ab T cells, those with a gd T-cell phenotype which have an aggressive course being referred as “primary cutaneous gamma-delta T-cell lymphoma”; (2) in addition to the later category, two other provisional entities have been introduced, ie “primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma” and “primary cutaneous small/medium CD4+ T-cell lymphoma”.

Recent advances gained from genome-wide profiling analyses have provided novel insights into the classification and the pathogenesis of some PTCLs entities, a prerequisite needed to identify targets for new therapies that are expected to improve the poor outcome of most PTCL patients, when treated with conventional chemotherapy regimens. In this respect, efforts will be needed to evaluate promising innovative therapies in prospective clinical trials.

Norbert Schmitz, MD, PhD

Professor Schmitz is head of the department of hematology, oncology and stem cell transplantation at the Asklepios Hospital St. Georg in Hamburg, Germany, since 2001. He graduated as a medical doctor in 1976 and specialized in internal medicine in 1985 and in hematology in 1988. He worked as a resident physician at the Justus Liebig University in Gießen and at the Christian Albrechts University in Kiel and was a visiting physician at the department of hematology and bone marrow transplantation of the City of Hope Medical Center in Duarte, USA. From 1986 to 2001, he was head physician of the transplant program of the second department of internal medicine of the Christian Albrechts University, where he was provisional director in 1998. Dr Schmitz obtained his PhD in 1977 and became a professor at the Christian Albrechts University in 1996. His current research interests focus on therapy of lymphoma and on autologous and allogeneic stem cell transplantation.

Professor Schmitz is a member of several scientific societies, including the American Society of Hematology and the European Haematology Association. He is a former secretary of the European Group for Blood and Marrow Transplantation, where he is currently chairman of the T-cell subcommittee. He also was chairman of the German Study Group for Bone Marrow and Stem Cell Transplantation. Currently, he is chairman of the German Study Group for high grade non-Hodgkin's Lymphoma.

Professor Schmitz has published some 60 book chapters, more than 300 articles in peer-reviewed journals and more than 530 abstracts. In addition, he is an editorial board member of the Journal of Clinical Oncology.

Conventional Therapy in T-Cell Lymphomas

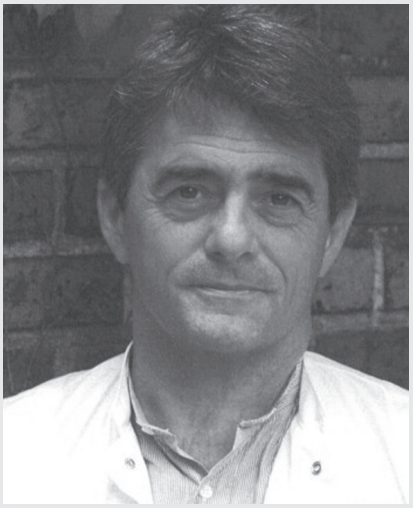
Norbert Schmitz

Asklepios Klinik St.Georg, Hamburg, Germany

T-cell lymphomas are heterogenous dieases generally thought to carry a poor prognosis. T-cell lymphomas frequently presenting with involvement of the bone marrow (leukemic T-cell lymphomas) and cutaneous T-cell lymphomas show different clinical features, need different treatment, and carry a different prognosis. The nodal and extranodal T-cell lymphomas comprising the anaplastic lymphoma kinase (ALK)- positive or negative anaplastic large cell lymphomas (ALCL), the angioimmunoblastic T-cell lymphomas (AILT), and the mature T-cell lymphomas, not otherwise specified (NOS) form the most frequent groups of mature T-cell lymphomas. Other rare subentities are the hepatosplenic T-cell lymphomas, the enteropathy-associated T-cell lymphomas, and the panniculitis-like T-ell lymphomas. Although these entities also show substantial variation of their clinical presentation treatment usually consists of CHOP or CHOP-like regimens. The prognosis of these entities largely depends on the histologic subtype with the ALK-positive ALCLs showing the by far best prognosis in all recent analyses; the other subgroups have very similar prognoses with the International Prognostic Index (IPI) separating the patients into those with a relatively good prognosis (IPI 0 and 1) and the other patients (IPI > 1) who carry a poor prognosis.

We recently were able to show that the addition of etoposide to CHOP significantly improves EFS and OS of patients with mature T-cell lymphoma. Nevertheless, patients with IPI > 2 (excluding patients with ALK-positive ALCL) do poorly and need improved treatment strategies. While conventional chemotherapy with alternative drugs is unlikely to improve outcomes, new drugs like pralatrexate, romidepsin, denileukin diftitox and new antibodies (brentuximab vedotin for ALK-positive ALCL) have shown interesting remission rates and are under further investigation. The German High-Grade Lymphoma Study Group is currently investigating the role of allogeneic and autologous transplantation for younger patients with T-cell lymphoma. Patients beyond the age of 60 years are offered to participate in a study comparing CHOP with CHOP plus alemtuzumab.

Further study is necessary to better characterize the molecular background of T-cell lymphoma, to understand the differences in prognosis, and to design new treatments which should be tailored for the specific defects underlying each of these fascinating entities.



Francesco d´Amore, M.D., DrMedSc

A) date and place of birth:
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B) Position and title:

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Clinical Research Institute
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C) Education:

1980 M.D. University of Genoa, Genoa, Italy
1981 Authorisation to practice Medicine in Italy
1981 Educational Commission for Foreign Medical Graduates (ECFMG) Examination (USA)
1981 Professional and Linguistic Assessment Board (PLAB) Examination, the General Medical Council (UK)
1981 Authorisation to practice Medicine in the UK
1982 Authorisation to practice Medicine in Denmark
1985 Specialist degree in Internal Medicine in Italy
1985 Specialist degree in Internal Medicine in Denmark
1997 Specialist degree in Haematology in Denmark

D) Academic dissertations and degrees:

1985 Specialty thesis, Faculty of Medicine, Genoa University, Genoa, Italy: "Phenotypical and functional characterisation of the malignant cell population in Hodgkin´s disease"
2000 Dr. Sc. Med. thesis, Faculty of Medical Sciences, Aarhus University, Aarhus, Denmark: "Prediction of high risk disease in non-Hodgkin´s lymphoma: Identification of clinicopathologic and molecular pretreatment prognostic factors in specific patient subsets"

E) Clinical Appointments

1980-1982 Resident, Genoa University Hospital, Genoa, Italy
1984-1987 Senior House Officer, Dept. of Internal Medicine, Vejle Hospital, Vejle, Denmark
1987-1990 Senior Registrar, Dept. of Hematology, Odense University Hospital, Odense, Denmark
1996-1997 Senior Registrar, Dept. of Hematology, Aarhus University Hospital, Aarhus, Denmark
1997-1999 Senior Registrar/Consultant, Dept. of Oncology, Aarhus University Hospital, Aarhus, Denmark
1999- … Consultant, Dept. of Hematology, Aarhus University Hospital, Aarhus, Denmark

F) Academic Appointments

1982-1984 Postgraduate Research Scholarship (forskningsstipendium) from the Danish Ministry of Education at the University of Copenhagen, Lab. of Cancer Biology, Dept. of Hematology, Rigshospitalet
1990-1994 Research Fellow (klinisk assistent) at the University of Odense, Depts. of Hematology and Pathology
1994-1995 Postdoctoral Research Associate, Dept. of Pathology, University of Nebraska Medical Center, Omaha, Nebraska (Grant from the Danish Cancer Society and the Danish Medical Research Council)
1999-2010 Associate Professor, Faculty of Medical Sciences, Aarhus University, Aarhus, Denmark
2005 Visiting Professor, Dept. of Pathology, University of Nebraska Medical Center, Omaha, Nebraska (project: 'Clonal genetic progression in t(14;18)-positive follicular lymphomas'), June-September 2005
2010-… Clinical Professor, Dept. of Hematology, Aarhus University Hospital, Aarhus, Denmark

G) Teaching activities

1999- 2006 Responsible coordinator (kursusleder) of the clinical course for 8th and 9th semester medical students at Aarhus University Hospital (Aarhus Sygehus – Tage Hansens Gade)
1999- … Theoretical and bedside teaching of 8th and 9th semester medical students; theoretical teaching of 12th semester medical students
1999-… Teaching at: PhD courses, A-courses for medical specialist training (e.g. haematology, oncology, nephrology, pediatrics, nuclear medicine), international educational symposia, educational nurse courses etc.
2001-… Member of the Examination Commission for Internal Medicine, Aarhus University, Faculty of Medicine
2010 June Educational session on peripheral T-cell lymphomas – European Hematology Association, Barcelona, Spain.

H) GCP-related activities

Internal Review Board (IRB) certification test, University of Nebraska Medical Center, Omaha, Nebraska, USA, July 2005.
Teaching Faculty, National GCP Course for monitors, research nurses and clinical trial officers, GCP Unit, Århus University, April 2009

I) Administrative positions

One of the three administrative heads (funktionsleder) of the Lymphoma Unit, Dept. of Hematology, Aarhus University Hospital

J) Other present positions

Chairman of the Danish Lymphoma Group
Chairman of the Working Group on T-cell lymphomas of the Nordic Lymphoma Group

Member of the Board of The Nordic Lymphoma Group
Member of the Board of The Danish Hematological Cancer Group (Fælles Hæmatologisk DMCG)
Member of the Board of The Danish Hematological Database (Fælles Hæmatologisk Database)
Member of the Board of the Danish Cutaneous Lymphoma Group
K) Reviewer and Editorial Board activities 2005-2011
UK Cancer Research – Grant application reviewer
External application reviewer for professorship in 'Targeted Therapy' at Manchester University
Faculty Member of the educational lymphoma site www.treatingnhl.com 2005-2007
Leukemia and Lymphoma
European Journal of Hematology
Radiotherapy and Oncology
Blood, The Journal of the American Association of Hematology
Reviewer of Ph.D project proposals, Aarhus University

New Drugs in the Treatment of T-Cell Lymphomas

Francesco d'Amore
Aarhus University hospital in Aarhurs, Denmark

Up till recent years, no major therapeutic advances have been achieved in peripheral T/NK-cell lymphomas (PTCL). Overall survival (OS) values for most of the systemic entities have been in the order of 25-35% at five years. Furthermore, there has been a rather consistent lack of PTCL-specific clinical trials, partly due to the rarity of this condition, and partly to diagnostic difficulties and controversial views on whether immunophenotype-specific treatment strategies should be adopted. As a consequence of the WHO classification of malignant lymphomas, modern diagnostic approaches identify PTCL entities based upon immunophenotype in association with clinical, morphological, and molecular genetic data. These advances have represented a crucial step forward towards the recent implementation of PTCL-specific clinical trials.

Analogue to the treatment strategy applied in diffuse large B-cell lymphoma, combination chemotherapy with CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or CHOP-like variants has up till now been the most frequently used first line therapy also in PTCL. Given as standard schedule every three weeks, this approach does not seem to benefit more than 25-30% of the patients, while schedule intensification, e.g. shortening of the time-interval between courses and/or addition of etoposide or high-dose methotrexate, has by some authors been reported to improve outcome. However, reported OS values have been varying, often depending on the included number of prognostically more favourable cases belonging to the histological subtype anaplastic large cell lymphoma (ALCL), *alk*-positive.

Based on small-scale observations on single-agent efficacy, gemcitabine has shown encouraging response rates in both cutaneous and systemic PTCL, but of relatively short duration.

High-dose therapy with autologous stem cell transplant (HDT/ASCT) proved feasible in both relapsed/refractory and treatment-naïve PTCL. Overall results suggest a more favorable impact of this approach in first line as compared to salvage treatment. However, most data are of selected and retrospective nature. At present, only a few PTCL-restricted phase II trials investigating HDT/ASCT as part of a first-line therapeutic approach have been reported. Of these only very few have a sufficient cohort-size to compensate for the heterogeneity of this group of disorders. Data from the Nordic phase II trial (NLG-T-01), the largest trial (N=166) performed so far in systemic PTCL, will be shown.

Combinations of chemotherapy with T-cell specific monoclonal antibodies (MoAb) have shown high overall response rates (ORR) and are currently being investigated in ongoing phase II clinical trials.

Due to the rarity of T/NK-cell neoplasms, no large PTCL-restricted phase III trials have yet been completed. However, the first international effort (ACT trial) has recently been launched. A brief update on the ACT trial, in the context of the present European PTCL trial scenario, will be presented.

New drugs such as antifolate compounds (e.g. pralatrexate), histone deacetylase inhibitors (e.g. romidepsin), monoclonal antibodies used as unconjugated (alemtuzumab, zanolimumab) or conjugated (brentuximab vedotin, denileukin diftitox) molecules have shown significant effect at monotherapy level in relapsed/refractory PTCL. They will therefore be important tools to improve on conventional approaches and will influence a new generation of clinical trials in PTCL based on biologically meaningful drug combinations. An overview of recent trial results with the most promising of these new compounds will be presented.

Topics of the talk

- General considerations
- Clinical work-up
- Treatment strategies
  - Conventional chemotherapy
  - ASCT-based therapy
  - New treatment approaches

PTCL
Statements and Comments

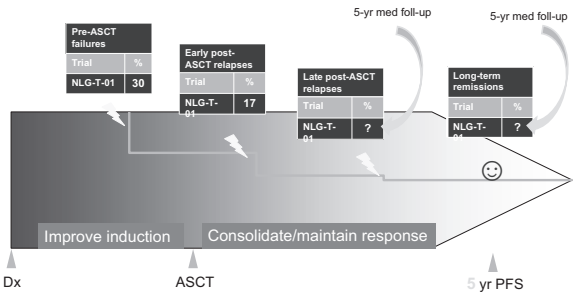
- **Rare disease**
  - Yes, but not more unfrequent than MCL or HL. However, much more heterogeneous than MCL and HL and histopathologically more difficult to assess.
- **More frequent in Asia**
  - Occurrence and distribution of T-NHL in Asia and in Europe/US differs only for NK/T-cell lymphoma, clearly more frequent in Asia, and for ETCL, clearly more frequent in western countries (>> HLA-DR associated)
- **Poor prognosis**
  - Generally yes, however marked heterogeneity among subtypes
- **No therapeutic gold standard**
  - True, strong need for T-NHL specific prospective trials

WHO 2008: The mature T-cell and NK-cell neoplasms	
T-cell prolymphocytic leukemia	Leukemic
T-cell large granular lymphocytic leukemia	
Chronic lymphoproliferative disorder of NK-cells (*)	
Aggressive NK cell leukemia	
Extranodal NK/T cell lymphoma, nasal type	**Extranodal**
Enteropathy-*associated T-cell lymphoma*	
Hepatosplenic T-cell lymphoma	
Subcutaneous panniculitis-like T-cell lymphoma	
Mycosis fungoides	Cutaneous
Sézary syndrome	
Primary cutaneous CD30+ T-cell lymphoproliferative disorder	
Lymphomatoid papulosis	
Primary cutaneous anaplastic large-cell lymphoma	
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (*)	
Primary cutaneous gamma-delta T-cell lymphoma	
Primary cutaneous small/medium CD4+ T-cell lymphoma (*)	
Peripheral T-cell lymphoma, not otherwise specified	**Nodal**
Angioimmunoblastic T-cell lymphoma	
Anaplastic large cell lymphoma (ALCL), ALK+	
Anaplastic large cell lymphoma (ALCL), ALK– (*)	
Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)	Virus-associated
Hydroa vacciniforme-like lymphoma	
Adult T-cell leukemia/ lymphoma	

The failing PTCL patient
Three main clinical scenarios

Type of failure	Clinical course	Subtypes	Possible strategy
Primary refractory	No signs of chemosensitivity. Progression during induction treatment	Often HSTCL, some ETCL, some NK/T n/nt	➢ New biological induction approach needed
Early relapse	Responds to induction. If eligible → ASCT. Relapses shortly after completion of 1.line therapy	A fraction of pts in most subtypes	➢ Improvement of induction ➢ Early consolidation
Late relapse	Chemosensitive. Reaches CR. Long cCR. Relapses > 1 yr after completion of 1.line therapy	someT-ALCL, PTCL-NOS and AILT	➢ Improvement of induction ➢ Consolidation and/or maintenance

Prospective PTCL trials
Patterns of response/failure

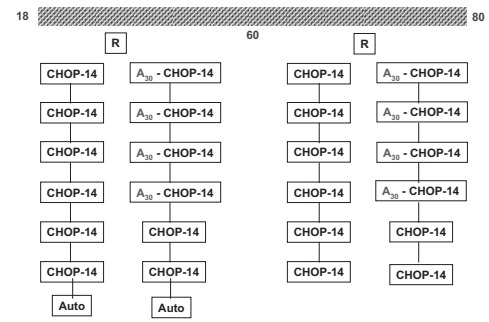


The largest trials in systemic PTCL

Study	Histology	Treatment line	Design	Intention-to-treat population	Accrual status	Ref.
NLG-T-01	sPTCL	1st line	phase 2	160	Closed	EHA 2009
NCI/Romdps	sPTCL	rel/ref	phase 2	130	Closed	JCO 2009
ACT	sPTCL	1st line	phase 3	**120**	**Ongoing**	
PROPEL	sPTCL	rel/ref	phase 2	115	Closed	CCR 2010
GOELAMS	sPTCL	1st line	phase 3	88	Closed	BJH 2010
Reimer et al.	sPTCL	1st line	phase 2	83	Closed	JCO 2009

The ACT trial

NORDIC LYMPHOMA GROUP NLG-T-02 DSHNHL- 2006-1B



Accrual pr. January 2011: **114 pts (ACT-1: 64 ; ACT-2: 50)**

ORRs of selected compounds given as **monotherapy** in non-cutaneous, systemic PTCL

Trial	Compound	ORR	Response assessment	Target group
Enblad et al, Blood 2004	Alemtuzumab (CD52)	36%	invest	Rel/refract
O'Mahony et al, ASH 2007	Siplizumab (CD2)	31%	invest	Rel/refract
Pohiman et al, ASH 2009	Belinostat	25%	invest	Rel/refract
Coiffier et al, ASH 2010	Romidepsin	34%	Central (invest)	Rel/refract
d'Amore et al, BJH 2010	Zanolimumab (CD4)	26%	invest	Rel/refract
FDA report, Clin Cancer Res 2010	Pralatrexate	27 (39)%	Central (invest)	Rel/refract
Shustov et al, ASH 2010	Brentuximab vedotin (CD30)	87%	invest	Rel/refract

Pralatrexate in rel/ref systemic PTCL

PROPEL study

Clin Cancer Res; 16(20); 4921–7. ©2010 AACR.

Clinical Cancer Research

Report from the FDA

Folotyn (Pralatrexate Injection) for the Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: U.S. Food and Drug Administration Drug Approval Summary

Shakun M. Malik, Ke Liu, Xu Qiang, Rajeshwari Sridhara, Shenghui Tang, W. David McGuinn, Jr., S. Leigh Verbois, Anshu Marathe, Gene M. Williams, Julie Bullock, Christoffer Tomoe, Sue Ching Lin, Terrance Ocheltree, Milinda Vialpando, Alice Kacuba, Robert Justice, and Richard Pazdur

Experimental Design: This review was based on study PDX-008, a phase II, single-arm, nonrandomized, open-label, international, multicenter trial, designed to evaluate the safety and efficacy of pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation in patients with relapsed or refractory PTCL.

Results: The overall response rate was 27% in 109 evaluable patients [95% confidence interval (CI), 19–36%]. Twelve percent of 109 evaluable patients (95% CI, 7–20%)] had a response duration of ≥14 weeks. Six of these 13 patients achieved a complete response, and one patient had complete response unconfirmed. The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis, and neutropenia.

Romidepsine

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

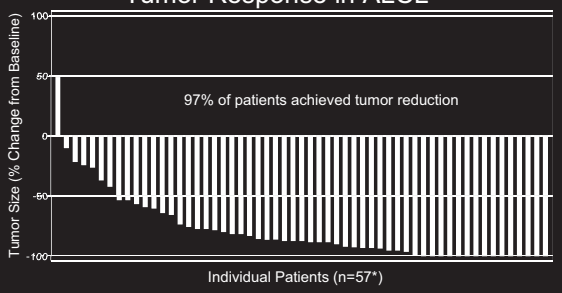
Sean J. Whittaker, Marie-France Demierre, Ellen J. Kim, Alain H. Rook, Adam Lerner, Madeleine Duvic, Julia Scarisbrick, Sunil Reddy, Tadeusz Robak, Jürgen C. Becker, Alexey Sarmtov, William McCulloch, and Youn H. Kim

Rel/ref CTCL: ORR 34%; No grade 3-4 toxicity; Mild, reversible prolongation of Q-T interval on ECG was observed in some pts

Final Results from a Pivotal, Multicenter, International, Open-Label, Phase II study of Romidepsine in Progressive or Relapsed PTCL Following Prior Systemic Therapy
Coiffier B et al. ASH 2010, abstr. 114

IRC Evaluations (n = 130)	Radiology	Clinical
CR + CRu n (%)	19 (15%)	17 (13%)
PR, n (%)	15 (12%)	17 (13%)
SD, n (%)	36 (28%)	32 (25%)
ORR (CR + CRu + PR), n (%)	34 (26%)	34 (26%)

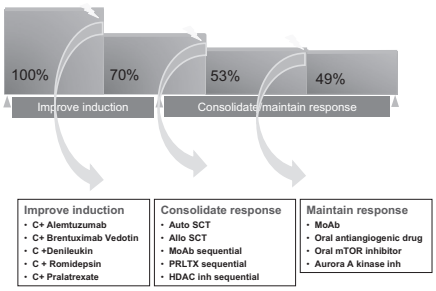
Brentuximab Vedotine Tumor Response in ALCL



* 57 of 58 patients with post-baseline CT assessments

Interventional scenario

1st line treatment of PTCL



Anna Sureda, (MD, PhD) (Cambridge, UK) graduated with a degree in Medicine from the Autonomous University of Madrid in 1986 and completed her residency in Haematology at the Hospital Ramón y Cajal of Madrid in 1990. After 20 years of working as a Consultant (and responsible of the Outpatient Department since 2033) in the Department of Haematology of Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, Anna Sureda has recently moved to Cambridge, UK where she has been appointed as a Senior Consultant on Lymphomas and Stem Cell Transplantation in the Department of Haematology in Addenbrooke's Hospital.

Dr. Sureda has focused her career on clinical investigations into the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma patients evaluating novel therapies such as immunotherapy combined with stem-cell transplantation. Throughout the course of her investigations she has participated in many phase II and III clinical trials for lymphoma patients. As a result of part of her clinical investigations, she recently achieved her PhD with the work entitled "Autologous Stem Cell Transplantation in Patients with Hodgkin's Lymphoma". Dr. Sureda has been an active member of the Spanish Cooperative Group of Lymphomas and Haematopoietic Stem Cell Transplantation (GELTAMO) since 1993 and in 2004 she was appointed Chairperson of the Lymphoma Working Party of the European Group for Blood and marrow Transplantation (EBMT). After a period of 3 plus 3 years of chairpersonship, she was elected as Secretary of the EBMT in March / 2010.

Dr. Sureda is a regular reviewer for the journals *Annals of Oncology, Bone Marrow Transplantation*, *The Hematology Journal*, *The European Journal of Hematology* and *Annals of Hematology* and has been the author or co-author of numerous chapters and peer-reviewed journal articles.

The Role of Stem Cell Transplantation in T Cell Lymphomas

Anna Sureda

Hematology Department Addenbrooke's Hospital, Cambridge, United Kingdom

Peripheral T-cell lymphomas (PTCLs) represent approximately 10 to 15% of all non-Hodgkin's lymphomas (NHL) in Western countries. Most patients are of older age (median age > 60 years) and usually present with advanced stage disease. PTCLs in general show an aggressive course and most studies detect the T-cell phenotype as an independent negative prognostic factor. Both the international prognostic index (IPI) and the prognostic index for T-cell lymphomas (PITs) that also include the bone marrow involvement, have shown prognostic value in PTCL and determine the outcome of patients with nodal PTCL.

The prognosis of PTCL is poor with the exception of the ALK (anaplastic lymphoma kinase) expressing anaplastic large cell lymphoma (ALCL) with a more favourable outcome after conventional chemotherapy (CT) and the primary cutaneous T-cell lymphoma (CTCL) that usually show an indolent clinical course. In contrast, for the remaining PTCL the outcome following anthracycline-based CT is worse compared to aggressive B-cell lymphomas even with a median overall survival (OS) of 9 to 42 months.

So far, no accepted standard treatment could be defined for PTCL. This mainly results from the lack of PTCL-restricted randomized trials and the heterogeneity of most published series. Although CHOP and CHOP-like regimens are widely used first-line, these protocols have never been prospective tested in the setting of PTCL and are rather adopted from treatment strategies for aggressive B-cell lymphomas.

To improve the results in PTCL more aggressive strategies such as high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) and allogeneic stem cell transplantation (allo-SCT) seem attractive strategies for PTCL patients.

Autologous Stem Cell Transplantation

Autologous Stem Cell Transplantation as Second-Line Therapy. ASCT has become the standard of care for primary refractory and relapsing patients with high-grade B-cell lymphomas. In PTCL, prospective randomized studies on salvage ASCT are lacking. To date, at least 16 retrospective analyses, each one including more than 15 patients have been published. These studies were heterogeneous in terms of histological subgroups included, patient characteristics, prognostic factors, conditioning regimen used and duration of follow up. Nevertheless and as a summary of all published information it seems that an ASCT strategy is feasible and safe in this group of patients with a low mortality and morbidity rate. The overall survival (OS) in these series ranged from 35% at 2 years to 70% at 5 years, respectively and the disease free survival (DFS) or event free survival (EFS) from 28% at 2 years to 56% at 5 years, respectively. Although earlier results tend to show somewhat better results than the recently published series, when subgroup or matched control analyses were performed, the OS results of PTCL were equivalent to the long-term outcome of patients with aggressive lymphomas.

It is unclear whether histology impacts the outcome of PTCL after salvage ASCT. In some series, ALCL showed a favourable outcome than other histologies but unfortunately, the ALK status was not determined in all series. Disease status at the time of ASCT often correlates with a better outcome after savage CT and ASCT. In fact, several authors have found a better long-term survival in patients transplanted in complete remission (CR) than in patients receiving the autologous transplant in other disease status. Nevertheless, this finding was not confirmed by other surveys. In this sense and due to the retrospective nature of these studies, the value of this observation needs further evaluation.

Autologous Stem Cell transplantation as Consolidation Treatment after First-Line Chemotherapy. Some retrospective studies dealing with the possible role of early intensification with an ASCT in patients with PTCL have been reported in the literature. As in the salvage setting, a comparison of all these series is hampered by their heterogeneity. Some patients mainly reported on patients with low or intermediate-low IPI, whereas others were based on patients with unfavourable prognostic index. The OS of these series ranged from 53% at 3 years to 62-68% at 5 years, respectively. Interestingly, the DFS / EFS did not seem to be much lower than OS in most groups of patients; this might indicate a substantial curative potential for this approach in previously untreated PTCL. The Lymphoma Working Party (LWP) of the European Group for Blood and Marrow Transplantation (EBMT) published the largest study in this setting. Kyriakou et al reported data on 146 patients with angioimmunoblastic T-cell lymphoma (AITL) showing an actuarial OS of 67% and 59% at 2 and 4 years, respectively. About two thirds of the patients were autografted in first CR or partial remission (PR) and, interestingly, those patients receiving total body irradiation (TBI) as part of the conditioning regimen showed a lower relapse rate (RR) after ASCT.

Prospective randomized studies restricted to PTCL patients assessing the role of ASCT as first consolidation therapy are lacking. Two French studies performed by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) published data on ASCT as front line therapy for patients with high-risk PTCL. In the intent-to-treat analysis, none of both studies demonstrated a benefit for ASCT as opposed to more conventional treatment. However, the limited number of patients in the high-dose group as well as the restriction to high-risk patients only, did not allow to definitely clarify the role of ASCT in this situation. In a similar way, the German High-Grade non-Hodgkin's Lymphoma Study Group (DSHNHL) analyzed the outcome of 33 patients with PTCL treated with escalated CHOP plus etoposide with repeated ASCTs. Compared to aggressive B-cell NHL, PTCL showed a significantly worse OS and EFS at 3 years.

So far, five large prospective PTCL-restricted trials have published data on 372 patients with front line high dose therapy and ASCT (table 1). These prospective series are more homogeneous. Median age ranged between 43 and 57 years and PTCL unspecified, AITL and ALC accounting for almost 100% of the different histologies. Age-adjusted IPI was intermediate-high or high in 46 to 72% of the patients. The most commonly used conditioning regimen was BEAM and disease status at transplantation was CR or PR in 59% to 76% of the patients. In these trials, OS ranged from 48 to 73% at 3 years to 34% at 12 years and progression free survival (PFS) between 36 to 53% at 3 years and 30% at 12 years. One of the consistently found problems of upfront high-dose therapy and ASCT has been the early progressive disease leading to about one

Table 1. Prospective clinical trials for patients with peripheral T cell lymphoma treated with an autologous stem cell transplantation as part of first line therapy.

Author, year	N, age	Histology	IPI	Conditioning Therapy	Status at ASCT	ASCT rate	DFS/EFS/ PFS	OS	FU (mo)
Corradini, 2006	62, 43	PTCLu 45% ALK+ 30% AITL 16% Other 9%	0/1 19% ≥ 2 71%	Mito/Mel BEAM	CR 56% PR 16%	71%	30% (12 year)	34% (12 year)	76
Rodriguez, 2007	26, 44	PTCLu 42% ALK+ 31% AITL 27%	0/1 28% 2/3 72%	BEAM	CR 65% PR 8%	73%	53% (7 year)	73% (3 year)	35
Mercadal, 2008	41, 47	PTCLu 49% AITL 29% Other 12%	0/1 22% 2 32% 3 22% 4/5 24%	BEAM / BEAC	CR 49% PR 10%	41%	30% (4 year)	39 (4 year)	38
Reimer, 2009	83, 47	PTCLu 39% ALK- 16% AITL 33% Other 12%	0/1 49% 2/3 51%	Cy/TBI	CR 47% PR 24%	66%	36% (3 year)	48% (3 year)	33
D'Amore, 2009	160, 57	PTCLu 39% ALK- 19% AITL 19% Other 23%	0/1 18% ≥2 72%	BEAM	No data	71%	49% (3 year)	57% (3 year)	45

third of the patients in intent-to-treat-analysis finally failing to achieve the autologous transplantation procedure.

With regards to these prospective data, once again, the remission status at the time of transplantation was one of the most important prognostic factors. In addition, IPI and PIT also show prognostic value in some of the studies.

N. Number of patients; ASCT. Autologous Stem Cell Transplantation; DFS. Disease free survival; EFS. Event free survival; PFS. Progression free survival; OS. Overall survival; FU. Follow up; PTCLu. Peripheral T-cell lymphoma unspecified; ALK. Anaplastic lymphoma kinase; AITL. Angioimmunoblastic lymphoma; BEAM. BCNU, etoposide, ara-c, melphalan; BEAC. BCNU, etoposide, ara-c, cyclophosphamide; Cy. Cyclophosphamide; TBI. Total body irradiation; CR. Complete remission; PR. Partial remission.

Allogeneic Stem Cell Transplantation

In contrast to the cytotoxic effect of high-dose therapy and ASCT, allogeneic stem cell transplantation (allo-SCT) could add a graft-versus-lymphoma (GVL) effect to the myeloablative or reduced intensity conditioning (RIC) regimen, potentially improving the therapeutic outcome. However, the experience with allo-SCT is nowadays limited. To date, no relevant data in the upfront setting are available and besides some case reports, only five retrospective series were more than 10 patients have been reported in patients with relapsing and refractory PTCL. The largest series was recently published by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire including 77 pre-treated patients who basically underwent a myeloablative allo-SCT. In this series, the 5-year OS and PFS were 57% and 53%, respectively. Non-relapse mortality was 33% at 5 years, with no significant differences between RIC and conventional conditioning protocols. In the multivariate analysis, resistant diseases at the time of allo-SCT as well as the development of grade ¾ acute graft-versus-host disease (GVHD) were the strongest adverse prognostic factors for OS.

Two prospective clinical trials have been published so far. In the Italian phase II trial by Corradini, 17 patients underwent a RIC-allo as salvage therapy. Eight of them had already failed an ASCT. After a

median follow up of 28 months, the estimated 3-year OS and PFS were of 81% and 64%, respectively. Non-relapse mortality was impressively low, only 6% and response to donor lymphocyte infusions given at the time of disease relapse / progression indicated the presence of a beneficial GVL effect. In the German study by Wulf et al, 10 patients were treated with CT combined with alemtuzumab and followed by a RIC-allo. OS was 70% with 6 patients being in CR after a median follow up of 7 months.

Finally and in order to further investigate the role of stem cell transplantation as consolidation therapy in the front line setting, the DSHNHL in co-operation with other groups has recently launched a prospective randomized clinical trial comparing upfront ASCT versus allo-SCT following dose-dense induction chemotherapy.

In summary, due to their general poor prognosis after conventional CT more effective therapies are urgently needed in the PTCL setting. Nevertheless, the value of upfront ASCT has still to be demonstrated yet as there is contradictory information in this setting as well as the potential superiority of allo-SCT over ASCT in this disease.

New Advances in Pediatric ALL

The advent of high resolution genome-wide analyses have provided insights into leukemogenesis and identified several novel genetic abnormalities, such as *IKZF1* deletion, *CRLF2* over-expression, and *JAK* mutations in childhood acute lymphoblastic leukemia (ALL). Some of the genetic abnormalites have prognostic significance and others are potential therapeutic targets. Professor Rob Pieters will describe some of the newly discovered genetic abnormalities and their clinical and biological implications. Parallel to these biological advances is the remarkable improvement in the treatment outcome. Even with overall 5-year event-free survival rates of over 80%, there are still several challenging subtypes of ALL such as early T-cell precursor ALL, infant ALL with *MLL* rearrangement, hypodiploid ALL, and ALL with induction failure. Professor Ching-Hon Pui will discuss the current management and the potential novel therapies for these cases. Historically, compared with younger children, adolescents had a much worse treatment outcome because of an increased prevalence of high-risk leukemia and a poorer tolerance and adherence to therapy. Adolescents now enjoy similarly high cure rates as those of younger children owing to the use of risk-adjusted intensive chemotherapy but suffer from more treatment-related toxicities. Professor James Nachman will discuss current treatment approach for adolescents to increase their cure rate while minimizing the acute and late toxicities.

Ching-Hon Pui, MD

Robrecht Pieters, MD

Born at 17 december 1959, Utrecht.
Married to Caroline Wellens, 2 children (Marten born 1989, Eline 1991)

TRAINING

1978-1987: Faculty Human Movement Studies, Vrije Universiteit, Amsterdam
1979-1987: Faculty of Medicine, Vrije Universiteit, Amsterdam
1987-1991: PhD, research laboratory of Pediatric oncology, Vrije Universiteit, Amsterdam (Dutch Cancer Society 87-17). PhD degree March 1991. Thesis "Drug resistance in childhood leukemia (promotor prof dr AJP Veerman)
1991-1995: Training Pediatrics, Vrije Universiteit, Amsterdam
1995-1998: Pediatrician, division of pediatric oncology/hematology/immunology, Vrije Universiteit
1996-1998: Clinical fellowship Dutch Cancer Society
Departments of hematology Free University Hospital Amsterdam (prof Huygens), pediatic bone marrow transplantation Leiden University Medical Center (prof Vossen), pediatric oncology/hematology/immunology, Free University Amsterdam (prof Veerman), pediatric oncology Academic Medical Center Amsterdam (prof Voute)
1996-1999: Associate professor pediatric oncology/hematology (UHD), Vrije Universiteit Amsterdam
1999-present: Head department of pediatric oncology/hematology, Erasmus MC-Sophia Childrens Hospital, University Medical Center Rotterdam
2000-present: Professor pediatric oncology, Erasmus MC-Sophia Childrens Hospital, University Medical Center Rotterdam

RESEARCH ACTIVITITIES

1991-1998: Supervisor of the research program Pediatric Oncology of the Free University Hospital in cooperation with prof dr A.J.P. Veerman. This program studies cell biological features, cytostatic drug resistance and late effects of anticancer therapy in childhood cancer.
1999-present: Director research program Pediatric Oncology/Hematology "Biological determinants of leukemogenesis and treatment outcome and development of targeted therapies in childhood leukemia" of the Erasmus MC, University Medical Center Rotterdam/Sophia Childrens Hospital

PUBLICATIONS

More than 350 international publications and book chapters in the field of pediatric oncology

AWARDS

1991 Young Investigators (2nd) of the Dutch Pediatric Association
1991 Kabi Pharmacia Research Grant
1992 7th Schweisguth Prize of the International Society of Paediatric Oncology

NATIONAL BOARDS/COMMITTEES

- Chairman Supervisory Board Dutch Childhood Oncology Group, 2008-present
- Chairman ALL disease committee of the Dutch Childhood Oncology Group (DCOG), 2002-present
- Chairman DCOG ALL-10 protocol, 2004-present
- Chairman DCOG ALL-11 protocol, 2010-present
- Chairman infant ALL committee DCLSG/DCOG, 1996-present.
- Chairman DCOG Ph+ ALL committee, 1999-present
- Member of "Oncologisch Beraad", Erasmus MC Rotterdam, 1999-present.
- Member Internal Scientific Board of the Erasmus Stem Cell Institute, 2009- present
- Member faculty MSc Molecular Medicine programme Erasmus MC, 2005-present
- Member Dutch Health Council committee "Origin of Chilhdood Leukemia", 2010-present
- Chairman of the Working Group Pediatric Oncology of the Integraal Kanker Centrum Rotterdam (IKR), 2002-2007.
- Member of "Commissie Bevordering Wetenschappelijk Personeel" Erasmus MC, 2007-2010
- Chairman of "Beraadsgroep Voortplantingsgeneeskunde" ErasmusMC, 2006-2009
- Member Committee Project Topkwaliteit Klinische Trials (TKT) Erasmus MC, 2006-2008
- Member Steering Committee Kenniscentrum Palliatieve Zorg Erasmus MC, 2005-2008
- Chairman Pediatric Research Committee Erasmus MC-Sophia, 1999-2008
- Secretary Dutch Childhood Oncology Group (DCOG), 2002-2007
- Board Member Dutch Childhood Leukemia Study Group, 1999-2002
- Member Research Committee DCLSG/DCOG, 1997-2006
- Member committee ANLL-94, Dutch Childhood Leukemia Study Group (DCLSG), 1995-1996
- Projectleader theme Hematologic Malignancies, Oncology Research School Free University, 1996-1998

INTERNATIONAL BOARDS/COMMITTEES

- Chair Interfant group, international study group for treatment of infants with ALL, chair Interfant-99 protocol, Interfant-06 protocol,

1999-present
- Member EsPhALL study committee, international treatment protocol for children with Ph+ ALL, 1999-present
- Board member of I-BFM, international consortium for children with hematologic malignancies, 2008-present
- Member of Ponte di Legno Group, international consortium for diagnostic and treatment guidelines for childhood ALL, 2000-present
- Member of Acute Lymphoblastic Leukemia Strategy Committee, International BFM Study Group, 1996-present
- Member of Biology and Diagnosis Committee International BFM Study Group, 1996-present
- Scientific Advisor of the German Kompetentznetz Pädiatrische Onkologie, 1999-2005
- Member Scientific Committee International Society of Pediatric Oncology (SIOP), 2004-2009
- Chair Scientific Committee International Society of Pediatric Oncology (SIOP) 2010-present
- International Study Coordinator Interfant 06 protocol, international treatment protocol for infants with ALL, 2006-present
- Member Biology and Preclinical Evaluation Committee Innovative Therapies for Children with Cancer (ITCC), 2004-present
- Member European Hematology Association (EHA) Selection Committee EHA Fellowship Program 2010
- Member European Hematology Association (EHA) Scientific Program Advisory Committee, 2005-2009
- Member of the Children's Cancer and Leukaemia Group Scientific Steering Committee of Cancer Research UK, 2007-2011
- Member Scientific Committee on Blood Disorders in Childhood, American Society of Hematology, 2009-2010
- Chair Scientific Committee on Blood Disorders in Childhood, American Society of Hematology, 2011-2012

INTERNATIONAL DATA SAFETY MONITORING COMMITTEES
- Chairman Dana Farber Cancer Institute Data Monitoring Committee, 2008-present
- Chairman Data Safety Monitoring Board HOVON/EORTC-ALL 100 study, 2009-present
- Member of Data Monitoring Committee of the COALL Study 08-09, 2010-present
- Member of data Monitoring committee of the GMALL recombinant pegylated asparaginase study (Pegasp.1/Adults) within the frame of the GMALL protocol 07/ 2003, 2010-present

MEMBERSHIP OF ASSOCIATIONS
- Dutch Pediatric Association (NVK)
- Dutch Hematology Association (NVvH)
- Dutch Oncology Association (NVvO)
- International Society of Paediatric Oncology (SIOP)
- Dutch Childhood Oncology Group (DCOG)
- American Society of Hematology (ASH)
- European Hematology Association (EHA)

EDITORIAL BOARD
- Editor pediatric section of European Journal of Cancer, 2010-present
- Editorial Board Haematologica, 2008-present
- Associate editor Pediatric Blood and Cancer, 2009- present
- Editorial Board the open Leukemia Journal 2008-present
- Editor Cochrane Childhood Cancer Review Group, 2005-present
- Editorial board European Haematology, 2010-present
- Editorial Advisory panel US Hematology, 2009-present
- Editorial Board member European Journal of Clinical & Medical Oncology, 2009-present
- Editorial Board Pediatric Blood and Cancer, 2004-2009
- Editorial Board Member, Investigational New Drugs, the journal of new anticancer agents, 1997-1999
- Board member Pediatric Clinics of Amsterdam 1994-1995

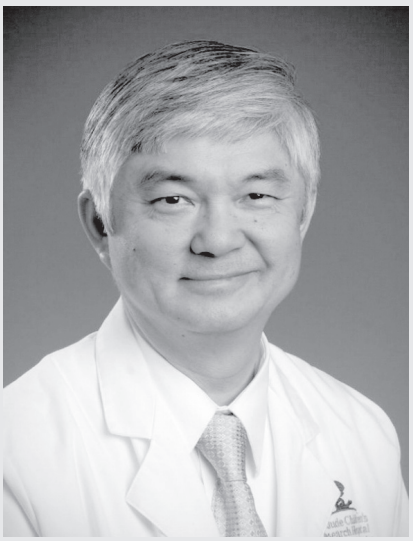
MEETINGS

Chair meetings:
- Co-chair organising committee 3-yearly International Symposium on Drug Resistance in Leukemia and Lymphoma, Amsterdam (1992, 1995, 1998, 2001)
- Chair organising committee yearly symposium Pediatric Oncology Centre Rotterdam, 1999-present
- Member organising committee International Congress of the International Society Pediatric Oncology (SIOP), Amsterdam 2000.
- Co-chair organising committee International Erasmus Workshop on Molecular Therapeutics in Acute Leukemia 2003, 2005
- Chair organising committee yearly Pediatric Research Day, ErasmusMC-Sophia Rotterdam, 2002-2009
- Co-chair organising committee 17th Annual meeting International BFM Study Group, Noordwijkerhout, 2006
- Chair organising committee 5th International Bi-annual Symposium on Childhood Leukemia, Noordwijkerhout, 2006
- Chair Scientifi program annual SIOP meeting 2010-

Program committee:
- Scientific committee SIOP (International Society of Pediatric Oncology) 2004-2009
- European Haematology Association (EHA) Scientific Program Committee Advisory Board 2005-present
- American Society of Haematology (ASH) Scientific Committee on Blood Disorders in Childhood 2009-2012

TEACHING
- Medical students Amsterdam (1991-1998) and Rotterdam (1999-present)
- Residents pediatric department.
- Pediatric Nurses

- Dutch Association for Oncology Nursing - course pediatric oncology, 1996-present
- School for Pediatric Oncology Nursing
- Research training medical students and biology students
- Invited lectures at international and national meetings
- Postgraduate Course on Controversies and Recent Advances in Medical Oncology 1993
- European Scociety for Oncology/ International Society of Pediatric Oncology/American School of pediatric Oncology (ESO/SIOP/ASPO), yearly Postgraduate Course on Translational Research in Pediatric Oncology, 1999-present
- Educational course for pediatric oncologists, SIOP
- Postgraduate Education for pediatricians, Amsterdam (1997-1999) and Rotterdam (1999-present)
- Junior Med School 2008-present
- Minor Pediatric Oncology 2010



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ACADEMIC DEGREES

M.D. 1976 National Taiwan University, Taiwan

POSITIONS

1975-76	Intern, National Taiwan University, Taiwan
1976-77	PL-1, St. Louis City Hospital, St. Louis, Missouri
1977-79	PL2-3, St. Jude Children's Research Hospital, Memphis, Tennessee
1979-81	Fellow in Pediatric Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1981-82	Research Associate, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1982-86	Assistant Member, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1986-1989	Associate Professor, Department of Pediatrics, University of Tennessee, School of Medicine, Memphis, Tennessee
1986-1989	Associate Member, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1987-1989	Associate Member, Department of Pathology and Laboratory Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee
1990	to Professor, Department of Pediatrics, University of Tennessee, Memphis, School of present Medicine, Memphis, Tennessee
1990	to Member, Departments of Hematology-Oncology and Pathology, St. Jude Children's present Research Hospital, Memphis, Tennessee
1991	to Member, Center for Pediatric Pharmacokinetics and Therapeutics, University of present Tennessee, Memphis, School of Medicine, Memphis, Tennessee
1992-2006	Director, Leukemia/Lymphoma Division, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1994-1998	Vice Chairman for Research, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1995	to Program Director, Hematological Malignancies Program, St. Jude Children's Research present Hospital, Memphis, Tennessee
1997-1998	Interim Chairman, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1998-2006	Vice Chairman, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
1999	to Fahad Nassar Al-Rashid Chair of Leukemia Research, St. Jude Children's Research present Hospital, Memphis, Tennessee
2006	to Chairman, Oncology Department, St. Jude Children's Research Hospital, Present Memphis, Tennessee

SOCIETIES

Tennessee Pediatric Society, 1977-1983
American Academy of Pediatrics, 1977-1983; 1988 - present (No. 123114)
American Society of Clinical Oncology, 1982-present (No. 13026)
American Association for Cancer Research, 1983-present (No. 2907)
American Society of Hematology, 1983-present (No. 122819)
Pediatric Oncology Group/Children's Oncology Group, 1985-present
Society for Pediatric Research, 1987-present
American Association for the Advancement of Science, 1992 – present (No. 02280663)
American Society for Clinical Investigation, 1996 – present
FASEB, 1996-present
Association of American Physicians, 1999 - present

CERTIFICATION

E.C.F.M.G., 1975 (No: 0-250-835-6)
FLEX, 1977
V.Q.E., 1977
American Board of Pediatrics, No. 24618 (15 June 1980)
Sub-Board Pediatric Hematology-Oncology, No. 629 (8 October 1982)

MEDICAL LICENSURE

Tennessee MD 11453
Oklahoma MD 11463

HOSPITAL APPOINTMENTS

1977 - present - St. Jude Children's Research Hospital

RESEARCH INTERESTS

Biology and treatment of childhood leukemia and lymphoma

AWARDS AND HONORS
Book Coupon Award, 1971, 1974 and 1975, National Taiwan University
Society for Pediatric Research, 1987
Honorary Professor, The University of Hong Kong, 1993
Member, American Society for Clinical Investigation, 1996
Consultant Professorship, Shanghai Second Medical University, 1998
Fellow, American Association for the Advancement of Science, 1998
The Best Doctors in America, 1998 to Present
Member, Association of American Physicians, 1999
Fahad Nassar Al-Rashid Chair of Leukemia Research, St. Jude Children's Research Hospital, 1999
Kuebel Memorial Lectureship, Washington University, St. Louis, MO, January 3, 2002
Honorary Professor, Beijing Children's Hospital Affiliates of Capital University of Medical Sciences, 2002
American Cancer Society FM Kirby Clinical Research Professor, 2002.
Angel Grant Award from National Cancer Coalition, 2002
Wolf Zuelzer lectureship, Children's Hospital of Michigan, 2002
Guest Professor, The Capital University of Medical Sciences, Beijing, China, 2003
One of the Most Highly Cited Researchers in Clinical Medicine in the past two decades, Thomson ISI Essential Science Indicators, 2004
Daniel Burton Endowment Fund lectureship, Hospital for Sick Children, Toronto, Canada, May 11, 2005.
Scientific Board member, Asia-Pacific Education Center of Clinical Research and Translational Medicine, 2005
First Professor Rina Zaizov Lectureship, Schneider Children's Medical Center, Tel Aviv, Israel, April, 2006
Medical Advisory Board, Curing Kids' Cancer "Dream Team", 2006
Anne T. Bass Endowed Lecture in Hematology, Oncology and Stem Cell Transplantation. Lucile Salter Packard Children's Hospital. Stanford University, 2007.
Greater Memphis United Chinese Association Achievement Award, 2007.
2009 AACR Team Science Award (team leader), 2009
Castle Connolly National Physician of the Year Award for Clinical Excellence, 2010
Honorary Consultant, the Taiwan Pediatric Oncology Group, 2010
Honoree, American Cancer Society Gala, 2011
AACR-Joseph H. Burchenal Clinical Research Award, 2011

Treatment Strategies of High-Risk Childhood ALL

Ching-Hon Pui

St. Jude Children's Research Hospital, Memphis, United States of America

The cure rates of 80% or more achieved in childhood acute lymphoblastic leukemia (ALL)[1,2] attest to the effectiveness of risk-directed therapy developed through well-designed clinical trials. Current research on the optimal use of existing antileukemic drugs, precise risk assessment, host pharmacogenetics, target therapy, and genetic basis of drug resistance of leukemic cells promises to further improve not only the cure rates but also the quality of life of patients.

Paralleling to the treatment advance has been the improved biological understanding of leukemogenesis and mechanisms of drug resistance. Recent genome-wide analyses have identified novel genotypic subtypes of ALL. T-cell ALL cases can be classified into distinct genetic subgroups that correspond to specific T-cell development stages: *HOX11L2*, *LYL1* plus *LMO2, TAL1* plus *LMO1* or *LMO2*, *HOX11*, and *MLL-ENL*.[3] While *HOX11L2* confers a poor prognosis, *HOX11* and *MLL-ENL* are generally associated with a favorable outcome.[4] Among other mutations identified in T-cell ALL, *NOTCH1* or *FBXW7* mutations are associated with a favorable prognosis, *NUP214-ABL1* fusion is responsive to tyrosine kinase inhibitors, and the absence of biallelic TCRγ deletion is associated with early treatment failure.[4,5] In B-cell precursor ALL, several novel genetic abnormalities have been identified and are associated with higher risk of relapse: deletion or mutation of *IKZF1* deletion, *JAK* mutation, *CRLF2* rearrangement, *CREBBP* mutations, and ERG deletion.[6-11] Additional studies are needed to determine if they have independent prognostic significance in the context of contemporary therapies. While the finding of *JAK* mutations has led to a phase I trial with JAK inhibitor,[7] the other discoveries have yet resulted in target therapies.

Allogeneic hematopoietic stem cell transplantation is commonly used for patients who are predicted to respond poorly to intensive chemotherapy. However, the indications for transplant must be periodically reassessed because of continuous improvement in chemotherapy, transplantation procedures and risk assessment. Currently, the most important prognostic factor is the treatment response to remission induction therapy and the leukemic cell genetic abnormality per se can no longer be used as an indication for transplantation.[12] It is because of considerable heterogeneity within specific genetic subtypes due to a combination of variables, including secondary cooperating mutations, developmental stage of the target cells undergoing malignant transformation, and host pharmacodyamics and pharmacogenetics.[12] Several selected high risk groups are briefly discussed here.

Philadelphia Chromosome [BCR-ABL1]-positive ALL

Childhood ALL with the t(9;22)(*BCR-ABL1*) is a heterogeneous disease such that a substantial proportion of patients, i.e., those with low leukocyte count and age younger than 10 years, could be cured with chemotherapy alone.[13] This finding was confirmed by two large international studies.[14,15] The latter study of 610 patients treated without tyrosine kinase inhibitors between 1995 and 2006 showed that the overall outcome had improved with advances in chemotherapy and transplantation, that transplantation with matched-related and matched-unrelated transplantation yielded similar results, and that transplantation improved disease-free survival but not overall survival.[15] However, in a recent Children's Oncology Group study, intensive chemotherapy plus continuous imatinib treatment after conventional remission induction therapy yielded a 3-year event-free survival rate of 80%, which was more than twice that of the historical controls and comparable to those treated with matched-related or matched-unrelated transplant.[16] Although the follow-up duration of this study is too short to determine if the intensive chemotherapy plus imatinib truly improved cure rates and did not merely prolonged disease-free survival, many investigators now reserve transplantation for relapse in patients with this genotype. The recent advent of more potent tyrosine kinase inhibitors might further improve treatment outcome.

Infant ALL with MLL Rearrangement

Although selected small series suggested that transplantation improved outcome of infant cases with *MLL* rearrangement, results of three large cohort studies failed to show an survival advantage of transplantation over chemotherapy.[17-19] In fact, patients underwent mismatched transplantation had a significantly worse outcome than those treated with chemotherapy alone in one earlier study.[17] While in the Interfant-99 study, a very high-risk subgroup of infants with *MLL* rearrangement (age <6 months with either poor response to glucocorticoid treatment or initial leukocyte count ≥ 300 x 10^9/L) benefited from transplantation,[20] the finding of this subset analysis needs confirmation because of very small of patients that were transplanted (n=10) and the retrospective nature of the study. Moreover, the indications for transplantation should also be evaluated in the context of emerging molecular therapies such as FLT3 inhibitors and DNA methyltransferase inhibitors.[21-23]

High-risk T-cell ALL

Early T-cell precursor ALL is a recently identified subset of T-cell ALL with immature immunophenotypic features (CD1a-negative, CD8-negative, CD5-weak expression, and the expression of stem-cell and/or myeloid markers) and a dismal prognosis (event-free survival of ~20%), despite the fact that half of the patients in the study received transplantation due to high MRD levels after remission induction.[24] Whether transplantation with KIR mismatch donor has a therapeutic role in this group of patients remains to be determined.

Hypodiploid ALL

ALL with hypodiploidy <45 chromosomes occurs in only 1% of childhood ALL. In an international collaborative group study, patients with chromosomal number less than 44 in their leukemic cells fared significantly worse than those with 44 chromosomes.[25] In this study, transplantation was performed in first remission in only 9 patients, 5 of whom had an adverse event subsequently. Although there was no significant difference in outcome between patients who were or were not transplanted, the efficacy of transplantation could not be adequately addressed because only a very small number of patients were transplanted.

Poor Early Responders

Early response to treatment is the most important prognostic factor because it accounts for the drug

sensitivity or resistance of leukemic cells; the host pharmacokinetics, pharmacodynamics and pharmacogenetics; the treatment efficacy; and the treatment adherence.[26] Remission induction failure has been considered as one of the worst prognostic factors, with disease-free survival ranging from 21% to 36% in recent studies,[27-29] and has been universally regarded as an indication for transplantation. Because of the potential heterogeneity in this group of patients, a large international study is ongoing to determine if prognosis varies according to genotype and phenotype in this group of patients. Some studies suggested that patients with 1% or more leukemic cells at the end of 4 to 6 weeks of remission induction have a prognosis that is almost as poor as that of patients who fail to achieve clinical remission by traditional morphologic standard, an observation that challenged the current definition of induction failure (i.e., 5% or more blasts by morphology).[26] In the recently completed St. Jude Total Therapy Study XV, transplantation was performed in 9 patients with 1% or more leukemic cells in bone marrow at day 46 of remission induction, and yielded a 5-year event-free survival of 55.6% ± 26.2% and 5-year survival of 87.5% ± 13.8%.[1] Additional studies are needed to determine if transplantation with KIR mismatch donor would improve outcome of these patients.

Acknowledgments: This work was supported by grants (CA21765, CA36401, and GM92666) from the National Institutes of Health, and by the American Lebanese Syrian Associated Charities (ALSAC).

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Treatment Strategies of Adolescents and Young Adults with ALL

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INTRODUCTION

Modern chemotherapy regimens produce long-term survival rates of 80% to 95% for children and young adults with acute lymphoblastic leukemia (ALL).[1,2] Chemotherapy regimens for adult ALL produce long-term survival rates of only 30% to 50%.[3,4]

This review deals with adolescent and young adult patients (AYA) between the ages of 16 and 30 years of age at diagnosis. A rationale for this definition comes from a report of a Spanish trial utilizing a "pediatric" type regimen for adults with ALL which showed no difference in outcome for patients 15 to 18 years old (n= 35) compared with patients 19 to 30 years old (n=46). Patients between 16 and 21 -25 years of age may be treated by either pediatric or medical oncologists.

BIOLOGIC AND CLINICAL FEATURES OF ALL IN THE AYA POPULATION

T cell ALL is more frequent in AYA patients with ALL (25%) than in children or in older adults with ALL (10% to 15%).[5] The incidence of Philadelphia chromosome (Ph) -positive ALL is 2% to 3% in childhood, about 5% to 10% in AYA patients (higher in the 22 – 30 age group than the 16 – 21 year age group), and increases to 15% to 25% in older adults with ALL.[6] Favorable cytogenetic abnormalities are less common in AYA patients with ALL compared to younger patients. A hyperdiploid karyotype is noted in only 10% to 15% of AYA patients with ALL, while the TEL-AML1 translocation is rarely seen in the AYA group.[7,8] Lymphoblasts from older adolescents have decreased in vitro sensitivity to vincristine, prednisone, and asparaginase compared with younger patients.[9] There are no significant differences in clinical or biologic features of ALL among patients 10 to 15 years old and those 16 to 21 years old. [11]

Table 1. Potential Reasons for Differences in the Prognosis of Childhood and Adult ALL.

- Differences in the biology (cytogenetic-molecular) in different age groups
- Intensive use of non-myelosuppressive agents such as steroids, vincristine, and asparaginase
- Earlier and more intensive use of intrathecal central nervous system prophylaxis (e.g. 16-20 intrathecals in pediatric regimens compared with 2-16 intrathecals in adult regimens).
- Longer duration of maintenance therapy with 6-mercaptopurine, vincristine, methotrexate, and prednisone (POMP maintenance), typically 2 – 2 and a half years in pediatric regimens compared with < 1 to up to 2 years in adult regimens.
- Adherence to treatment regimen by both physicians and patients, in particular as it relates to insurance under parent versus patient own insurance and/or lack of insurance; socioeconomic status of adolescents or young adults at the time of disease diagnosis.

WHY DO CHILDREN HAVE A BETTER PROGNOSIS THAN ADULTS WITH ALL? (SEE TABLE 1)

Biologic factors

The significantly lower incidence of favorable genetic chromosomal abnormalities and the higher incidence of PH+ALL in adult patients explains some of the difference in outcome favoring younger patients with ALL.

Table 2. Differences in the Incidences and Outcome of Cytogenetic-Molecular Abnormalities in Children and Adults with ALL

	Incidence (Percent)		
CG-molecular group	Pediatric	Adult	Cure (Percent)
· Ph-positive	<5%	20-30%	Adult - <5% Pediatric - 28%
· Hyperdiploid Karyotype >50 chromosomes	28%	<5%	50-79%
· TEL-AML; t(12;21)	25-30%	<5%	90%

Medical Factors

Both treatment related mortality and morbidity increase with age. Adults may have significantly greater toxicity associated with asparaginase ad-

ministration compared to younger patients. The salvage rate for older patients who experience ALL relapse is significantly lower compared to the salvage rates for younger patients[12,13] although the salvage rate for adolescents with ALL are quite poor as well.

Treatment Factors

Until recently, significant treatment differences existed between adult and pediatric ALL protocols and likely accounts for some of the outcome differences for children and adults.

TREATMENT – EVOLUTION OF PEDIATRIC AND ADULT REGIMENS OVER TIME

Evolution of Pediatric Regimens

Pediatric regimens for ALL feature higher cumulative doses of the nonmyelosuppressive agents vincristine, asparaginase, and steroids compared to adult treatment protocols and the use of earlier and more intensive intrathecal therapy. Adult ALL regimens utilize higher cumulative doses of myelosuppressive chemotherapy agents including anthracylines, cytarabine and cyclophosphamide.

Since the early 1980's, treatment for AYA patients utilized a BFM type regimen which included an intensive induction-consolidation followed by an interim maintenance and delayed reinduction-reconsolidation phases, before proceeding with 1 – 2 years of maintenance therapy. CNS prophylaxis consisted of cranial radiation and intrathecal therapy. Over time, the use of cranial radiation has decreased significantly and, for patients who still require radiation, the dose of radiation has been reduced. Utilizing this BFM type regimen, the Children's Cancer Group (CCG) identified a group of patients with >25% marrow blasts after 7 days of induction (slow early responders) with an approximate 40% event free survival (EFS) when treated with BFM type therapy. Patients with <25% blasts had an EFS of approximately 75%.

CCG investigators developed a novel regimen to treat slow responding patients, deemed "augmented" BFM. The hypothesis was that treatment failure in such patients resulted from a relative rather than an absolute resistance to the standard drugs used in ALL therapy. Augmented BFM maintained the basic BFM backbone but markedly increased the dose intensity of vincristine and asparaginase. In addition, intravenous methotrexate was used without leucovorin rescue in interim maintenance phases.[18] A second interim maintenance and delayed intensification phase was also added.

In the first year of therapy, the augmented BFM regimen delivered twice as many doses of vincristine and three times as many doses of asparaginase compared with standard BFM. The augmented BMF regimen also delivered 10 courses of intravenous methotrexate without rescue. The total doses of cytotoxic drugs delivered on augmented BFM compared to other regimens are shown in Table 3.

Table 3. Dose Intensity of Induction and Consolidation Maintenance in Children Cancer Group (CCG) versus Common Acute Leukemia Group B (CALGB) regimens (Reference 16)

A. Induction with CCG versus CALGB		
Agent/Therapy	CCG	CALGB
Prednisone (mg/m^2)	1680	1260
Vincristine (mg)	8	8
L-asparaginase (U/m^2)	54,000	36,000
Daunorubicin (mg/m^2)	100	135
Cyclophosphamide (mg/m^2)	--	1200
IT-methotrexate	Day 14	--
IT-cytarabine	Day 0	--

B. Consolidation with CCG-BFM (Berlin-Frankfurt Muster) versus augmented BFM versus CALGB			
Agent/Therapy	CCG-BFM	A-BFM	CALGB
Dexamethasone (mg/m^2)	210	420	140
Vincristine (mg/m^2)	22.5	45	14
L-asparaginase (U/m^2)	90,000	318,000	48,000
Doxorubicin (mg/m^2)	75	150	90
Cyclophosphomide (mg/m^2)	3000	4000	3000
IT methotrexate (mg/m^2), Cranial XRT [cGy]	132 + XRT or 216,, no XRT	132 [1800]	105 [2400]

In the pilot trial of augmented BFM therapy, many patients required dose reductions of vincristine and there was a relatively high incidence of asparaginase allergy. Following completion of the pilot trial, National Cancer Institute (NCI) high-risk patients with slow early response were randomized to receive either augmented BFM or standard BFM. Patients receiving augmented BFM had a statistically significant improvement in both EFS and survival compared with patients receiving standard BFM.[18]

In the successor CCG 1961 study, conducted from 1996 to 2002, CCG investigated whether the incorporation of elements of augmented BFM therapy would improve the outcome for NCI high-risk patients who showed a rapid response to induction

therapy. The basic question was whether increasing the dose intensity of therapy – additional vincristine and asparaginase during consolidation/reconsolidation courses and the use of intravenous methotrexate without rescue during interim maintenance phases or the addition of a second interim maintenance and delayed intensification, or both interventions would improve outcome.[19]

The 5 year EFS was 82% (SE 5.4%) for young adult rapid responders who were randomized to augmented intensity therapy, versus 67% (SE 6.7%) for patients randomized to standard intensity therapy (P=.07).. There was no statistical difference in EFS for young adults rapid responder patients randomized to 1 or 2 delayed intensification phases. Therefore, augmented BFM with a single delayed intensification is the current standard therapy for rapid responder patients.

Evolution of Adult Regimens

Most adult regimens have included induction with vincristine, steroids, and anthracyclines; multiple consolidations with high doses of cytarabine, methotrexate, plus or minus asparaginase, and maintenance therapy with POMP in conjunction with CNS prophylaxis. In contrast to the evolution of pediatric regimens, many adult ALL protocols began investigating myelosuppressive or ablative therapies (allogeneic and autologous transplant in first remission). At the same time, the intensity of nonmyelosuppressive therapies and intrathecal therapy was reduced. The duration of maintenance therapy was also shortened. Adult therapy regimens generally followed the principles of adult AML therapy protocols.

Table 4. Comparison of Adult versus Pediatric regimens in Adolescents and Young Adults with ALL

Country (Reference)	Regimen	Age	No.	%CR	% EFS (Years)
United States (16)	CCG	16-21	197	90	63 (7)
	CALGB		124	90	34 (7)
France (17)	FRALLE 93	15-20	77	94	67 (5)
	LALA94		100	83	41 (5)
Holland (18)	DGOG	15-18	47	98	69 (5)
	HVON		44	91	34 (5)
United Kingdom (21)	ALL97	15-17	61	98	65 (5)
	UKALLXII		67	94	49 (5)
Italy (19)	AIEOP	14-18	150	94	80 (2)
	GIMEMA		95	89	71 (2)
Finland (22)	NO PHO	10-25	128	96	67 (5)
	ALL		97	97	60 (5)
M. D. Anderson Cancer Center (24,29)	Hyper CVAD	13-30	175	97	70 (3)
	Augmented BFM	14-36	48	95	82 (2)

The major differences between pediatric and adult ALL regimens may account, in part, for the significant differences in outcomes for AYA patients treated on pediatric versus adult ALL regimens (summarized in Table 4). Dosages of chemotherapeutic agents utilized in the CCG versus CALGB regimens are shown in table 3.

COMPARISON OF OUTCOME FOR AYA PATIENTS TREATED ON PEDIATRIC VERSUS ADULT PROTOCOLS

The first study comparing AYA patients treated on either a pediatric or an adult ALL trial was reported by Stock et al[16]. Patients 16 – 21 years of age at diagnosis were included. The investigators performed a retrospective comparison of 321 AYA patients treated on CCG and CALGB studies from 1988 to 2001. There were no significant differences in either presenting clinical features or cytogenetics between the two patient groups, but the majority of CCG patients were either 16 or 17 years of age while the majority of CALGB patients were 18 – 21 years of age. While the CR rates were identical, 90%, patients treated on CCG protocols had a significantly higher 7-year EFS rate (63% versus 34%) and survival rate (67% versus 46%). As noted in Table 2, the CCG regimen provided significantly higher doses of dexamethasone (about 2-fold), vincristine (about 2 fold), and asparaginase (about 3 fold), as well as earlier and more intensive CNS prophylaxis.

Similar studies conducted in the Netherlands, Italy, Sweden, and the UK all showed better outcomes for AYA patients treated on pediatric protocols.[17,18,19,20,21]

WHY DO PEDIATRIC REGIMENS PRODUCE BETTER OUTCOMES FOR AYA PATIENTS

Analyses of the above trials suggest many possible reasons for the better results observed utilizing pediatric protocols: 1) dose intensity and cumulative dosage of nonmyelosuppressive agents; 2)administration of long term maintenance therapy; 3) less utilization of allogeneic SCT in first CR, which in the case of AYAs may increase mortality without improving outcome; 4) earlier and more intensive use of intrathecal therapy for CNS prophylaxis and

5) a cluster of less tangible factors including expertise in caring for younger patients with ALL, better familiarity with supportive care measures, compliance to therapy on the part of both physicians and patients. [16-24]

Many adult ALL regimens offer allogeneic stem cell transplant (SCT) in first remission if a suitable donor is available. In some studies, patients without a suitable donor have been randomized to autologous SCT versus chemotherapy. In a recent joint Medical Research Council (MRC) and Eastern Cooperative Oncology Group (ECOG) study, the 5-year survival for 234 Ph-negative patients younger than 20 years of age was only 43%. In a group of patients considered as having "standard" risk ALL – age less than 35years, no t(9;22), B precursor and WBC count less than 100 x 10^9/L or T and WBC less than 30x 10^9/L – a significant survival advantage was observed among patients with a suitable donor for allogeneic SCT. The 5-year survival rate was 62% for patients with a donor versus 52% for patients without a donor (P=.02). However, these patients constituted only about 12-15% of the total study group. In contrast, the remaining patients (age 35 years or older, Ph-positive ALL, other high-risk features) did not benefit from allogeneic SCT. In addition, this MRC-CCG study reported a significantly worse survival with autologous SCT compared with maintenance therapy, except in the subset of T-cell ALL in which the 2 approaches appeared equivalent. Within the COG 1961 trial, 16 – 21 year old patients meeting the standard risk criteria of the MRC-ECOG had a 5-year EFS and survival rate of 73% and 80%, respectively. This suggests that pediatric regimens are effective for AYA patients with favorable prognostic features and preclude the need for routine allogeneic SCT in first remission.

The most recent COG trial for NCI high-risk ALL included patients 16 to 30 years old. Patients were initially randomized to receive either dexamethasone (10mg/m^2 for 14 days) or prednisone (60mg/m^2 for 28 days) during induction, and either escalating doses of methotrexate without rescue or high dose methotrexate with leucovorin rescue. The induction steroid randomization was discontinued because of a high rate of avascular bone necrosis in the dexamethasone arm. The study recently closed. A benefit was observed for high dose methotrexate versus Capizzi methotrexate. In younger patients, dexamethasone produced a better outcome compared to prednisone

An adult trial for AYA patients which utilizes the dexamethasone and Capizzi methotrexate arm of the COG trial is also ongoing.

Outcome of AYA Patients with ALL Treated by Medical Oncologists Utilizing Pediatric-like Regimens

Based on the better outcome for young adult ALL patients treated on pediatric protocols, several adult groups have begun to treat AYA as well as older patients (up to the age of 50 years) on pediatric regimens.

French investigators recently reported the outcome of 215 patients with ALL aged 15 to 60 years old treated on a pediatric-based regimen, GRALL-2003. The overall remission rate was 93%, the 42-month EFS rate was 55% and the survival rate was 60%. In this study, the cumulative dose of prednisone was 8.6 fold higher than in the previous adult protocols, the vincristine cumulative dose was 3.7-fold higher, and the cumulative dose of asparaginase was 16-fold higher. The best results were among patients 15 to 45 years old. [25]

Recently, the Dana Farber Cancer Institute (DFCI) adult consortium reported the results of a trial utilizing the DFCI pediatric treatment regimen for adults age 18 to 50 years. In this protocol, the emphasis was on an extended course of asparaginase for 30 weeks. Among 74 patients treated, the CR rate was 82%, the 2-year EFS was 72%, and the 2-year survival was 73%. Toxicities related particularly to nonmyelosuppressive agents were significant including severe pancreatitis in 13% and thromboembolic events in 19% of patients.[27] A modified DFCI pediatric regimen used by Canadian investigators in 68 patients (age 17 to 71 years) yielded a CR rate of 85%, a 3-year disease-free survival rate of 77% and a 3-year survival rate of 65%.[28]

Some currently utilized adult regimens more closely resemble pediatric protocols. The hyper-CVAD regimen developed at M. D. Anderson Cancer Center continues to use dose intensive nonmyelosuppressive therapy and prolonged POMP maintenance but has de-emphasized asparaginase intensification because of the potential neurotoxicity among older patients. The hyper-CVAD regimen has accrued 175 patients aged 13 to 30 years (83 patients aged 13 to 21 years, 92 patients aged 22 to 30 years). The overall CR rate was 97%, the 3-year survival rate was 69% and 3-year disease-free survival rate 70%.[24] These results are not different from those reported by DeAngelo et al and Storring et al.[27,28] An ongoing study at M. D. Anderson Cancer Center utilzes the pediatric augmented BFM regimen among AYA with ALL. So far, 48 patients (median

age 20 years; range 14 to 36 years) have been treated. The CR rate was 95% and the estimated 2-year survival rate 82%.[29] The results of this study will be compared to similarly aged patients treated with hyper-CVAD. It appears that the general consensus in the evolution of adult ALL regimens is to utilize more nonmyelosuppressive agents during induction, consolidation and maintenance,with particular emphasis on asparaginase.

SPECIFIC SUBGROUPS

About 5% to 8 % of AYAs with precursor B-ALL have Ph-positive ALL. Until recently, standard Ph-positive ALL therapy resulted in EFS rates of less than 30% to 50%. Rapid early response to induction, younger age, and WBC < 50 x 10^9/L were favorable prognostic features. Most groups recommended allogeneic SCT in first remission for patients with Ph-positive ALL if suitable donors were available. A recent COG study combined chemotherapy with a BCR-ABL tyrosine kinase inhibitor, imatinib, for the treatment of Ph-positive ALL. The preliminary results were encouraging with estimated 3-year EFS rates of 80% without the use of allogeneic SCT. Thus, it is not clear whether allogeneic SCT in first remission is the best option for patients with Ph-positive ALL who have a rapid early response to chemotherapy and imatinib. Longer follow-up is required to assess whether chemotherapy and imatinib will prevent or only delay relapse.

TREATMENT COMPLICATIONS

In all pediatric cooperative group trials, AYA patients have experienced increased treatment-related morbidity and mortality compared to children with ALL. In the CCG 1961 study, AYA patients had significantly higher incidence of side effects including hyperglycemia, stroke, encephalopathy, and avascular necrosis (AVN) compared to children.

AVN has been recognized as a complication of long term steroid use and was first reported as a significant complication of ALL therapy on the CCG 1882 study. The incidence of AVN was 0.9% for patients less than 10 years of age and 14.2% for patients 10 years of age or older. In this trial, the CCG compared standard and augmented BFM therapies for slow responder patients (more than 25% blasts on a day 7 marrow aspirate). For patients 10 years or older with slow early response, the incidence of AVN was 16.4% with standard BFM and 23.2% with augmented BFM.

In the CCG 1961 trial, the use of discontinuous dexamethasone during delayed intensification phases produced a 50% decrease in the incidence of AVN.

In the AALL0232 study, NCI high risk patients randomized to dexamethasone at 10 mg/$m^2$for 14 days during induction had a significantly higher incidence of AVN compared with patients randomized to prednisone at 60mg/m^2 for 28 days. Therefore, the dexamethasone arm was discontinued for patients greater than 10 years of age and these patients are assigned to prednisone therapy during induction. It appears that the lowest incidence of AVN (approximately 10%) is seen in the prednisone/high dose methotrexate arm of the trial.

ADOLESCENT AND YOUNG ADULTS WITH ALL – THE FUTURE

Determination of the presence of minimal residual disease (MRD), either by flow cytometry or PCR techniques, in conjunction with cytogenetic analysis (both standard and molecular) is the basis for post induction risk stratification in most current ALL trials. MRD at end induction, alone or in combination with MRD at the end of consolidation, has been shown to be a highly significant prognostic factor in both adult and pediatric ALL trials. Many groups use MRD determinations, usually at a post consolidation time point to determine which patients should receive an allogeneic SCT in first remission.

Gene profiling may identify different subgroups with differing prognoses and may be instrumental in determining new therapeutic targets. Ikaros gene deletions and rearrangement in CRLF2 are examples of genetic mutations associated with poor outcome for which targeted therapy may soon exist.[30]

New drugs have become available which may impact EFS and overall survival. These include clofarabine in precursor B-ALL and nelarabine for T cell ALL.[31,32]

The development of new tyrosine kinase inhibitors has the potential to further improve cure rates in patients with Ph-positive ALL. Combinations of the more potent BCR-ABL inhibitors, e.g. dasatinib, with chemotherapy as initial treatment for Ph-positive ALL are under investigation.[33]

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Pediatric Acute Myeloid Leukemia

The cure rate of children with acute myeloid leukemia (AML) has improved impressively over the past three decades and long-term survival rates of more than 60% could be reached. This has been achieved by several courses of intensive chemotherapy based on a combination of the most important drugs: anthracyclines and cytarabine, the latter given in high doses. In addition, advances in supportive care were of major importance. The optimal time for stem cell transplantation was evaluated in several trials, which showed that slightly less relapses occurred when stem cell transplantation was performed in 1st remission; however, overall survival was similar with or without stem cell transplantation in 1st remission (presented by B. Gibson). The survival rates of children and adolescents with AML recurrences treated according an international relapse protocol with intensive treatment including stem cell transplantation after remission have also improved remarkably (which will be shown by GJ Kaspers). U. Creutzig will present the current strategy of risk adapted treatment in children with AML.

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The Place of Stem Cell Transplantation in 1st Remission in Pediatric AML

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The role of stem cell transplantation in CR1 of AML in children is arguably the most important question in the management of children with AML. With increasingly favourable outcomes reported for children treated with chemotherapy alone, the benefit of SCT over high dose Ara- C or anthracycline containing chemotherapy as post remission consolidation treatment in CR 1 AML is controversial. Whilst it is accepted that allo-SCT is effective anti-leukaemic therapy and in most studies has been shown to significantly reduce the relapse risk, long-term survival benefit is variably reported. For a reduction in relapse rate to transfer into an improvement in overall survival the magnitude of reduction has to be sufficiently large to absorb the predicted transplant related mortality. The balance of risk benefit may depend on the donor type, risk group allocation and CR status.

Which donor?

Both autologous (A-SCT) and allogeneic SCT (allo-SCT) are employed in AML CR1 as consolidation therapy. A meta-analysis found insufficient data to prove benefit for A-SCT compared to non-myeloablative chemotherapy[1]. Furthermore, ASCT is associated with significant long-term morbidity and for this reason, in the absence of evidence of clear benefit, few cooperative groups now employ A-SCT. Some allocate donor type by risk group stratification, reserving sibling donors for standard risk patients and allowing VUD or haplo-identical donors for high risk AML patients. This is an increasingly difficult strategy to support as family demographics change and fewer children have a sibling donor; a changing pattern reflected in the increasing dependency on VUDs across disease types. However, those who do support higher risk transplants for higher risk disease

Table 1. Multivariate Analysis Comparing MSD with URD with mmRD

	mmRD vs MSD		URD vs MSD		URD vs mmRD	
Outcome	RR (95% CI)	P	RR (95% CI)	P	RR (95%CI)	P
Acute GvHD 2-4*	2.70 (2.13-3.42)	< .001	1.76 (1.42-2.18)	< .001	0.65 (0.49-0.86)	.003
Acute GvHD 3-4†	3.41 (2.38-4.89)	< .001	2.54 (1.78-3.64)	< .001	0.75 (0.49-1.14)	.177
Chronic GvHD‡	3.09 (2.24-4.27)	< .001	3.92 (3.00-5.13)	< .001	1.27 (0.88-1.82)	.198
TRM§	3.01 (2.10-4.33)	< .001	3.48 (2.54-4.77)	< .001	1.16 (0.77-1.64)	.739
Relapse¦	0.90 (0.65-1.24)	.516	0.98 (0.76-1.27)	.874	1.09 (0.74-1.60)	.661
Disease-free Survival¶	1.38 (1.09-1.75)	.008	1.41 (1.16-1.70)	< .001	1.02 (0.77-1.35)	.904
Overall survival#	1.55 (1.21-1.98)	< .001	1.46 (1.18-1.80)	< .001	0.94 (0.71-1.26)	.686

Blood 2010 (116) ; 4007-4015

do so on the grounds that the greater procedure-related mortality and morbidity associated with VUD transplantation may negate the benefit in standard risk disease but be justified for its greater graft versus leukaemia affect in high risk disease. Increasingly transplanters claim similar outcomes for VUD and MSD transplants and argue that if SCT is indicated, both MSD and URD should be permissible. A recent report from the CIMBTR comparing outcome for 1208 MSD v 266 8/8 allelic–matched unrelated donors (UDR) v 151 0-1 HLA–antigen mmRDs concluded that the recipients of MSD transplants had less transplant–related mortality, acute graft–versus–host disease (GVHD) and chronic GVHD , along with better DFS and OS than the URD and mmRD recipients[2] (table1). Outcomes may improve with allele level typing, but there is not yet a large enough study to prove this.

Which risk group?

A predicted relapse risk exceeding 35% has been suggested as a useful threshold to identify younger adults who may gain net benefit from allogeneic transplant in CR13[3]. The relapse risk in MRC AML 12 by risk group was good, standard and poor risk 20%, 35% and 50% respectively. Good risk patients with a low relapse risk are unlikely to benefit from SCT in CR 1 and most groups now exclude this group from SCT in CR1. MRC and BFM trials show no advantage for SCT in CR1 for any risk group, whilst COG trials report advantage and continue to transplant both standard and poor risk patients in CR. Improved risk group stratification may change this approach.

Which CR?

Should SCT be reserved for 2nd CR and spare those who would not have relapsed the morbidity and mortality of SCT? There is agreement that stem cell transplantation in CR2 offers a superior outcome compared to chemotherapy alone. MRC data from AML10 and 12 reports a survival advantage for SCT in CR2 compared to chemotherapy of 56% v 45%; p=0.04 (based on 182 SCT v 96 chemotherapy patients - non–randomised). A similar SCT outcome was reported by AIEOP for a retrospective analysis of 63 children (0.2 - 17 years) who received an allo-SCT in 2nd CR of AML (MFD 46% ; VUD 54%); 5 year OS and LFS were 53% and 49% respectively[4].

Exploitation of the GvL effect of allo-SCT may benefit children with high risk/refractory disease who would otherwise be unsalvageable.

Thirteen children[5] (median age 2.2 years) with high risk AML underwent SCT from an unrelated (11) or identical donor (2) after a preparative regimen of Busulphan, Cyclophosphamide and Melphalan. Three children were poor risk in 1st CR, 3 in 2nd CR, 5 in PR and 2 had resistant disease. Immunotherapeutic strategies were employed to maximise the GVL effect. 10/13 (77%) were alive in CR at a median of 41 months from SCT. There was no TRM but 3 children relapsed and died 3, 4, 17 months after SCT. Similar outcomes have been informally reported for high risk/refractory disease by other groups employing a similar chemotherapy regimen.

Evaluation of the benefit of SCT

Evaluation of benefit of SCT is complicated by a number of factors including the method of analysis. In the absence of randomised trials, this has historically been based on donor versus no donor analysis which includes SCT from alternative donors in the non SCT arm. This does not adequately answer the question faced by physicians in an era

Table 2.

Trial	Total No	Risk Group	Patient No	DFS (%)	p	OS(%)	p
AML 88	50	HR 63%	17 allo	74			
			31 auto	74			
CCG 2891	537	NS	181 allo	55		60	
			177 auto	42		48	
			179 chemo	47	0.01	53	0.05
MRC10	359	GR 28%	85 donor	60		68	
		SR 52%	230 no donor	50	0.1	59	0.3
		HR 20%	50 auto	68		70	
			50 chemo	46	0.03	58	0.2
CCG 251, 213, 2861, 2891, 2941	1464	NS	373 allo	47		54	
			217 auto	42		49	
			688 chemo	34	0.004	42	0.06
AML BFM 98 *	494	HR 64%	58donor	47		55	
			166 no donor	40	0.4	54	0.16

* results at 5years ;all others 8 years. Adapted Bone Marrow Transplantation 2008(42)[6]

of diminishing sibling donors of whether or not SCT from an alternative donor is superior to intensive chemotherapy alone as consolidation therapy in CR1. Many of the published trials are old and changes in risk group stratification, transplantation practices, chemotherapy and supportive care compound the difficulty.

SCT practices

A marked transatlantic divide in SCT practice in 1st CR AML in children has emerged with SCT either not employed for any risk group or reserved for poor risk patients in Europe, but still employed for standard and poor risk patients in the US. European practice is guided by an inability to translate a reduction in relapse rate into an improvement in OS (table 2). Complex differences between study design and treatments makes comparison difficult. Any benefit for SCT is dependent on the intensity of chemotherapy given prior to SCT and SCT may have greater advantage when included in protocols of lesser intensity.

Horan et al[7] reported a meta-analysis of the comparative outcomes by risk group for SCT and chemotherapy for 1373 children who received an allo-

Table 3. Risk-stratified Outcomes Comparing Matched Sibling BMT & Chemotherapy Alone in MRC AML10, POG 8821, CCG 2891 and CCG 2961

		Therapy		
		BMT	Chemotherapy	
Outcome by Risk Group		*Estimate (%)	Estimate (%)	P
Favourable	RR	21	30	.06
	TRM	16	9	.08
	DFS	63	61	.58
	OS	73	71	.85
Intermediate	RR	26	54	< .001
	TRM	16	7	.022
	DFS	58	39	< .001
	OS	62	51	.006
Poor	RR	67	56	.69
	TRM	0	9	Estimates do not converge
	DFS	33	35	.82
	OS	33	35	.80
Non-classifiable	RR	32	44	.004
	TRM	16	6	.012
	DFS	52	50	.14
	OS	60	61	.49

* Eight-year estimates are shown, except for BMT patients with poor-risk disease; for this group, estimates are for 4 years because of limited follow-up
Adapted from Journal of Clinical Oncology 2008[7]

Table 4. New Targets for MRD

- Gene over expression
  - WT1: PRAME
- Chimeric fusion genes
  - t(8,21), inv 16, t(15,17)
- Somatic mutations
  - Nucleophosmin, FLT3, CEBPA
- Aberrant gene expression
  - Ectopic virus integration -1 (EVL1)

geneic SCT for AML in 1st CR. Data were combined from four cooperative group clinical trials: POG 8821, CCG 2891, CCG 2961 and MRC AML10. Patients were stratified into favourable, intermediate, and poor risk based on cytogenetics and the percentage of marrow blasts after the first course of chemotherapy.

At 8 years intermediate risk group patients who received an allo-HSCT had an estimated DFS of 58% compared to 39% for those treated with chemotherapy alone and an OS of 62% v 51% (table 3). Both differences were significant ($p<0.01$).

There was no significant differences for survival for good or poor risk patients or in non-risk stratified patients. However, the study is weakened by the large number of non classifiable patients (MRC AML10 – SCT 20% : chemotherapy 12%; POG/CCG – SCT 39% : chemotherapy 37%) and the inconsistency of ABMT handling. Furthermore the comparison suffers from the limitations of a meta-analysis.

Allo-SCT is unlikely to benefit good risk patients and may only benefit poor risk patients if the anti-leukaemic effect can be exploited. The largest number of relapses come from standard risk patients and the challenge is to identify those destined to relapse. Measurement of minimal residual disease may identify those patients with persistent low level disease. However, most studies of MRD in AML have employed flow cytometry and have reported MRD to be less consistently of prognostic value than in ALL. Methodology, discriminatory levels and targets need to be refined. New molecular targets may prove to be more predictive than immunophenotyping (table 4). Furthermore the true prognostic significance and benefit of intervention remains to be confirmed by clinical trial.

The role of SCT in children with AML in 1st CR will need to be reassessed as the field evolves. There is consensus about benefit in CR2 and possibly for refractory disease and lack of benefit for good risk patients. The role in standard and poor risk disease may be redefined by improved risk stratification by the identification of new prognostic markers, by clearer understanding of the benefit in controversial areas such as internal tandem duplication of the FLT3 gene, and by MRD monitoring. In addition, future advances in chemotherapy, particularly targeted molecules may further reduce the need for SCT, unless advances in transplantation occur at a similar pace.

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Relapse Treatment and New Treatment Options

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Introduction

About 5% of children with newly diagnosed acute myeloid leukemia (AML) still have ³5% leukemic blasts in their bone marrow after 2 courses of combination chemotherapy, which is usually called refractory (or resistant) disease. Moreover, about 20% of patients who achieve complete remission (CR) as defined conventionally, have minimal residual leukemia (0.1% - 5% leukemic blasts) at the end of two cycles of induction therapy. The prognosis of these children with resistant, minimal residual disease (MRD-) positive or relapsed AML is relatively poor (Langebrake 2006; Rubnitz 2010; van der Velden 2010).

The most frequent event for newly diagnosed patients with AML is a relapse, occurring in about one in three children (Kaspers 2005). Bone marrow usually is involved, and the central nervous system (CNS) in up to 10% of cases (including combined relapses). About 50% of patients have an early relapse, arbitrarily defined as within one year from initial diagnosis, and 50% have a late relapse after one year.

Prognostic factors

Outcome from relapse is significantly better in case of a longer duration of CR1 (Stahnke 1998; Webb 1999; Kaspers 2008). However, the international study Relapsed AML 2001/01 showed early treatment response to be an even more important prognostic factor (Kaspers 2009). In that study, early response was determined by morphological examination of the bone marrow obtained at day 28 from start of reinduction, and defined as good in case of less than 20% AML blasts, and poor in case of 20% or more of such blasts. Day 28 in practice is between days 28 and 42 from the start of reinduction therapy. In addition to treatment response, favorable cytogenetics t(8;21) and inv(16), as initially identified in studies with newly diagnosed children, also seem to be a favorable prognostic factor at relapsed AML (Kaspers 2010; Webb 1999).

Current treatment

Treatment for refractory and relapsed AML usually consists of high-dose cytarabine with an anthracycline, although other regimens might be effective as well (Webb 1998). The effect of cytarabine can probably be improved by addition of fludarabine, and perhaps also by adding Clofarabine (Evoltra®). Although still unpublished, the recently completed study Relapsed AML 2001/01 demonstrated that adding liposomal daunorubicin (DaunoXome®) to the combination of fludarabine, cytarabine and G-CSF increased the initial antileukemic efficacy of the reinduction chemotherapy (Kaspers 2009). Liposomal daunorubicin has the theoretical advantage that it is less cardiotoxic. Although this has not been proven yet in randomized studies, several preclinical and clinical studies do suggest so (Kaspers 2007). Cardiotoxicity is a concern in pediatric AML in general, and at relapse in particular (Creutzig 2007; Temming 2011). It is unknown whether adding another drug at reinduction chemotherapy, such as etoposide, has additional antileukemic activity. Overall, second CR can be achieved in 50-80% of the relapsed AML cases. Patients with AML that express CD33 can be treated with gemtuzumab ozogamicin (Mylotarg®) alone or in combination with other agents (Zwaan 2010). Study Relapsed AML 2010/01, that has been developed by the Relapsed AML Working Group and AML committee of the International BFM Study Group and that will open for accrual in 2011, will investigate in a randomized fashion whether adding gemtuzumab ozogamicin to the backbone of fludarabine, cytarabine plus liposomal daunorubicin will improve outcome.

In order to achieve a good quality CR, at least two courses of reinduction chemotherapy are probably required. The hypothesis here is that a good quality CR means a low amount of MRD, which is likely to implicate a better prognosis after allogeneic stem cell transplantation (allo-SCT), as proven to be the case in acute lymphoblastic leukemia (ALL). Such an allo-SCT is currently recommended for all children who achieve subsequent CR, using allografts from related or unrelated HLA-matched donors. The use of a very high-risk allo-SCT must be balanced against the possibility that patients

Table I. Outcome of cohorts of pediatric relapsed AML patients treated with curative intention.

Study group	Time period	Overall survival from relapse	Reference
DCOG	1980 - 1998	16%	Goemans 2008
AML-BFM	1987 - 1996	21%	Stahnke 19998
St. Jude	1987 - 2002	23%	Rubnitz 2007
MRC AML10	1988 - 1985	24%	Webb 1999
CCG2951	1997 - 2001	24%	Wells 2003
TACL	1995 - 2004	29%	Gorman 2010
LAME 89/91	1988 - 1998	33%	Aladjidi 2003
NOPHO	1988 - 2003	34%	Abrahamsson 2007
AML-BFM	1998 - 2007	34%	Sander 2010
I-BFM-SG	2001 - 2009	35%	Kaspers 2009

can survive relapsed AML after treatment with chemotherapy only (Goemans 2008). If required, time to transplant must be bridged by consolidation chemotherapy, either intensive or less intensive depending on the condition of the patient and the time period that must be bridged. As a general last remark, and in view of the relatively high incidence of CNS involvement at relapse, CNS-directed therapy with intrathecal chemotherapy seems indicated.

Outcome from relapsed AML

Study Relapsed AML 2001/01 and several other recently published studies report a probability of long-term survival from relapsed AML of more than 30%, as summarized by Goemans et al. (2008) and as illustrated in Table I. A significant chance of survival is even seen in patients that relapsed after having had an allo-SCT in CR1 and in patients with an early relapse. Therefore, reinduction chemotherapy should be offered to all children and adolescents with relapsed AML who can tolerate intensive treatment. However, patients that respond poorly to the first course of reinduction chemotherapy, patients that do not achieve a second complete remission, and patients that relapse again could be offered more experimental therapy in that setting of a very dismal prognosis. Of course, no further chemotherapy but palliative care instead should be considered as well. Fortunately, innovative treatment seems achievable within 10-20 years from now (see below).

Innovative therapy

Innovative therapy may be achieved by better risk-group adapted treatment and by improvements of the treatment itself (Kaspers 2007). Regarding the first, better and thus more discriminating prognostic factors still must be identified in pediatric relapsed AML. Possibilities are cytogenetic and molecular abnormalities, micro-array profiles, and monitoring of MRD and the AML stem cell burden before and during treatment. However, it is likely that innovative treatment itself is going to be most beneficial. On the longer term, new treatment modalities such as vaccination studies and manipulating and increasing the graft-versus-leukemia effect may become important. Meanwhile, novel drugs are likely to provide most benefit on the short-term. Novel drugs may concern drug analogues, such as liposomal daunorubicin and clofarabine. These new but conventional agents may make a significant contribution to improved treatment, but truly novel antileukemic agents are more appealing. Proteasome inhibitors are relatively new, and bortezomib will be tested in pediatric relapsed AML patients by the COG. It has been suggested that this drug selectively kills leukemic stem cells. Especially drugs that selectively target leukemic cells are of major interest, an approach which we commonly designate as targeted therapy.

Targeted therapy: Drugs with novel mechanisms of action, often targeted at leukemia-specific abnormalities, are now becoming available for AML. Typical examples are monoclonal-antibody mediated treatment such as with gemtuzumab ozogamicin (targeting CD33-positive cells) and with tyrosine kinase inhibitors (TKIs, targeting e.g. *FLT3*- or *kit*-mutated AML cells). TKIs such as lestaurtinib, dasatinib, sorafenib and midostaurin (PKC412) are in phase II/III trials in adult AML. The success of combining a TKI (imatinib) with chemotherapy in Philaldephia-positive ALL has not been mimicked in AML yet. However, there is proof-of-principle that the concept of using TKIs in AML patients with an activating mutation in e.g. Flt3 or kit is effective (Fischer 2010; Metzelder 2010; Levis 2011). However, the clinical development of these agents has to be completed, because e.g. drug-inactivation and drug resistance is encountered. Study Relapsed AML 2010/01, as well as the AML-BFM protocol for newly diagnosed children with AML, will evaluate the toxicity and efficacy of sorafenib added to conventional chemotherapy in Flt3-mutated patients. A similar study is being done by the COG and UK CLCG groups, using lestaurtinib. Results are eagerly awaited. Meanwhile, the European pediatric community is evaluating dasatinib and midostaurin.

Challenges and perspectives

Prognosis of pediatric AML has improved significantly to even above 70% long-term survival in some recent unpublished clinical studies. The biggest challenge is to further improve outcome to a cure rate of well above 90% with reasonable side-effects and limited late effects of treatment. Current conventional chemotherapy cannot be intensified further, because of toxicity. Some novel but conventional (non-targeted) drugs, such liposomal daunorubicin and clofarabine will likely make an improvement, but main steps forward are more likely to be achieved with really novel drugs. Examples are tyrosine kinase inhibitors and monoclonal antibody mediated treatment.. Studies on such novel agents in subgroups of pediatric AML will require international collaboration, because of the rarity of these subgroups. An important challenge in such international collaborative studies is that ideally a common chemotherapeutic backbone is being used. Although most pediatric groups worldwide are now using four to five courses of intensive chemotherapy, there still are many differences in drugs, doses and schedules. Another main challenge is the performance of clinical trials under the EU directive and good clinical practice guidelines. Although this directive has a positive effect on the number of clinical studies on new agents in children with cancer, it has become a very complicated process in which unfortunately not all countries apply the EU directive similarly. Investigator-initiated studies have become much more cumbersome and there is a risk that such studies will be done less often. That would be a major problem, because company-driven studies are still rare in children with cancer including AML.

Despite these challenges, the pediatric community has always been able to improve the treatment and outcome of all types of malignancies. Techniques are rapidly improving to identify subgroups that should be treated differently. More and more novel drugs emerge that could be used in different subgroups. Therefore it seems realistic to expect long-term survival in more than 90% of pediatric AML patients, with an acceptable quality of life during treatment and with limited late effects.

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Risk Adapted Treatment in Pediatric AML

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Acute myeloid leukaemia (AML) in children has become a curable disease with survival rates in the range of 60%(Kaspers & Creutzig, 2005). This success was only possible by a stepwise intensification of chemotherapy from study to study. Compared to the previous study, results of study AML-BFM 2004 improved (overall survival 73%) due to therapy intensification, better supportive care, and also due to improved treatment of patients with relapse or nonresponse. Future treatment concepts will consider even more individual risk factors. Therefore, new, highly sensitive diagnostic methods including immunphenotyping, cytogenetics and molecular genetics are necessary.

The main aim in pediatric AML is to improve outcome without increasing acute and longterm toxicity. Since 1978, the AML-BFM study group has performed six consecutive multicenter studies – initially in Germany and later on including Austria, Switzerland and the Czech Republic(Creutzig et al, 2005). During that period, five-year overall survival (OS) improved from 41% to 73%.

In order to spare those patients, who will have good survival rates with standard chemotherapy, unnecessary toxicities we have defined risk groups according to the results of the previous studies AML-BFM 83/87. Patients were stratified into a standard (SR) or high-risk (HR) group according to morphology, cyto-/molecular genetics, and therapy response at day 15 ([1]) (Creutzig et al, 1999). Later on, FLT3-ITD positivity was defined as a stratification criterion for the HR group.

In study AML-BFM 93 the intensification with high dose Ara-C/Mitoxantrone (HAM) as second induction was introduced for HR risk patients only.

([1]) Standard risk: FAB M1/M2 with Auer rods, FAB M4eo or favorable cytogenetics [t(8;21) or inv(16)], no FLT3-ITD and blasts in the bone marrow on day 15 <5%, and FAB M3 (all patients). High-risk: all others.

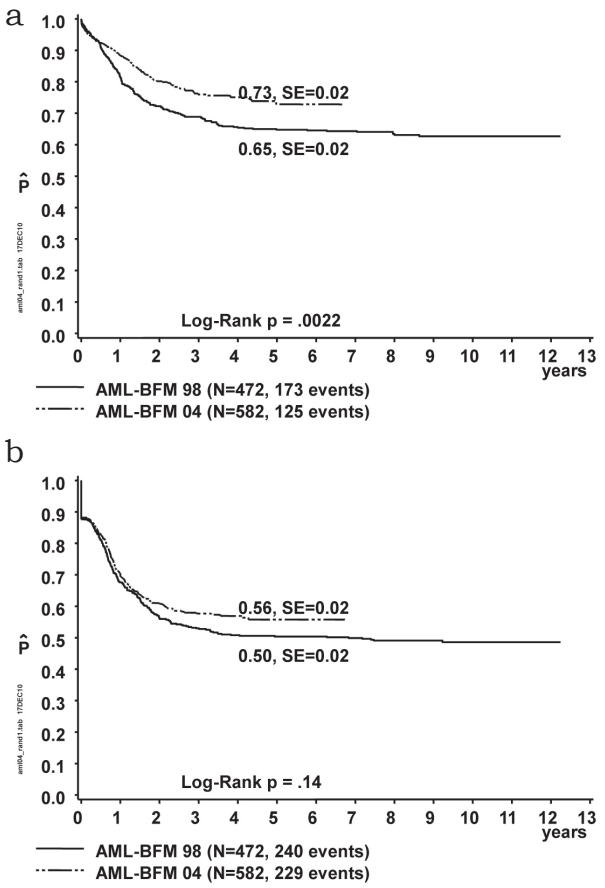

Figure 1. Estimated probability of (a) survival (pOS), (b) event-free survival (pEFS) in patients of studies AML-BFM 98 and-2004, SE = standard error.

Results showed an improved outcome in this HR group, EFS increased from 44%; SE 3% in study 93 compared to 31%, SE 3% in study 87(Creutzig et al, 2001).

Allogeneic stem cell transplantation (SCT) is an effective but highly toxic antileukemic therapy. Therefore we included SCT from matched related donors in first CR only for high risk patients. SCT was performed in about 10% of these patients.

Study AML-BFM 2004 aims to improve prognosis in both, standard and high-risk children and adolescents with AML (<18 years) by intensification of chemotherapy for all patients by (1) the randomized introduction of liposomal daunorubicin (L-DNR) in a higher equivalent dose than idarubicin during induction (L-DNR 80mg/m²/day/3x) in comparison to the standard induction with idarubicin 12mg/m²/day/3x (equivalent dose 60mg/m²), each combined with cytarabine and etoposide (L-DNR offers the possibility to increase cumulative dosages of anthracyclines with lower cardiotoxicity) and (2) randomised introduction of 2-chloro-2-deoxy-adenosine (2-CDA, 2x6mg/m²) as intensification during the cytarabine/idarubicin (AI) consolidation for high-risk (HR) patients. (3) Another aim was to verify the equivalence of a prophylactic CNS irradiation by randomizing a total dose of 18 Gy vs. 12 Gy (randomization over two study periods).

Results

Interim results of AML-BFM 2004 (patient recruitment until 12/2009) improved compared to the previous study AML-BFM 98: Overall survival estimates at 5 years (pOS) in 582 patients (excluding myeloid leukemia in Down syndrome) were 73% + 3% vs. 65% + 2% (AML-BFM 04 n=582 vs. AML-BFM 98 n=472), plogrank=0.002 (Figure 1a); the 5-year event-free survival (pEFS) was 56% + 2% vs. 50% + 2%, plogrank=.14 (Figure 1b). Results in the 202 SR patients (35% of the patients) were excellent: pOS 90% + 2% vs. 79% + 3% (n=182), plogrank=.003, EFS 72%, + 3% vs. 65% + 4%, plogrank=.16. Results in the HR patients also improved: pOS 63% + 3% (n=380) vs. 56% + 3% (n=290), plogrank=.02, EFS 47%, + 3% vs. 41% + 3%, plogrank=.23. OS improvement was partly due to better results after treatment of relapse or nonresponse(Sander et al, 2010) (3-year pOS after nonresponse/relapse in 192 patients of study 2004 = 42% + 5% vs. 32% + 3% in 198 patients in AML-BFM 98, plogrank=.006).

Results of the 1st randomization (L-DNR vs. idarubicin during induction) were similar. However, there were less early deaths (3 vs. 7 patients) and less treatment related deaths in remission in the L-DNR group (1 vs. 4 patients). The rate of severe infections and cardiotoxicity was slightly lower with L-DNR. Results of the 2nd randomization in HR patients (AI/2-CDA vs. AI) were also similar. Toxicity rates of the intensification with 2-CDA were tolerable.

Results of the 3rd randomization showed that that there was no disadvantage for patients irradiated with a reduced CNS dose of 12 Gy regarding OS, EFS and rate of relapse(Creutzig et al, 2010).

Conclusion

Interim results of study AML-BFM 2004 show notable improvement compared to the previous study

AML-BFM 98. This may be attributable to therapy intensification/increased anthracycline doses by introduction of liposomal daunorubicin, better supportive care and improved treatment of patients with relapse or nonresponse. Given the reduced toxicity of L-DNR and slightly better survival rates by adding L-DNR during induction and 2-CDA during HR consolidation, we will continue to use these agents in the forthcoming AML-BFM study.

Cranial irradiation (RT): As significantly less relapses occurred after randomly assigned cranial irradiation in study AML-BFM 87, RT was continued in the following AML-BFM studies. However, results improved considerably in general irrespective of RT since study -87 due to intensification of chemotherapy. Since the results of other international pediatric AML studies indicate that prophylactic CNS-RT does not improve outcome in the context of current chemotherapy regimens and because intensified chemotherapy elements with improved CNS efficiency such as high-dose cytarabine and liposomal daunorubicin have been introduced in the AML-BFM treatment schedule after study -87, the next trial will replace CNS-RT by a triple intrathecal therapy in order to avoid irradiation related long-term sequelae(Creutzig et al, 2010).

The improvement of overall results is not only due to more intensive chemotherapy, but also based on a high standard of experience regarding both the treatment itself and supportive care in the participating hospitals.

Intensity of chemotherapy can hardly be increased in the future. Therefore, new therapy options including targeted therapy will be introduced in the forthcoming study. Consequently, the new treatment concepts are more oriented towards individual risk factors which implicates that results of immunophenotyping, cytogenetics and molecular genetics have to be available for all patients shortly after diagnosis. The new risk stratification, which is mainly based on cytogenetics and molecular genetics will be presented.

**supported by the Deutsche Krebshilfe e.V.*

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A CASE OF PERIPHERAL T CELL LYMPHOMA PRESENTING WITH INFLAMMATORY ARTHRITIS, CUTANEOUS VASCULITIS AND HYPEREOSINOPHILIA

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P020 ID: 34

THE SIMULTANEOUS PRESENTATION OF PERIPHERAL T-CELL LYMPHOMA WITH RHINO-MAXILLARY ASPERGILLOSIS

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MULTIPLE MYELOMA

P021 *ID: 36*

RETROSPECTIVE ANALYSIS FOR CLINICAL AND LABORATUARY FINDINGS OF MULTIPLE MYELOMA PATIENTS

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NON-HODGKIN'S LYMPHOMA

P022 *ID: 38*

NON-HODGKIN'S LYMPHOMA: 18 YEARS EXPERIENCE OF A SINGLE INSTITUTION

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CHRONIC LYMPHOCYTIC LEUKEMIA

P023 *ID: 40*

RELAPSE OF INVASIVE THYMOMA WITH A PRESENTATION OF AUTOIMMUNE HEMOLYTIC ANEMIA AND PERIPHERAL T CELL LYMPHOCYTOSIS

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NON-HODGKIN'S LYMPHOMA

P024 *ID: 41*

A CASE OF MANTLE CELL LYMPHOMA IN A PATIENT WITH SYMPTOMS OF PROSTATISM

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ACUTE MYELOBLASTIC LEUKEMIA

P025 *ID: 47*

A RARE CASE REPORT:CYST HIDATIC DISEASE IN LIVER AND INTRAPERITONEAL CAVITY WITH ACUT MYELOID LEUKEMIA

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HODGKIN'S LYMPHOMA

P026 *ID: 48*

HEMOPHAGOCYTIC SYNDROME ASSOCIATED WITH HODGKIN LYMPHOMA IN CHILDHOOD

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ACUTE MYELOBLASTIC LEUKEMIA

P027 *ID: 49*

AZACITIDINE HAS LIMITED ACTIVITY IN REAL LIFE PATIENTS WITH MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

[1]Murat Özbalak, [1]Mustafa Çetiner, [1]Hüseyin Bekoz, [1]Elif Birtaş Ateşoğlu, [1]Cem Ar, [1]Ayşe Salihoğlu, [1]Nükhet Tüzüner, [1]Burhan Ferhanoğlu.
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ACUTE LYMPHOBLASTIC LEUKEMIA

P028 *ID: 50*

TOLL-LIKE 4 (TLR-4), NOD2, DECTIN-1 POLYMORPHISMS AND SUSCEPTIBILITY TO INFECTIONS, RELAPSE AND OTHER COMPLICATIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

[1]Tiraje Celkan, [2]Mehmet Güven, [1]Nihal Özdemir, [2]Bahadır Batar, [1]Gülen Tüysüz, [1]Hilmi Apak.
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NON-HODGKIN'S LYMPHOMA

P029 *ID: 51*

THE ASSOCIATION OF TOLL-LIKE 4 (TLR-4) AND NOD2 POLYMORPHISMS AND FEBRILE NEUTROPENIA IN CHILDREN WITH BURKITT LYMPHOMA

[1]Nihal Özdemir, [2]Mehmet Güven, [2]Bahadır Batar, [1]Hilmi Apak, [1]Gülen Tüysüz, [1]Safa Barış, [1]İnci Yıldız, [1]Tiraje Celkan.
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ACUTE LYMPHOBLASTIC LEUKEMIA

P030 *ID: 52*

RENAL TUBULAR ACIDOSIS AS A COMPLICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA

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P031 ID: 54

SUCCESSFUL TREATMENT OF EARLY RELAPSE WITH ICE–RITUXIMAB CHEMOTHERAPY AND SUBSEQUENT BONE MARROW TRANSPLANTATION IN A PATIENT WITH BURKITT LEUKEMIA AND INVERTED DUPLICATION OF 1Q

[1]Barış Malbora, [1]Zekai Avcı, [1]Betül Orhan, [1]Asburce Olgac, [1]Namık Özbek.
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MULTIPLE MYELOMA

P032 *ID: 59*

PLASMA CELL LEUKEMIA WITH SKIN INVOLVEMENT

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CHRONIC MYELOID LEUKEMIA

P033 *ID: 60*

TOXIC DERMATITIS RELATED TO IMATINIB

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NON-HODGKIN'S LYMPHOMA

P034 *ID: 61*

PRIMARY GASTROINTESINAL NON-HODGKIN LYMPHOMA IN A RENAL TRANSPLANT RECIPIENT CHILD

[1]Tiraje Celkan, [1]Nihal Özdemir, [2]Lale Sever, [2]Salim Çalışkan, [3]Mehmet Eliçevik, [4]Hilal Akı.
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MULTIPLE MYELOMA

P035 *ID: 62*

CARDIAC TAMPONADE: AN UNUSUAL PRESENTATION OF MULTIPLE MYELOMA

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CHRONIC MYELOID LEUKEMIA

P036 *ID: 63*

CHRONIC MYELOID LEUKEMIA AND MYELOFIBROSIS AS A SEPARATE ENTITY IN A PATIENT WHOSE FIBROSIS IMPROVED DESPITE NOT ACHIEVING A CYTOGENETIC RESPONSE

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CHRONIC LYMPHOCYTIC LEUKEMIA

P037 *ID: 64*

CHLORAMBUCIL-INDUCED INAPPROPRIATE ANTIDIURESIS IN A MAN WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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NON-HODGKIN'S LYMPHOMA

P038 *ID: 65*

BURKITT LYMPHOMA ORIGINATING FROM THE SPHENOID SINUS

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MYELOPROFILERATIVE DISORDERS

P039 *ID: 68*

''MEAN PLATELET VOLUME'' IN DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOSIS

[1]Betül Erişmiş, [2]Selami Koçak Toprak, [2]Sema Karakuş, [2]Gül İlhan, [1]Sevinç Can.
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MULTIPLE MYELOMA

P040 *ID: 69*

HLA-DRB1*13 AND *15 ARE ASSOCIATED WITH RESPONSE TO THALIDOMIDE IN PATIENTS WITH MULTIPLE MYELOMA

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ACUTE MYELOBLASTIC LEUKEMIA

P041 *ID: 70*

COEXISTING LYMPHOMA AND LEUKEMIA IN THE BONE MARROW TREPHINE BIOPSY: A CASE REPORT

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NON-HODGKIN'S LYMPHOMA

P042 *ID: 71*

EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA, NASAL TYPE : A CASE REPORT

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CHRONIC LYMPHOCYTIC LEUKEMIA

P043 *ID: 72*

CHRONIC LYMPHOCYTIC LEUKEMIA/ PROLYMPHOCYTIC LEUKEMIA WITH SKIN INVOLVEMENT: A CASE REPORT

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MULTIPLE MYELOMA

P044 *ID: 73*

PLASMA CELL MYELOMA LACKING CD138 AND CD38 EXPRESSION: A CASE REPORT

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HODGKIN'S LYMPHOMA

P045 *ID: 74*

A CASE REPORT:MARKED HIPEREOSINOPHILIA IN HODGKIN'S DISEASE

[1]Funda Ceran, [1]Simten Dağdaş, [1]Cenk Sunu, [1]Oğuzhan Oğuz, [1]Mustafa Tahtacı, [1]Mesude Falay, [1]Gülsüm Özet.
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ACUTE LYMPHOBLASTIC LEUKEMIA

P046 *ID: 75*

THE LONG TERM RESULTS OF CHILDHOOD ALL AT TWO CENTERS FROM TURKEY: 15 YEARS OF EXPERIENCE WITH ALL-BFM 95 PROTOCOL

[1]Adalet Meral Güneş, [2]Hale Ören, [1]Birol Baytan, [2]Şebnem Yılmaz, [1]Melike Sezgin Evim, [2]Salih Gözmen, [2]Özlem Tüfekçi, [2]Tuba Karapınar, [2]Gülersu Irken.
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P047 ID: 76

ASSESSMENT OF ENDOCRINOLOGIC AND CARDIOLOGIC LATE EFFECTS AMONG SURVIVORS OF CHILDHOOD LEUKEMIA

[1]Pakize Karakaya, [1]Şebnem Yılmaz, [1]Mustafa Kır, [1]Ece Böber, [1]Salih Gözmen, [1]Özlem Tüfekçi, [1]Tuba Karapınar, [1]Gülersu Irken, [1]Hale Ören.
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P048 ID: 77

A RARE COMPLICATION OF INTRATHECAL METHOTREXATE

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CHRONIC MYELOID LEUKEMIA

P049 *ID: 78*

PLEURAL AND PERICARDIAL EFFUSIONS IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS DURING LOW DOSE DASATINIB TREATMENT

[1]Ahmet Emre Eşkazan, [1]Ayşe Salihoğlu, [1]Emine Gültürk, [1]Şeniz Öngören, [1]Zafer Başlar, [1]Burhan Ferhanoğlu, [1]Yıldız Aydın, [1]Teoman Soysal.
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CHRONIC LYMPHOCYTIC LEUKEMIA

P050 *ID: 79*

CUT OFF VALUE FOR CD38 EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS

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ACUTE MYELOBLASTIC LEUKEMIA

P051 *ID: 81*

STANDARD DOSE OF CYTARABINE-INDUCED SINUSAL BRADICARDIA IN AML PATIENT

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HODGKIN'S LYMPHOMA

P052 *ID: 82*

THE RELATIONSHIP BETWEEN INHIBIN B, PUBERTY AND SECONDARY SEX CHARACTERISTICS IN CHILDHOOD CANCER PATIENTS AFTER GONADOTOXIC TREATMENT AND HAVE PROVIDED CURE

[1]Gülsüm Kadıoğlu Şimşek, [2]Emel Ünal, [2]Gülsan Yavuz, [2]Nurdan Taçyıldız, [2]Handan Dinçaslan, [3]Deniz Güloğlu, [5]Sema Büyükfırat, [3]Aydan İkincioğulları, [4]Merih Berberoğlu, [4]Gönül Öcal.
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P053 ID: 84

RETROSPECTIVE ANALYSIS OF HL PATIENTS FROM A SINGLE INSTUTITION

[1]Süheyla Aytac Arslan, [1]Ayşen Dizman, [1]Ebru Karakaya, [1]Mehtap Coşkun, [1]Ela Delikgöz Soykut, [1]Gonca Altınışık İnan, [1]Yıldız Güney.
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ACUTE MYELOBLASTIC LEUKEMIA

P054 *ID: 85*

SINGLE CENTER EXPERIENCE: IDA-FLAG TREATMENT IN PATIENTS WITH RELAPS/REFRACTORY ACUTE LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA.

[1]Abdullah Katgı, [2]Tuğba Başoğlu, [1]Selda Kahraman, [1]Özden Pişkin, [1]Mehmet Ali Özcan, [1]Güner Hayri Özsan, [1]Fatih Demirkan, [1]Bülent Ündar.
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NON-HODGKIN'S LYMPHOMA

P055 *ID: 86*

RADIOTHERAPY RESULTS FOR 36 ADULT NONHODGKIN LYMPHOMA PATIENTS

[1]Aysen Dizman, [1]Ebru Karakaya, [1]Mehtap Coskun, [1]Gülhan Güler, [1]Gonca Altınışık İnan, [1]Fatma Alioğlu, [1]Zafer Özdoğan, [1]Yıldız Güney.
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P056 ID: 87

SHORT TERM RADIOTHERAPY OUTCOMES FOR PATIENTS WITH GASTRIC MUCOSA ASSOCIATED LYMPHOID TISSUE LYMPHOMA

[1]Ebru Karakaya, [1]Ayşen Dizman, [1]Süheyla Aytaç Arslan, [1]Özlem Derinalp, [1]Ela Delikgöz Soykut, [1]Nuri Uslu, [1]Gokçe Kaan Olcay, [1]Yıldız Güney.
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CHRONIC LYMPHOCYTIC LEUKEMIA

P057 *ID: 88*

A CASE OF AGRESSIVE T-CELL CHRONIC LYMPOCYTIC LEUKEMIA PRESENTING WITH SKIN INVOLVEMENT

[1]VildanÖzkocaman, [1]YaseminKaracan , [1]FahirÖzkalemkaş, [1]Rıdvan Ali, [1]Tülay Özçelik, [1]AhmetTunalı.
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MULTIPLE MYELOMA

P058 *ID: 89*

PRIMARY DIAGNOSE OF A MULTIPLE MYELOMA IN MANDIBLE: A CASE REPORT

[1]Taylan Can, [1]Neşe Kahraman, [1]Banu Gürkan Köseoğlu, [2]Meliha Nalçacı, [3]Emre Osman Başoğlu, [4]Yavuz Dizdar.
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NON-HODGKIN'S LYMPHOMA

P059 *ID: 90*

PRIMARY B CELL LYMPHOMA WITH BONE MARROW INVOLVEMENT ACCOMPANIED BY HEMOPHAGOCYTOSIS

[1]Gönül Aydoğan, [2]Hilal Akı, [1]Deniz Tuğcu, [1]Ferhan Akıcı, [1]Zafer Salcıoğlu, [1]Arzu Akçay, [1]Hülya Şen, [1]Nuray Aktay Ayaz, [1]Ferhat Sarı, [1]Chousein Amet.
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P060 ID: 91

PRIMARY RENAL LYMPHOMA IN A CHILD

[1]Deniz Tuğcu, [1]Ferhan Akıcı, [1]Arzu Akçay, [1]Gönül Aydoğan, [1]Zafer Salcıoğlu, [1]Hülya Şen, [1]Aysel Kıyak, [3]Öner Doğan.

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ACUTE LYMPHOBLASTIC LEUKEMIA

P061 *ID: 93*

THE DEVELOPMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH GAUCHER DISEASE AFTER ENZYME REPLACEMENT THERAPY

[1]Sinem Civriz Bozdağ, [1]Işınsu Kuzu, [1]Mutlu Arat, [1]Pervin Topcuoğlu.

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NON-HODGKIN'S LYMPHOMA

P064 ID: 98

DISSEMINATED INTRAVASCULAR COAGULATION INT CELL LARGE GRANULAR LYMPHOMA AT DIAGNOSIS: A RARE PRESENTATION

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HODGKIN'S LYMPHOMA

P065 *ID: 99*

FOLLICULAR HYPERPLASIA OF THE LYMPH NODE MISDIAGNOSED AS HODGKIN'S LYMPHOMA BY FINE NEEDLE ASPIRATION: A CASE REPORT

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NON-HODGKIN'S LYMPHOMA

P066 *ID: 100*

HIGH GRADE PROSTATIC CARCINOMA METASTATIC TO CERVICAL LYMPH NODE MISDIAGNOSED AS LYMPHOMA: A CASE REPORT

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P067 ID: 101

PERIPHERAL T CELL LYMPHOMA MISDIAGNOSED AS LANGERHANS CELL HISTIOCYTOSIS: A CASE REPORT

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MOLECULAR HEMATOLOGY – CYTOGENETICS

P068 *ID: 102*

EXPRESSION OF CHEMOKINE RECEPTORS CCR1 AND CCR2 IN CD10+ B-CELL LINES AND IN CD10+ PERIPHERAL BLOOD B-CELLS OF PATIENTS WITH B-CELL LYMPHOPROLIFERATIVE DISORDERS

[1]Irina Kholodnyuk, [1]Vaira Irisa Kalnina, [1]Svetlana Kozireva, [1]Irina Piscura, [2]Alla Rivkina, [2]Sandra Lejniece, [1]Modra Murovska, [3]Stefan Imreh, [3]Elena Kashuba.

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MULTIPLE MYELOMA

P069 *ID: 106*

ZOLEDRONIC ACID (ZOL) AND THALIDOMIDE (THAL) COMBINATIONS IMPROVED OVERALL SURVIVAL (OS) AND BONE ENDPOINTS IN THE MRC MYELOMA IX TRIAL: OPTIMISING BISPHOSPHONATE (BP) AND ANTIMYELOMA THERAPIES

[1]GJ Morgan, [1]FE Davies, [2]WM Gregory; SE Bell, [2]AJ Szubert, JA Child, [3]MT Drayson, [4]AJ Ashcroft, [5]RG Owen, G Cook, [6]FM Ross, [7]GH Jackson, [8]N Russell.

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NON-HODGKIN'S LYMPHOMA

P070 *ID: 107*

FOLLICULAR LYMPHOMA OF THE ORBIT PRESENTING WITH BILATERAL PTOSIS AND PROPTOSIS

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P071 ID: 109

CLINICAL CHARACTHERISTICS AND TREATMENT RESULTS OF 173 NON-HODGKIN LYMPHOMA PATIENTS

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ACUTE LYMPHOBLASTIC LEUKEMIA

P072 *ID: 111*

TREATMENT OF ADOLESCENTS AND YOUNG ADULTS WITH ALL: COG EXPERIENCE IN A SINGLE CENTER

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CHRONIC LYMPHOCYTIC LEUKEMIA

P073 *ID: 113*

THE REAPPEARANCE OF 11Q DELETION WITH COMPLEX KARYOTYPE IN A RARE CASE OF RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA MANIFESTING WITH EXTENSIVE NODAL INVOLVEMENT, LYTIC BONE LESIONS AND MALIGNANT HYPERCALCEMIA

[1]İpek Yönal, [1]Fehmi Hindilerden, [1]Esra Aydın, [1]Emre Osmanbaşoğlu, [1]Meliha Nalcacı, [2]Mehmet Ağan, [1]Sevgi Kalayoglu Beşışık.
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ACUTE LYMPHOBLASTIC LEUKEMIA

P074 *ID: 114*

COMPARISON OF TWO DIFFERENT INDUCTION REGIMENS IN ACUTE LYMPHOBLASTIC LEUKEMIA

[1]Sinem Civriz Bozdağ, [1]Şule Mine Bakanay, [1]Pervin Topcuoğlu, [1]Önder Arslan, [1]Meral Beksaç, [1]Nahide Konuk, [1]Günhan Gürman, [1]Muhit Özcan.
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MULTIPLE MYELOMA

P075 *ID: 115*

SKELETAL-RELATED EVENTS (SRES) IN THE MEDICAL RESEARCH COUNCIL (MRC) MYELOMA IX STUDY: ZOLEDRONIC ACID (ZOL) IS SUPERIOR TO CLODRONATE (CLO) IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (MM)

[1]Gareth J Morgan, [1]Faith E Davies, [2]Walter M Gregory, [2]Susan E Bell, [2]Alex J Szubert, [2]Nuria Navarro Coy, [3]Mark T Drayson, [4]Roger G Owen, [5]Graham H Jackson, [2]J Anthony Child.
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STEM CELL TRANSPLANTATION

P076 *ID: 116*

LONG-TERM RESULTS OF HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOETIC STEM CELL RESCUE FOR HODGKIN'S LYMPHOMA: ISTANBUL MEDICAL FACULTY EXPERIENCE

[1]İpek Yönal, [1]Sevgi Kalayoğlu Beşışık, [1]Fehmi Hindilerden, [1]Nuray Gürses Koç, [1]Deniz Sargın.
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MULTIPLE MYELOMA

P077 *ID: 118*

A CASE OF MULTIPLE MYELOMA WITH EXTRAMEDULLARY DISEASE OF STOMACH AND EVOLVING WITH SEROSAL INVOLVEMENT

[1]Hasan Sami Göksoy, [1]Yücel Aydın, [1]Mehmet Beşiroğlu, [1]Metin Kanıtez, [1]Sevgi Beşışık, [1]Fatma Deniz Sargın, [1]Öner Doğan, [1]Mehmet Ağar, [1]Meliha Nalçacı.
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ACUTE MYELOBLASTIC LEUKEMIA

P 078 *ID: 119*

AN ACUTE PROMYELOCYTIC LEUKEMIA CASE TREATED SUCCESFULLY DURING THE COURSE OF BREAST CANCER

[1]Füsun Özdemirkıran, [1]Niyazı Bozkurt, [2]Erdem Göker, [3]Mine Hekimgil, [1]Mahmut Töbü.
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P079 ID: 120

MAY PERIPHERAL BLOOD WT1 MRNA EXPRESSION LEVELS PREDICT MINIMAL RESIDUAL DISEASE (MRD) IN PATIENTS WITH NEWLY DIAGNOSED ACUTE LEUKEMIA?

[1]Bülent Eser, [1]Serdar Şıvgın, [2]Hülya Şıvgın, [2]Yusuf Özkul, [3]Mustafa Pehlivan, [3]Sacide Pehlivan, [1]Leylagül Kaynar, [1]Fatih Kurnaz, [1]Mustafa Çetin, [1]Ali Ünal.
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CHRONIC MYELOID LEUKEMIA

P080 *ID: 121*

RETROSPECTIVE EVALUATION OF PATIENTS WITH IMATINIB RESISTANT OR INTOLERANT CHRONIC MYELOID LEUKEMIA

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MULTIPLE MYELOMA

P081 *ID: 122*

FIBRINOLYTIC SYSTEM ACTIVATOR AND INHIBITOR LEVELS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPL MYELOMA

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HODGKIN'S LYMPHOMA

P082 *ID: 123*

CLINICAL FEATURES AND TREATMENT RESULTS OF PEDIATRIC HODGKIN LYMPHOMA: SINGLE CENTER EXPERIENCE

[1]Ferhan Akıcı, [1]Deniz Tuğcu, [1]Gönul Aydoğan, [1]Zafer Salcıoğlu, [1]Arzu Akçay, [1]Hülya Şen, [2]Serdar Şander, [3]Fulya Yaman Ağaoğlu.
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NON-HODGKIN'S LYMPHOMA

P083 *ID: 127*

DOES THE FORMATION OF THE ABDOMINAL SKIN OF A REACTIVE LESION OCCURRING? / IS INDOLENT LYMPHOMA? LYMPHOMATOID PAPULOSIS TYPE A AND TYPE B CASES

[3]Vildan Özkocaman, [3]Yasemin Karacan, [3]Fahir Özkalemkaş, [3]Rıdvan Ali, [3]Tülay Özçelik, [3]Hülya Nazlıoğlu, [3]Mustafa Merter, [3]Ahmet Tunalı.
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P084 ID: 129

BLASTIC TRANSFORMATION IN A PATIENT WITH PRIMARY GASTRIC LYMPHOMA

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CHRONIC LYMPHOCYTIC LEUKEMIA

P001 *ID: 7*

ASSOCIATION OF B CELL CHRONIC LYMPHOCYTIC LEUKEMIA AND ACUTE MYELOID LEUKEMIA: RAPIDLY PROGRESSION TO BLASTIC PHASE AFTER RITUXIMAB THERAPY

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Chronic lymphocytic leukemia (CLL) is a clonal proliferation of functionally incompetent B cell lymphocytes involving bone marrow, blood, and lymph nodes. It is the most common form of leukemia in adults and usually indolent. Presence of CLL and acute myeloid leukemia (AML) is a rare event. In the majority of reported cases, AML is diagnosed following treatment of CLL and is thought to be a secondary leukemia or therapy-related AML. Development of AML in untreated CLL seems to be a very rare phenomenon. A 61-year-old man with a 4-week history of immune thrombocytopenic purpura treated with 1 mg/kg of prednisone daily was referred for evaluation of thrombocytopenia to our hospital in September 2010. Physical examination was normal except petechiae and purpura in his skin. At CT scans wasn't observed lymphoadenomegalies and hepatosplenomegaly. White blood cell count (WBC) was 7600/µL (66% lymphocytes, 17% neutrophils and 13% blast with the presence of smudge cells), hemoglobin (Hgb) 11.8 g/dl, and platelet (Plt) 13000/µL. A bone marrow aspirate and biopsy revealed hypercelluler marrow and infiltration with approximately 51% mature appearing lymphocytes and 25% blasts with normal megakaryocytes and few erythroblasts. Immunohistochemical staining with CD20 and myeloperoxidase (MPO) were positive for lymphocytes and blasts, respectively. Bcr-1 was negative for lymphocytes. Blastic cells were positive for especially CD13, 33, 34, HLA-DR, and MPO with immunophenotyping analysis. Lymphocytes were characterized by a B-CLL immunophenotype: CD19+, CD5+, CD23+, CD20+. Bone marrow karyotype was normal. Molecular tests for t(8,21) AML 1-ETO, inv (16) CBF-MYH11 and t(9,22) BCR-ABL were negative. Diagnosis was coexistence of CLL and AML. R-CVP (Rituximab, Cyclophosphamide, Vincristine, and Prednisone) combination chemotherapy was started for CLL associated with immune thrombocytopenia, which is not response to prednisone treatment, before AML remission induction treatment. After 1 week from therapy, he admitted to hospital with fever. Blood studies showed a Hb level of 6.9 g/dl, WBC of 2700/µL with neutrophils 14%, lymphocytes 45%, blast 39%, and platelets 6000 / µL. A bone marrow aspirate and biopsy was hypercelluler and replaced by blastic cells with myeloid immunophenotype, while CD 20+ lymphocytic cell populations were decreased. A standard AML induction chemotherapy ('3 + 7' idarubicin and cytarabine) was started, but he died two weeks due to sepsis. We hypothesized that treatment with rituximab, a chimeric anti-CD20 monoclonal antibody, induces a rapid depletion of benign and malignant CD20+ cells. In conclusions, the reduced CD20+ lymphocytes counts with rituximab treatment may lead to progression of blastic clones.

PALLIATIVE CARE – SUPPORTIVE THERAPY

P002 *ID: 10*

SYMPTOM CONTROL IN HEMATOLOGICAL MALIGNANCIES

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The sample of the research was formed by 40 inpatients and 100 outpatients between the dates of 20.11.09-30.05.2010 in the Hematology Department of Internal Diseases in Aegean University Medical Faculty. Memorial Symptom Definition Scale, Patient Introduction Survey, Karnofsky Performance Sclae, SF-36 Life Quality Scale, Self-Care Agency Scale were used. Data obtained from the research were analyzed in the SPSS 15.0 software package programs.

According to the results of the study; %52 of the outpatients were found to be male, %34 of them were found to be in the 50-59 age group, %81 of them were found to be married, %28 of them were found to be high school graduates, %46 of them were found to be on pension, %42 of them were found to be on SSKpension, %57 of them were found to be living in urban areas, %51 of them were found to be living with their spouses and children and %46 of them were found to have equal income and spending. %57.5 of them inpatients were found to be female, %35 of them were found to be in the 18-29 age group, %67.5 of them were found to be married, % 32.5 of them were found to be high school graduates, % 22.5 of them were found to be on pension, %20 of them were found to be students, and the ratio of them getting pension from SSK and Pension Fund were found to be equal (%42.5). %32.5 of inpatients have HL, %25 of them have AML diagnosis, %43 of outpatients have NHL diagnosis. KPO score inpatients average was found as x:59.25±12.68, outpatients average was found as x:65.20±11.41.In the distribution of the subscales of the Memorial Symptom Assessment Scale (MSAS); Memorial Symptom Assessment Scale -GD1 (Global Distress Index) average was found as x: 1.537±0.79, Memorial Symptom Assessment Scale - physical average was found as x:1.30±0.77, Memorial Symptom Assessment Scale - psycho average was found as x:1.44±0.92, Total Memorial symptom Assessment Scale (TMSTS) average was found as x:1.13±0.57. Among the SF-36 QoL subgroups;mental health subscale score were found to be higher in inpatients and outpatients. Average score was found as x:66.36 foroutpatients and x:59.80 for inpatients. Rol limitation-physical were found to have the lowest scale score among two groups (x:15.50 for outpatients,x:25 for inpatients).According to the results of the t-test which was made to determine whether there were any differences between two groups; a statistically significant difference was found for the components of physical function, pain, social function and mental health($p<0.05$).Self-care power socre was found as x:103.32±18.92 in inpatients, and x:111.48±11.99 in outpatient.According to the analysis of the T-test results which was used for the comparison of outpatients and

inpatients; a statistically significant difference was found between two groups($p<0.05$). Self-care Agency scale score was not found high for both of the groups it was accepted as medium-level.

P003 *ID: 13*

A FEBRIL NEUTROPENIC CASE WITH TRICHOSPORON ASAHII RESISTANT TO AMPHOTERICIN B

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Objectives: Aim of this study is to present a febril neutropenic case with fungal infection with Trichosporon asahii resistant to Amphotericin B.

Case: A female patient with acute myelocytic leukemia at 48 age was under consolidation chemotherapy. Neutropenic patient was initiated sulbactam-cefoperazone combined with amikacin when she had fervescence. And then imipenem was given due to continuing fever at the 48 hours instead of them. Vankomycin was added after 72-hour of fever as there was no cultivation in blood, urine cultures and physical examination and computerized tomograpy (CT) were normal. At fifth days of fever, caspofungin was added to therapy. Respiratuar distress developed at seventh days and trimethoprim-sulphamethoxazloe and acyclovir were added to therapy although pysical examination was normal except with bylateral ronchi at respiratuar sound, second CT imagination and all blood and urine cultures taken in different times was normal, and also sputum was not obtained during the fever. Patient was admitted to intensive care unit for mechanic ventilation due to worsening the arterial blood gas analyse. Patient died at second days of mechanic ventilation under therapy including imipenem, linezolid, trimethoprim-sulphamethoxazole, acyclovir, caspofunfin. At third days after death, Trichosporon asahii was cultivated in two samples of blood cultures muchmore it was resistant to Amphotericin B, itraconazole and naturally to caspofungin and sensitive to voriconazole and fluconazole.

Conclusion: Liposomal Amphotericin B and caspofungin were described first line choices of empiric anti-fungal treatmnet at AI level in ECIL-2009/2 guide, but some fungal species can be unexpectedly resistant to anti-fungal drugs that is naturally effective as Trichosporon asahii is sensitive to Amphotericin B naturally. Although voriconazole was described third line choice of empiric anti-fungal therapy, it should be kept or initiated in patients with respiratuar distress.

P004 *ID: 14*

BREAK THROUGH OF ASPERGILLUS PNEUMONIA UNDER ORAL VORICONAZOLE

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Objectives: Aim of this study is to present a patient with Aspergillus pneumonia that has developed break through after regression under oral voriconazole therapy.

Case: A male patient with acute myelogenous leukemia at 52 age was under consolidation chemotherapy. Febrile neutropenic patient was initiated sulbactam-cefoperazone combined with amikacin when he had fervescence. And then imipenem was given due to continuing fever at the 48 hours instead of them. Vankomycin was added after 72-hour of fever as there was no cultivation in blood, urine cultures and physical examination and computerized tomograpy (CT) were normal. At fifth days of fever, amphotericin B (Fungizone®) was added to therapy. Due to acute reaction to Amphotericin B, Liposomal amphotericinB (Ambisome®)was substituted to standard amphotericin B. Chough has increased after anti-fungal therapy and thorax CT was implemented. Bilateral nodular infiltration and round-glass images were seen. Voriconazole (Vifend ®)was substituted to Liposomal amphotericin B (Ambisome®). Plasma galactomannan was positive. Nodular lesions were regressed under voriconazole therapy. Oral voriconazole was used as 200 mg q12h after one month of voriconazole therapy since patient was stable and pulmonary lesions were under regression. At first month of oral voriconazole, fever and cough appeared so thorax CT was re-checked. New nodules and progressive lesions were seen. Voriconazole was given intravenously. Fever decreased and cough cured. At the first month of intravenous voriconazole therapy, nodular lesions were regressed and very small that means to response to therapy in thorax CT. Oral voriconazole was given as 300 mg q12h twice. No sign and symptom and break through have developed and regression was re-established in thorax CT at first month of oral voriconazole therapy.

Conclusion: Voriconazole is recommended as AI level in ECIL-2009/2 guide in treatment of Aspergillus pneumonia or invasive Aspergillus infections. Although bioavailability of oral voriconazole was presented as 96%, progression can develop in 30% of cases under oral voriconazole therapy as cited in a study of Smith et al. So plasma voriconazole concentration should be monitored in patients under oral and intravenous voriconazole therapy and clinic and radiologic signs and plasma galactomannan level should be followed attentively due to inadequate therapy.

P005 *ID: 15*

ACUTE MYELOID LEUKEMIA PATIENT DIAGNOSED WITH SEVERE NEUROLOGICAL SIGNS IN THE ACCOMPANYING HYPONATREMIA; ETIOLOGICAL FACTOR AND THE THERAPEUTIC APPROACH

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28-year-old male patient diagnosed with Acute promyelocytic leukemia and chemotherapy was started. Lung infection occurred during neutropenia and Geotrichum capitatum was found in sputum as a factor of lung infection in the period of neutropenia. Intensive care needs of this period ; linezolid, tienam, cansidas and parenteral nutrition therapy(PNT) was begun. But after a while, confusion, hyperkinesia, agitation and rigidity occurred and understood that this condition caused by severe hyponatremia(113mEq / L). As a result of measurement of blood and urine osmolality showed that hyponatremia

due to inappropriate ADH. The patient's own disease, drugs, and the PNT was thought to be primarily causes ADH syndrome. Linezolid and TPN treatment immediately discontinued and with isotonic solutions was begün. Fungal lung infection was treated with voriconazole. 10 day after treatment, improved hyponatremia and clinical symptoms and associated with lung infections symptoms was decreased after 15 days.

As a result, In this case report, supported by the literature is concerned with clinical symptoms and related causes of hyponatremia that follow-up of patients with the diagnosis of acute leukemia.

CHRONIC MYELOID LEUKEMIA

P006 *ID: 16*

TRANSFORMATION OF ALL TO CML: CASE REPORT

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Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder that represents 1% of hematological malignancies. Natural clinical course is a chronic phase followed by acceleration and then a blastic phase. That is well established that one third of the blastic transformation is lymphoid in nature. However, to date, transformation from Acute Lymphoblastic Leukemia (ALL) to CML is not reported. 49 year old male had attended to our clinic complaining stiffness, sore throat, productive cough and weight loss. His hemogram was Hg: 10.7 gr/dl, WBC: 78940/uL and Plt: 154000/uL. Bone marrow revealed more than 90% of cells were blasts and on flowcytometry CD10: 66.22%, CD11b: 16.32%, CD13: 19.02%, CD19: 79.43%, CD20: 69.86%, CD22: 78.21%, CD33: 22.89%, CD34: 61.47%, CD45: 92.05%. Cytogenetic analysis by FISH revealed 88% Philadelphia Chromosome positivity. He had been diagnosed as Ph positive ALL L2 and Hoelzer chemotherapy had been begun alongside with Imatinib 400 mg/day. He was treated for two years in haematological remission without major problems but he only achieved minimal cytogenetic response. Three months after the end of the therapy, his leukocyte count was 40500, so we performed bone marrow examination. The bone marrow revealed a tdt negative hypercellular marrow (80%) with a dominance of myeloid lineage and his cytogenetic showed 98% Ph positivity. His flowcytometry was CD33: 97%, CD13: 75%, CD11b: 75.14, CD38: 59.5%. He was diagnosed as CML and Dasatinib 140 mg per day begun. He had achieved haematological response but not a major cytogenetic response yet. There is a clear relationship between CML and ALL transformation in the natural clinical course but we could not find any report related to the opposite.

MYELOPROFILERATIVE DISORDERS

P007 *ID: 17*

PALLIATIVE RADIOTHERAPY OF SYMPTOMATIC SPLENOMEGALY IN OLD PATIENTS WITH A CHRONIC MYELOPROLIFERATIVE DISORDERS

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Abstract: Chronic myeloproliferative disorders (CMD) are a disease of hematopoietic stem cells, which is characterized by varying tendencies toward bone marrow fibrosis, leukaemic transformation. Clinically, CMD evolve to produce progressive bone marrow failure with a leucoerythroblastic blood picture and marked splenomegaly from extramedullary haemopoiesis. CMD mostly occur in patients beyond the age of 60 years. Splenic irradiation has been used in CMD when other therapies were contraindicated or inefficient. Palliative splenic irradiation in CMD has often been used in selected situations which low-dose radiotherapy is effective in reducing the painful splenomegaly, clinical consequences of hipersplenism and also this could improve quality of life of patients.

We have assessed the effect of splenic irradiation in 6 patients with IMF between 2006 and 2009 at our center in this study. All of them were no longer responsive to usual treatments, and they presented constitutional symptoms, splenic pain, large splenic size, anemia requiring/2 units of red blood cell transfusion per month feaures. The radiotherapy schedule plan consisted of daily fractions of 0.5 Gy per fraction delivered to two or three times a week. The mean total dose of radiotherapy per treatment was 7.5 Gy (range, 5.5-10 Gy). Splenic pain was relieved in 87.5% of the patients. Mean spleen reduction rate of the splenomegaly was 64.5% (range 40%-90%). Splenic irradiation was effective on constitutional symptoms, splenic pain, splenomegaly and effectively achieved palliation. Splenic radiotherapy can be used as an alternative therapy for CMD patients refractory to standard therapies.

Table 1.

number	*Old/sex*	*Diagnosis*	*Medical therapy before RT*	*symptoms*	*RT dose (Gy/fr)*	*Time(T-SR)[4] (month)*
1	70/M	ET	HÜ[1],anagrelid	Anemia,SM[3],pain	10/0.5	15
2	71/W	PMF	HÜ,steroid,INF	Anemia,SM,pain	5.5/0.5	25
3	63/W	PMF	HÜ,steroid,INF	Anemia,SM, pain	8/0.5	36
4	63/M	PMF	HÜ, steroid,INF	Anemia,SM,pain	7/0.5	18
5	73/M	PMF	HÜ,steroid,IFN[2]	Anemia,SM,pain	7/0.5	120
6	66/W	PV	HÜ,flebetomi	SM,pain	8/0.5	32

CHRONIC MYELOID LEUKEMIA

P008 *ID: 18*

IMATINIB RELATED TO NAIL NECROSIS AND ALOPECIA

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Imatinib mesylate is the first line therapy for CML. Imatinib is generally well tolerated but various dermatologic effects have been noted including dermatitis, hypopigmentation, Sweet syndrome, pityriasis rosea-like eruption, erosive oral lichenoid reaction, erythema multiforme, acute generalized exanthematous pustilosis and Stevens - Johnson syndrome. A 53-year-old male with no history of drug allergy was diagnosed with CML and started on the Imatinib 400 mg daily. In the first four months only grade I periorbital oedema and diarrhoea were seen. 4 weeks later, grade II diarrhoea and grade II maculopapular rash affecting both forearms and mouth which might be related to imatinib developed. Glivec stopped for 18 days than again started 400mg/day. However, the rash continued to progress to grade 3 eythematous, maculopapular form affecting the torso and the limbs; exacerbated by exposure to sunlight and causing significant discomfort and itch. After 4 weeks, patient presented alopecia and paronychial inflammation probably induced by imatinib therapy (Figure 1,2). He was prescribed mometasone furorate ointment and continued on the same dose of imatinib. A skin biopsy was also performed, which showed interphase dermatitis with numerous prominent clusters of colloid bodies in accordance to a drug reaction. We continued on the current dose of imatinib, but closely monitored the response to topical steroids. Four days later, his symptoms improved slighty with decresed erythema and itch, however, on examination he continued to have a widespread excoriated dermatitis affecting the trunk and limbs with areas of sparing in the skin folds and axillae and also necrosis of the nails were seen. Therefore Imatinib stopped and a nail biopsy also showed necrosis. Imatinib 300 mg/day then restarted after one month as necrosis resolved and alopesia begun to improve. He has not required a dose reduction or interruption of imatinib and dose increased to 400 mg/day four months thereafter. Alopesia and necrosis resolved completely and he was in complete molecular response (Figure 3). Most skin reaction occurs in the first 12 weeks of Imatinib therapy and is usually self-limited and controllable. Skin rashes are usually mild, self-limiting, do not require dose interruption and generally respond to topical steroids, emollients and antihistamines, but may occasionally require oral steroids. More severe cases may require dose reduction or interruption until the rash improve to grade I, and re-challenge of imatinib at a lower dose (50-100mg/day) with steroid cover and gradual escalation is needed. We do not find any report of alopecia with nail necrosis related to Imatinib. In conclusion, dermatologic adverse events with imatinib are quite common, but generally are easily managed and only in a few cases require definitive drug discontinuation. We suggest a careful management and particular attention to tardive skin lesions that appear after first year of therapy.

Figure 1

Figure 2

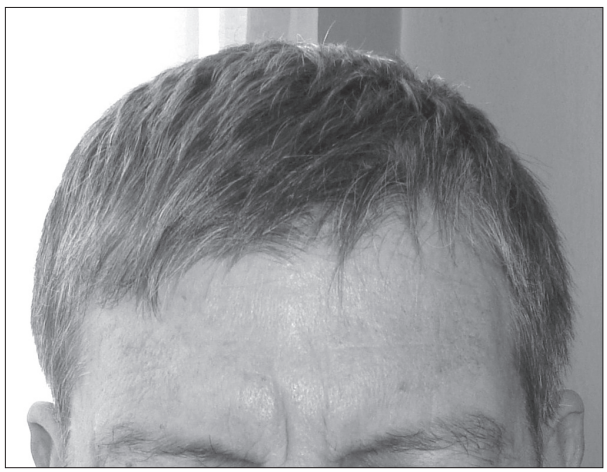

Figure 3

NON-HODGKIN'S LYMPHOMA

P009 *ID: 21*

A DIAGNOSTIC DILEMMA IF UNSUSPECTED: CASTLEMAN DISEASE

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Localized Castleman Disease is characterized by mediastinal or abdominal lymphadenopathy and its associated mass symptoms. 90% of patients are hyaline vascular type; the remainder are plasma cell type and a combination of both. The clinical course is mostly benign; only pain, discomfort and malaise that are associated with mass symptoms and anemia are seen. Diagnosis depends on examination of adequate lymph node tissue and it can be cured by surgical excision of the lymph node which is associated with complete resolution of symptoms with only rare local recurrences. However, diagnosis can be challenging by the fact that it can be confused with the other diseases associated with lympadenopathy and physician must have a high degree of suspicion before the diagnosis. On 2001, a 22 year old male patient who had been complaining malaise and chest pain had attained to hematology clinic.He had had anemia and his chest X-ray had revealed mediastinal widening.He had not sought any medical aid for two years, and then a hyper cellular bone marrow had been revealed by a hematologist. He had not further gone to outpatient visits again for another four years but his malaise had been aggravated and then he had had abdominal dullness and discomfort on the left upper quadrant. His work-up had revealed a Hg of 9.5 gr/dl, an enlarged spleen of 150 mm size and a mediastinal lympadenopathy of approximately 10 cm in another clinic. His blood film had shown lymphocytosis (62%). Hepatitis markers, Brucella agglutination, ANA, anti-dsDNA, ANCA, ASMA, CMV and Salmonella IgM had been found negative. A transbronchial lymph node biopsy had been performed and revealed reactive lymphoid hyperplasia. Mediastinoscopy had planned but patient refused further examination unless his attendance to our clinic in 2010. He had malaise and decreased work rate and abdominal discomfort on the same place but he had no fever, weight loss or sweating. Splenomegaly of 6 cm below costal margin was noted in physical examination but no lymph node was palpable. His hemogram was Hg: 9.5 gr/dl, Htc: 30.1%, WBC: 4600/uL Plt:574000/uL. Chest CT showed multiple lymphadenopathies in mediastinal region and there were no other lympadenopathies in another region revealed by MRI. Megakaryocytic series were increased, significant hemophagocytosis were seen and blast ratio was 7% in bone marrow. Flowcytometry was normal and BCR-ABL, tuberculosis and parasitic work-up (Fasciolasis, Toxocarasis, Leishmaniasis, Toxoplasmosis, and Echinococcosis) were negative in bone marrow. Surgical excision of lymph node was planned on suspicion of Non Hodgkin Lymphoma and biopsy showed Mixed Type Castleman Disease. Now the patient is followed-up with normal hemoglobin count; spleen shrunk to normal size and lymph nodes disappeared which were confirmed by CT. Localized Castleman Disease is a usually benign and self limited disease and treatment is usually satisfactory but diagnosis can be challenging as in our case

ACUTE LYMPHOBLASTIC LEUKEMIA

P010 *ID: 22*

A NOVEL HOMOZYGOUS DELETION AT JAK–2 GENE IN A PEDIATRIC B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduciton and Aim: Janus Kinase 2 (JAK–2) is a protein tyrosine kinase that transduces cellular signals through the JAK-STAT pathways, and it is active in both normal hematopoiesis and hematological malignancies. Mutations of protein tyrosine kinase have importance for the development of malignant process. Further novel mutations were identified in exon 12 which is located at the proximal region of the gene. These reported mutations impair the organization of JAK–2 kinase activity [1,2]. The aim of this study was to investigate the JAK-2 exon12 mutation in childhood leukemia and its correlation with clinicopathologic parameters.

Case-Methods:Twenty-month-old male patient suffering from persistent high fever, cough, and diarrhea admitted to the hospital. Physical examination revealed normal findings except for hepatomegaly. Complete blood count showed pancytopenia with 40% lymphoblasts in his peripheral blood smear. L1-type diffuse lymphoblastic infiltration was found at bone marrow smear. Precursor B-cell ALL was the final diagnosis with flow cytometric analyses. There were no additional cytogenetic aberrations. BFM-95 standard risk protocol was started. During the treatment, he had no problem and remission was achieved at 33rd day of chemotherapy. The patient is still in remission and continues his maintenance therapy.

Blood samples of the patient and his mother were collected at admission and remission and phenol-chloroform method was used to extract DNAs. Perfect-well matched primers were used to amplify and sequence the exon 12 of JAK-2 gene (Beckman Coulter,USA). All sequencing reactions were performed twice, on two different PCR products.

Results: Sequencing of the exon revealed a homozygous "G" deletion at nt 1584 resulted with a transition of arginine to serin at admission (Figure 1 and 2) in patient. This transition was a novel change. We did not observe "G" deletion in both the patient on remission and his mother.

Conclusions: Although it was reported that the JAK-2 V617F mutation is absent in childhood ALL; rare mutations were reported especially in patients with Down syndrome ALL. A 5 base deletion of the region was the first report from a Down syndrome patient associated with B-cell precursor acute lymphoblastic leukemia [3].As our cases' diagnosis was B-cell precursor acute lymphoblastic leukemia, a comprehensive mutational screen of all of the JAK-2 gene coding exons is warranted especially in patients with this type of ALL.

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patients. Leukemia 2008;22:870-873.2)Pardanani,A.D.,et all. Prevalence and clinicopathologic correlates of JAK-2 exon 12 mutations in JAK2V617F-negative polycythemia vera.Leukemia 2007;28:1-4.3)Malinge S.,et all.Novel activating JAK2 mutation in a patient with Down syndrome and B-cell precursor acute lymphoblastic leukemia.Blood 2007;10:(5):2202-4.

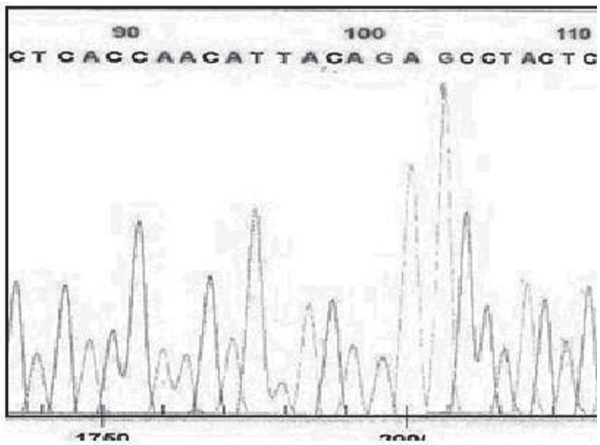

Figure 1. Sequencing analysis of exon 12 of JAK-2 gene; deletion of 1584 del G

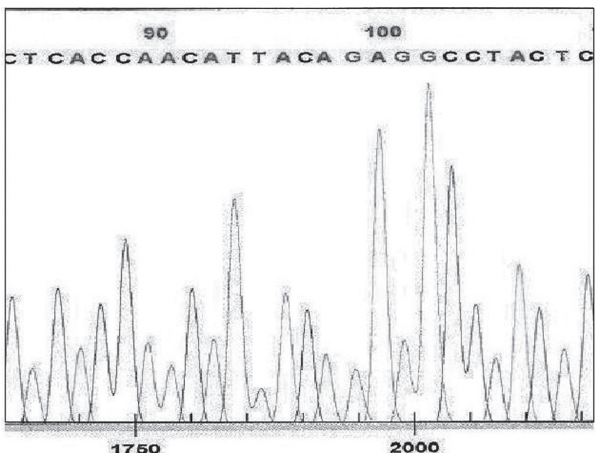

Figure 2. Sequencing analysis of exon 12 of JAK-2 gene; normal sequence

MYELOPROFILERATIVE DISORDERS

P011 *ID: 24*

CHARACTERISTICS OF PORTAL HYPERTENSION IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Background Portal hypertension is frequently a consequence of liver cirrhosis. Sometimes it appears in the evolution of chronic myeloproliferative neoplasms(MPN) due liver fibrosis or splachnic thrombosis.Aims To highlight some features of portal hypertension in patients with chronic myeloproliferative neoplasms and particularities of platelet function for MPN patients with portal thrombosis. Material si method The study was prospective and included two groups of patients-10 patients with portal hypertension secondary MPN(4 JAK2+ and 6 JAK2 -) and 30 patients diagnosed with liver cirrhosis. Haematological diagnosis was based on molecular testing of JAK2 mutation and bone marrow biopsy. Variables analyzed were hematologic values, biochemical indicators of liver function, ultrasound size of the liver, spleen and the portal and splenic vein. Statistical analysis was done using Anova method. Results The size of the liver and spleen were significantly increased in patients with MPN versus patients with liver cirrhosis: right lobe 16.4cm vs 12.94 cm, p = 0.0001, left lobe 8.2 cm vs 6.33, p = 0.09; spleen 13.98 vs 18.19 cm cm, p = 0.01. No significant differences were obtained for the portal vein diameter (12.2mm vs. 11.7mm, p = 0.61) and splenic vein (7.53 mm vs7.28, p = 0.53). The hepatoprive syndrome was more important in patients with liver cirrhosis vs MPN patients (cholesterol 109mg/dl vs 168 mg/dl; p= 0.03; total protein 7.05mg/dl vs 7.67mg/dl, p = 0.04; Albumins 3.9mg/dl vs 4.35 mg / dl, p = 0.01).The group of patients with cirrhosis had elevated transaminases vs MPN patients: TGO 81.2 U / l vs 41.31U / l, p = 0.01; TGP 61.4 U / l vs 23.17U / l, p = 0.04. We obtained significant differences for the number of leukocytes and platelets, which are much higher in MPN patients. (WBC 19785/mmc vs 6557.77/mmc, p = 0.001; platelets 529300/mmc vs 93877.77, p<0.00019). Platelet aggregation test showed normal values of amplitude for ADP and collagen curves in MPN patients JAK2+ (64.4 ADP, collagen 82.8). MPN patients JAK2- had low response (45.5 ADP, collagen 37). Compared with the control group (70.25 ADP, collagen 70.86) we found increased amplitude of the collagen curve in the group of MPN patients JAK2 +. The platelet response for epinephrine was lower in MPN patients JAK2+ than MPN patients JAK2- (49.75 vs. 5). The platelet response for ristocetin was slightly lower in both groups (44 vs. 56). Conclusions MPN patients with chronic portal hypertension have important hepatosplenomegaly and significant increase of leukocytes and platelets. Compared with this group, patients with cirrhosis presented hepatoprive syndrome, severe hepatoportal encephalopathy and low number of platelet. Platelet response is lower in MPN patients JAK- than MPN patients JAK+. This response was correlated with bleeding tendency. MPN patients JAK+ and portal vein thrombosis, have high amplitude for collagen curve.

NON-HODGKIN'S LYMPHOMA

P012 *ID: 25*

NEUROLOGYC SYNDROME AT ONSET OF CHRONIC

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Objective: Chronic lymphoproliferative syndrome sometimes presents at the onset extranodale determinations.Spinal determinations are rare events (5% of

extranodale determinations). Presence of spinal determination at the onset of lymphoma creates diagnosis difficulties and treatment dilemma in terms highlight of spinal tumors that develop relatively quickly cord compression who install a complete neurological deficit within the distal lesion. Material and methods : The study of two cases of spinal tumors and chronic lymphoproliferative syndrome.1. Female, 71 years old, with frequent hospitalization for thoracic column pain with intercostals irradiation, develop during latest hospitalization crural motor deficit, urinary retention and hypoesthesia and anesthesia at T7-T9 level. The patient installs paraplegia pending MRI. On MRI sequences to distinguish a left side epidural tumor T7- T9 which infiltrates the left pedicle, most part of the vertebral body and grow above. The surgical treatment was T7-T8-T9 laminectomy, with removals of the intraspinal tumor which had determined marked compression effect on the dural sac, the left T8 pedicle and partially, the endothoracyc tumor. The clinical evolution in postoperative period showed the improving of sphincter disturbance, minimal recovery of sensitivity and persistent paraplegia. Histopathologic exam -Nonhodgkin diffuse large cell lymphoma. The patient was received R-CHOP schedule chemotherapy. 2. Female, 42 years old, was admitted for thoracolumbar column pain and right L5-S1 sciatic pain trajectory root L5-S1, SPE paresis right>left.The CT diagnosis was L4 right herniated disc.The surgical treatment was L4-L5 right foraminotomy. Surprisingly, although the appearance of CT was conclusive for HDL is found an epidural tumor that partially infiltrates a L4 vertebral body. This tumor was totally removed.In postoperative period the back pain persists. After 5-6 days we develops strong paraparesis, urinary retention.The emergency thoracolumbar junction NMR highlights a giant tumor that infiltrates the T12-L1 vertebrae corpus with epidural extension and dural compression, with intrathoracyc extension of the tumor being intimate adherence inferior vena cava and aorta artery. The surgical treatment was L1 and T12 laminectomy. Histopathology diagnosis – extramedullary plasmacytoma.The bone marrow aspirate showed 60% plasmocytic infiltration. The serum protein electrophoresis monoclonal showed protein component in γ fraction (IgGλ at immunofixation techniques).The patient was treated with Bortezomib Dexamethasone. Conclusions: Clinical pictures of spinal determinations at the onset is nonspecific with pain and muscle contracture. Radiographic appearance of the spine is nonspecific.In the beginning, it made MRI in cases with severe and persistent pain in order to decide the surgical intervention before the onset of cord compression.

P013 *ID: 26*

PRİMARY HEPATİC LYMPHOMA İN PATİENT WİTH PROSTATE CANCER

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Introduction: Primary non-Hodgkin lymphoma (NHL) of the liver is an extremely rare lymphoma, representing 0,4% of extra nodal NHL, 0,016% of all lymphomas. However prostate cancer is the second most common cancer in men. In here, we'll present a patient has primary hepatic lymphoma (PHL) and prostate cancer together.

Case report: AN 83-year-old man was admitted to hospital because of right side pain, resistance to urine flow, weight loss and night sweating for two months. The patient had no complaint of fever. On physical examination, there was about a 1x2 cm nodule in thyroid lobe. The liver could be palpated 1 cm below the costal margin. Spleen and lymph nodes were not enlarged.

Laboratory results showed WBC 9500, platelet 270.000, hemoglobin 14,2, sedimentation 47 mm/hour, C- reactive protein (CRP) 107 mg/L, AST 56 U/L, ALT 32 U/L, alkaline phosphates 427 U/L (40-129), gama-glutamyl transferase 667 U/L (7- 49), LDH 1180 (240-480) U/L and normal thyroid function test results. Serum alpha-fetoprotein and CEA levels were normal. Serology was negative for hepatitis B, hepatitis C virus and HIV.

Computed tomography (CT) showed nodule in right lobe of liver (163 x 95 x 136 mm)Figure 1. The spleen size was 143 mm. Prostate size was enlarged (48 x 41 x 39mm). There were eight lymphadenopaties in retrocrural region; the largest one was 9 mm. No lymphadenopathies were revealed on CT. There was a 22 mm nodule on the thyroid on CT. The PET scan before chemotherapy was not performed because of technical insufficiency. Bone scanning was normal. A needle biopsy for liver was performed under the ultrasound. Histology was showed atypical lymphoid cells with slightly angulated or twisted nuclei. Immunostaining showed positive for CD 20, LCA. Bone marrow biopsy was normal. The prostate size was increased grade 1 and 1x1cm irregular nodular lesion was determined on the left lobe. A needle biopsy revealed prostatic adenocarcinoma. Also a needle biopsy of the thyroid nodule was performed. Repeated biopsies were revealed non-diagnostic material.

Liver tumor was diagnosed as primary diffuse large B cell lymphoma, stage I. We planned for total of 8 cycles of R-CHOP. Hormonal therapy was started for prostate carcinoma and after completion of lymphoma treatment; radiation therapy will be given for prostate.

Discussion: PHL defines a lymphoma of the liver with no or minimal nodal involvement. The real cause of PHL is unknown. There appears to be a strong association between PHL and HCV. Our patient was negative for HCV. The most common histological type of PHL is diffuse large B-cell lymphoma (60-70%). Our patient will be first report as primary NHL together with prostate cancer. There were some reports about coexistence with PHL and epidermoid lung cancer, leiomyosarcoma or hepatocelluler cancer.

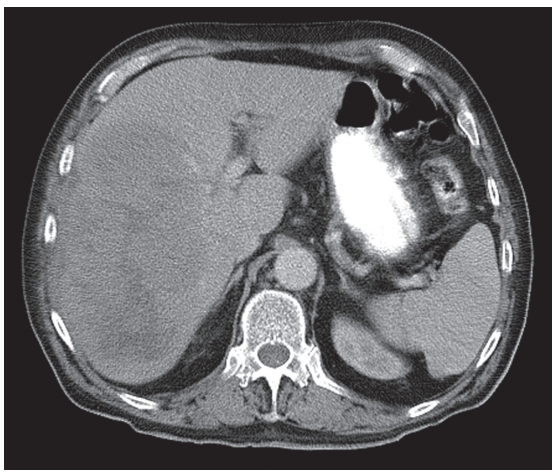

Figure 1. Computed tomography scan of abdomen showing a low density solid mass in the right lobe of the liver.

HODGKIN'S LYMPHOMA

P014 *ID: 27*

SECONDARY NEOPLASIAS IN CHILDREN WITH HODGKIN'S DISEASE RECEIVING MOPP AND RADIOTHERAPY

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Objective: The aim of this study is to analyze the patients with second neoplasms treated with MOPP and radiotherapy.

Materials-Methods:Thirty-nine children with newly diagnosed Hodgkin's disease were treated in Ankara University Department of Pediatric Hematology- Oncology between 1970 and 1984. There were 29 males,10 females. The median age was 10years with an age range of 3-15yrs. Majority of the patients were in Stage III-IV with a predominance of mixed cellularity histopathological subtype.

Results;Twenty-four patients received MOPP combination chemotherapy (10-12 cycles),whereas 14 patients were given sandwich therapy 3 MOPP+EF RT 25-35 Gy+ 3 MOPP.One patient was treated with CTX+VCR+ADM(4cycles) and MOPP (2 cycles)+38Gy mediastinal radiotherapy. Eleven patients were lost to follow-up. Among long term survivors,secondary neoplasias occurred in 4 out of 28 patients and the patients' details are as given below:

Case 1:Nine-year-old male patient who was diagnosed as clinical stage I HD with mixed cellular histopathology received local radiotherapy 40Gy to the neck region. He relapsed 3.5 years later with clinical stage IV disease. He was treated with 10 cycles off MOPP. He developed fibrosarcoma 8 years after the initial treatment, followed by thyroid carcinoma diagnosed 16 years and right retrobulbar meningioma 30 years later,consecutively.

Case 2:Fifteen-year-old male patient, who was diagnosed as clinical stage I HD with lymphocyte predominance histopathology received 3 cycles of MOPP and 40Gy radiotherapy to the neck region developed benign thyroid nodule 27 years after the treatment.

Case 3:Ten-year-old female patient with NS HD, who received nitrogen mustard + vinblastine and local radiotherapy 40Gy to the neck region developed mediastinal relapse 4 years after the initial treatment and was given CTX+VCR+ADM (4 cycles) +MOPP (2 cycles). She developed benign thyroid nodule 14 years later and invasive ductal carcinoma on her left breast 30 years after the therapy.

Case 4: Thirteen-year old male patient who was diagnosed as clinical stage III HD with MC histopathology received 40 Gy radiotherapy to the neck region and MOPP+maintenance MOPP (total 10 cycles), developed malignant schwannoma 28 years after the treatment.

Conclusion: Childhood Hodgkin's disease appears to be the most common malignancy to precede both hematologic and nonhematologic secondary neoplasias. Acute leukemias particularly acute nonlymphoblastic leukemias are the most common secondary malignancies followed by non-Hodgkin's lymphomas, bone and soft tissue sarcomas.Nonhematologic tumors developing after Hodgkin's disease are associated with radiation therapy, with two-thirds occurring within radiation sites. The follow-up of adult survivors of childhood cancer which includes monitoring for the detection of late effects necessitates a good collaboration between pediatric and adult oncology units.

NON-HODGKIN'S LYMPHOMA

P015 *ID: 28*

MOLECULAR GENE PROFILING FOR THE TREATMENT OF DIFFUSE LARGE B CELL LYMPHOMA IN TURKISH POPULATION

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Objectives: Cancer, disease of the era, is an important public health problem with increasing incidence. The heterogeneity of cancer makes its diagnosis and treatment even more challenging. Diffuse Large B Cell Lymphoma (DLBCL) is the most prevalent subtype of Non-Hodgkin Lymphoma. The criterias such as International Prognostic Index and Ann Arbor Tumor Staging System are known to be insufficient in diagnosis and treatment of this disease. For this purpose, a molecular signature independent of the above mentioned criterias has been determined by Lossos et al. (2004) through meta analysis of several microarray studies. The analysis identified molecular signature, comprising six genes (LMO2, BCL6, FN1, CCND2, SCYA3 and BCL2), that can be used for survival prediction.

Methods: In this study, we have conducted an analysis in order to determine whether the gene expression profile (GEP) of these six genes can be used as a marker in Turkish DLBCL cases for the prognosis of the disease. Quantitative real time PCR (qRT-PCR) technique was used as a gene expression profiling method for 12 Turkish DLBCL patient samples. The qRT-PCR data was analyzed with 2-ΔΔCt method.

Results: The mortality-predictor score was calculated with the formula in the Lossos et al. (2004) study. According to these results, half of the patients can be categorized in a short survival group and the remaining of them is in long survival group. The survival prediction success of this score for Turkish DLBCL patients was %60. Three of them were predicted with the 100% confidence. But the diagnosis date of the seven patients was not older five years (five years is a threshold value for the survival) so these results can only be confirmed within the next five years.

Conclusion: In summary, the benefits of using mortality-predictor score for Turkish population cannot be determined effectively because of sample size limitation and lack of five year survival data. For better results, the number of the samples must be increased and five year follow up should be conducted. This study has shown the importance of the confirmation of GEP studies in different populations.

HODGKIN'S LYMPHOMA

P016 *ID: 29*

VINBLASTINE INDUCED NEUROTOXICITY IN A PATIENT WITH HODGKIN LYMPHOMA

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Vinblastine is an asymmetric dimeric compound that acts to inhibit microtubules thus causing mitosis arrest. Its lipophility causes the accumulation of the drug intracellular region rather than extracellular one. Its major adverse effects are leucopenia and thrombocytopenia; neurotoxicity occurs as peripheral neuropathy and much more uncommonly cranial nerve palsies, ataxia, severe dysesthesias and foot drop but these are not seen as frequently as in Vincristine. A 35 year old man had come to our clinic complaining malaise, weight loss, sweating and cervical mass. In his physical examination, his skin and conjunctiva are pale, he had palpable lymph nodes in cervical and axillary area, and he had palpable spleen and liver below 4 cm of costal margin. His hemogram was; Hg: 8.4 gr/dl, Htc: 26.9%, WBC: 12800/uL, Plt: 506000/uL. Biopsy of cervical lymph node revealed Hodgkin Lymphoma of Nodular Sclerosing Type. Therefore ABVD chemotherapy started but ten days later bilateral foot drop, weakness starting on lower extremity and then ascending to upper one occurred. His neurological examination showed significant quadriparesia more severely affecting the lower extremity and severe sensorymotor-polyneuropathy is revealed by EMG (table). Vinblastine induced neurotoxicity was suspected by Neurology Department so symptomatic therapy with postponing the chemotherapy was used. Except for the persisting foot drop, both neuropathy-related and disease-related symptoms and findings waned within two months; while lymph nodes and spleen significantly shrink, his Hg count increased to 14 gr/dl without transfusion. Therefore second cure of ABVD was given to patient but two days later, peripheral facial paralysis occurred. Chemotherapy postponed once again until the resolution of paralysis. Decision was made to drop-off Vinblastine from the patient's regimen and he was given four additional cycles of chemotherapy without further neurological events. He was found to be in full remission as assessed by PET-CT after completing his therapy. His foot drop and other neurotoxicity-related symptoms also dissolved. Although peripheral neurotoxicity and to a lesser extent foot drop is associated with Vincristine and Vinblastine can cause disabling neurotoxic adverse effects; these adverse effects are much more uncommonly seen in Vinblastine. Here, we report a case who had suffered from Vinblastine induced neurotoxicity as foot drop, quadriparesia and facial nerve palsy effectively managed with symptomatic therapy.

Table 1.

Right	*Nerve*	*Transmission Time m/sec.*	*Distal transmission time*	*Amplitude*
*	N. Medianus (D)	39	3.1	7 μV
*	N. Ulnaris (D)	38	3.3	6 μV
*	N. Suralis (D)	No response		
*	N. Medianus (D)	49	4.2	2-2mV
*	N. Ulnaris (D)	40	3.5	1.5-1.5mV
*	N. Fibularis (D)	No response		
*	N. Tib. Post. (D)	No response		

P017 ID: 30

AUTOIMMUNITY AND HODGKIN LYMPHOMA: CASE REPORT

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Hodgkin Lymphoma is a lymphoproliferative disease with an incidence of 2-3 per 100000. Autoimmunity was strongly associated with Hodgkin and Non-Hodgkin Lymphoma because of deregulated lymphocyte production. In literature, there are reports and studies that showed link between Hodgkin Lymphoma and autoimmune disorders. A 59 year old female came to our clinic complaining malaise, arthralgia and weight loss. 3 years ago, she had been diagnosed as Sarcoidosis and had been given corticosteroid therapy from then. Her physical exam showed aphthous ulcers in mouth and dry eye. ANA, anti-Ro, anti-La and Schirmer test was positive and parotid involvement were detected in parotid scintigraphy; so a diagnosis of Sjogren Syndrome were made. On chest CT, mediastinal lymph nodes were detected; as there were B symptoms despite adequate steroid therapy for Sarcoidosis, other possibilities like lymphoproliferative diseases were suspected and an excisional biopsy revealed Hodgkin Lymphoma Mixed Cellular type. She was given 6 cycles of ABVD therapy and achieved full remission. The patient is still in remission after six years of follow-up. Patients with sarcoidosis have an increased risk of developing Hodgkin and Non-Hodgkin Lymphoma. In Sjogren, it is also true for Non-Hodgkin Lymphoma but this is not the case for Hodgkin Lymphoma. We found no report of a patient diagnosed as Hodgkin Lymphoma, Sarcoidosis and Sjogren Syndrome in literature; so we recommend careful follow-up of patients with autoimmune disorders for developing lymphoproliferative diseases.

CHRONIC LYMPHOCYTIC LEUKEMIA

P018 *ID: 32*

THE CLINICAL FEATURES OF 105 CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS FOLLOWED UP AT A SINGLE CENTER

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Introduction: Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in western countries. We evaluated the clinical features, survival and factors affecting prognosis in CLL patients followed up at our center.

Materials and Methods: We included 105 CLL patients diagnosed at Trakya University Medical Faculty, Division of Hematology. The diagnosis of CLL was based upon the criteria of International Workshop on CLL. The demographic data, clinical features, treatment modalities and response to treatment were recorded from hospital files. Rai staging system was used for clinical staging. The definitions of partial (PR) and complete response (CR) were the criteria of National Cancer Institute Working Group.

Results: Of 105 CLL patients, 65 were males and 40 were females (M/F=1.62). The median age of the patients was 64.8±9.1 years (range:37-88). According to Rai staging system, 22 patients (21%) were stage 0, 18 (17.1%) were stage I, 19 (18.1%) were stage II, 25 (23.8%) were stage III, and 21 (20%) were stage IV. Autoimmune haemolytic anemia was diagnosed in 8 (7.6%) CLL patients. 6 patients developed a secondary malignancy, and 4 had Richter's transformation. 18 (30.5%) of early stage Rai patients and 46 (100%) of advanced stage patients were decided to be given chemotherapy. The initial treatment modality in 23 cases was chlorambucil, it was fludarabine plus cyclophosphamide in 15 cases, COP in 12 cases, CHOP in 9 cases, and fludarabine only in 5 cases. Of early stage patients at initial diagnosis, 6 (33.3%) had CR and 5 (27.8%) had PR to initial treatment modalities. 4 (8.9%) of advanced stage patients had CR and 17 (37.8%) had PR to initial treatment modalities. Unresponsiveness to initial treatment modalities was significantly more frequent in advanced stage patients (24 cases, 53.3%) than in early stage patients (6 cases, 33%) ($p<0.05$). The duration of median follow-up was 40 months (1-140 months). The median duration of overall survival according to disease stages at the time of initial diagnosis was 112 months in early stage disease (Rai 0,I,II) and 68 months in advanced stage disease (Rai III,IV). The 5-year survival in early stage CLL was 86.5% and in advanced stage patients it was 54%. Patients younger than 60 years at the time of diagnosis had significantly longer survival than elder patients (120 and 76 months, $p=0.01$). Patients with initially high LDH levels tended to have shorter survival than others (106 and 42 months, $p=0.001$). According to Cox multivariable regression analysis, being older than 60 years at the time of initial diagnosis (OR:3.2, $p=0.014$), high LDH level (OR:6.25, $p=0.01$) and advanced stage Rai disease (OR:5.9, $p=0.01$) were independent poor prognostic parameters.

CONCLUSION: The analysis of 105 CLL patients followed up at our center revealed that older age and advanced stage at the time of initial diagnosis were independent poor prognostic parameters.

NON-HODGKIN'S LYMPHOMA

P019 *ID: 33*

A CASE OF PERIPHERAL T CELL LYMPHOMA PRESENTING WITH INFLAMMATORY ARTHRITIS, CUTANEOUS VASCULITIS AND HYPEREOSINOPHILIA

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Introduction: Many data suggest that the frequency of hematologic malignancies like lymphoma are more frequent in rheumatoid arthritis(RA) and Sjögren syndrome. In addition,some patients with hematologic malignancies might develop findings similar to inflammatory arthritis. Nevertheless,the progression of arthritis and vasculitis to lymphoma is quite rare.We present one patient who had inflammatory arthritis,cutaneous vasculitis,and eosinophilia and who later developed peripheral T-cell lymphoma unspecified(PTCL-U).

Case report:Our 49-year-old male patient presented with pain and swelling of bilateral proximal interphala ngeal,metacarpophalangeal,wrist,knee,and ankle joints which have been present for 4 months.He had morning stiffness longer than one hour.His physical examination revealed swelling and tenderness of the joints.Laboratory data showed erythrocyte sedimentation rate,42mm/hr, CRP, 1.8 mg/dl (N<0.8), hemoglobin, 13.6 g/dl, leucocytes, 13400/mm^3, platelets, 450000/mm^3, creatinine, 0.8 mg/dl.There were 23% eosinophils on the peripheral blood smear.Rheumatoid factor,anti-CCP,antinuclear antibody,and ANCA antibodies were negative. Hepatitis B and C serologies were also negative. Hand X-ray showed no erosions.The patient was diagnosed as RA and put on therapy with deltacortril 7.5 mg/day, diclofenac 150 mg/day and methotrexate 10 mg/week.The patient was rehospitalized 2 months later with symmetrical polyarthritis and morning stiffness.He had arthritis and a new-onset cutaneous rash over pretibial regions and dorsum of feet. Thorax and abdominopelvic tomographies were normal.Skin biopsy showed leucocytoclastic vasculitis. Bone marrow aspiration revealed 20% eosinophils.The search for the cause of eosinophilia did not yield anything.Low dose steroids and diclofenac were restarted. During hospitalization, he developed lymphadenopathies in bilateral cervical, axillary and inguinal areas.The repeated tomographies showed multiple lymph nodes and hepatosplenomegaly.He started having widespread pinkish plaques over his body. The excised lymph node was diffusely infiltrated with CD3(+),CD2(+),CD5(+),CD 7(+),CD8(+),CD45RO(+),CD4(-),CD20(-),CD56(-),CD57(-) lymphocytes.The same cells were also seen in the skin biopsy.The patient was diagnosed as PTCL-U and administered 3 courses of CHOP.He was refractory to CHOP and given 2 courses of ICE.He developed sepsis and disseminated intravascular coagulation and died 7 months after initial hospitalization.

Discussion:Arthritis,vasculitis and hypereosinophilia might be a very rare presentation of lymphoma.The findings of arthritis might be reminiscent of RA: the

differentiating features are the absence of erosions on hand X-ray and negative RF,anti-CCP antibodies.In the presence of suspect laboratory values like hypereosinophilia,the diagnosis of RA should be reconsidered.It should be borne in mind that that the immune activation and differentiation in lymphoma might result in presentation with autoimmune disease.

P020 *ID: 34*

THE SIMULTANEOUS PRESENTATION OF PERIPHERAL T-CELL LYMPHOMA WITH RHINO-MAXILLARY ASPERGILLOSIS

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Introduction: Lymphomas that involve the sinonasal cavities are encountered very rarely. We present our patient who was initially diagnosed with rhinomaxillary aspergillosis and shortly turned out to have concomitant rhino-maxillary peripheral T-cell lymphoma.

Case report: A 46-year-old male patient was referred to the ear-nose-throat department because of three months' duration of swelling over right side of his face, obstruction of the right nare, and fever. Biopsy from the maxillary sinus and nasal cavity revealed necrotic tissues. Mucosal surface showed fungal infection consistent with aspergillosis. He was administered liposomal amphotericin B at a dose of 5 mg/kg/day. As there was progression of his symptoms, a second biopsy was obtained. The nasal cavity and the maxillary sinus were debrided. Deeper sections of the biopsy material showed multifocal cellular infiltration with inflammatory and atypical lymphoid cells. The atypical lymphoid cells were round to irregular with vesicular nucleus, scanty cytoplasm, and ill-defined cellular borders. Immunohistochemically neoplastic lymphocytes were positive with CD3, some of them with CD4. There was a high percentage of CD30 and CD56 expression on the atypical lymphocytes. Serum galactomannan test was positive. Liposomal amphotericin B was discontinued and caspofungin 50 mg/day was started. The patient progressively developed cytopenias and disseminated intravascular coagulation. CHOP chemotherapy was planned to be administered, but, the patient died.

Discussion: Most of the lymphomas which involve the maxillary sinuses are of B-cell origin. T-cell lymphomas of the maxillary sinus are extremely rare and have very poor prognosis. Colonization of Aspergillus in the upper respiratory tract is common. Because of the depressed immunologic state of the patient, Aspergillus can differentiate into hyphal forms producing toxins that destroy epithelial tissues. Aggressive antifungal therapy and chemotherapy should be undertaken. When there is aspergillosis of the sinus cavities, a search for coexistent lymphoma should be conducted.

MULTIPLE MYELOMA

P021 *ID: 36*

RETROSPECTIVE ANALYSIS FOR CLINICAL AND LABORATUARY FINDINGS OF MULTIPLE MYELOMA PATIENTS

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Background: Multiple myeloma (MM), a neoplasm of plasma cells, accounts for approximately 10% of lymphohematopoietic cancers (LHC), and 1% of all cancers.

Aim: The aim of this study was to perform a retrospective analysis of cases of MM in the 3rd internal medicine department, Izmir Bozyaka Training and Research Hospital, Turkey in the period of 2000-2010.

Patients and methods: Clinical, demographical, radiological and immunopathological data were collected from 72 patients. Stage was defined on the basis of criteria established by Durie-Salmon. The treatment type and survival data were also evaluated.

Results: There were 72 MM patients (33 Male/39 Female)..The M/F ratio was 0.85. The median ages of the patients were 65 (44-84) years. The median disease duration of the patients were 6 (1-13) years. Common clinical presentations were fatigue (54.2%) arthralgia/bone pain (44.4%) and fracture (1.4%). 29.2% of the patients did not have bone lesions. On the other hand 62.5%had diffuse bone lesions and 8.3% had localized lesions.

The median calcium, creatinine, LDH, albumin, hemoglobin, and ESR values were as follows: 9.5 (6.8-17.5), 1.2 (0.4-15.7), 238 (76-1810), 3.35 (1.6-6.1), 9 (4.1-13.6), and 116.5 (62-156) respectively. The types of immunglobulins were: IgG (55.6%), IgA (18.1%), light chain (free kappa and lambda, 16.7%), non-secretory (8.3%), and IgD (1%). According to the stage, 73.6% of the patients were at stage 3, 20.9% were at stage 2, and 5.6% were at stage 1.

In our clinic, 20.8% of the patients received bortezomib, 29.2% received thalidomide, 2.8% received lenalidomide, and 6.9% of the patients underwent bone marrow transplantation. In follow-up 36.4% of the patients were died.

Conclusion: Although multiple myeloma remains incurable with conventional treatments, management of the disease has recently been transformed with the introduction of three novel agents, bortezomib, thalidomide, and lenalidomide. This study suggest that new and novel agents for the treatment of multiple myeloma, can yield high response rates and can defer disease progression for a long period. This study therefore focuses on the extensive clinical data available from studies of these drugs in the treatment of newly diagnosed and advanced MM.

NON-HODGKIN'S LYMPHOMA

P022 *ID: 38*

NON-HODGKIN'S LYMPHOMA: 18 YEARS EXPERIENCE OF A SINGLE INSTITUTION

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Aim: Survival rates in non-Hodgkin's lymphoma (NHL) have increased significantly in the last decades. This study aims to assess the demographic data and treatment results of children with NHL treated in a single institution.

Methods: 97 children (66 male, 31 female) with NHL, treated in the İstanbul University, Oncology Institute, between 9/1989-2/2008 were evaluated retrospectively.

Results: Demographic results. The median age was 8(2-18) years. Histopathologic subtypes were: 13 lymphoblastic, 16 large cell, 68 nonlymphoblastic Burkitt/ Burkitt-like. The primary location was abdomen 40, mediastinum 7, head/neck 32, other 18 (bone 8, breast 2, ovaries 2, skin 2, paravertebral 2, primary unknown 2). 40 patients had stage I+II, 38 III, 19 IV disease. 14 had bone marrow, 6 CNS involvement. The median LDH level at diagnosis was 730 U/l (180-13000).

Treatment. Until Oct.1991, all early stage and non-lymphoblastic advanced stage NHL recieved COMP, advanced stage lymphoblastic patients recieved the New York protocol. After then, all recieved BFM protocols. Nonlymphoblastic patients recieved BFM protocols with 5 g/m2 methotrexate(MTX) until October 1995 and 1 g/ m2 MTX thereafter.

Treatment results.24 patients (18 progressive disease, 4 toxicity, 2 secondary neoplasms) died. 10 year survival and event-free-survival in the whole group was 75 and 74% respectively. According to histopathological subtypes10 year survival was 73% in lymphoblastic, 87.5% in large cell, 73 in nonlymphoblastic Burkitt/Burkitt-like. 10 year survival was 90, 72 and 47% in stage I+II, III, and IV. Considering only advanced stage nonlymphoblastic patients, 10 year survival rates were significantly higher in patients recieving modified BFM regimen with 1 g/ m2 MTX, than in ones recieving COMP or BFM protocol with 5 g/m2 MTX (10 year survival 79%, 33%, 44% respectively).

Conclusions: Survival rates in the whole group are in paralel with advances attained in the world in NHL. The significantly higher survival rates achieved in patients with advanced stage nonlymphoblastic patients recieving modified BFM(1g/m2MTX) may be due to the decreased toxicity seen in this group and to the advances in supportive care in the last decade. In another major center in the same university that used the same protocol with 5 g/m2 MTX in the same time period, similar survival rates suggest that 1 g/m2 MTX which is cheaper and less toxic is also as effective in these patients.

CHRONIC LYMPHOCYTIC LEUKEMIA

P023 *ID: 40*

RELAPSE OF INVASIVE THYMOMA WITH A PRESENTATION OF AUTOIMMUNE HEMOLYTIC ANEMIA AND PERIPHERAL T CELL LYMPHOCYTOSIS

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Thymoma is a neoplastic disease of thymic epithelial cells frequently accompanied by various clinical presentations including autoimmune disease. Peripheral T-cell lymphocytosis is a rare condition associated with malignant thymomas. We describe a patient with myasthenia gravis and thymoma who relapsed with peripheral T cell lymphocytosis and Coombs positive immune hemolytic anemia 20 years after thymectomy. Analysis of lymphocytes in peripheral blood and bone marrow revealed a T cell phenotype. He was commenced on steroids because of autoimmune hemolytic anemia. His hemoglobin levels were stabilised and lymphocytosis disappeared. Our and previous observations suggest that peripheral T cell lymphocytosis may manifest as a rare clinical feature of relatively aggressive thymomas which might reflect perturbation of immune system such as autoimmune hemolytic anemia as in our case. The case is interesting as being very rare among the literature with a presentation suggesting a paraneoplastic phenomenon i.e. autoimmune hemolytic anemia and peripheral T cell lymphocytosis years after primary diagnosis.

NON-HODGKIN'S LYMPHOMA

P024 *ID: 41*

A CASE OF MANTLE CELL LYMPHOMA IN A PATIENT WITH SYMPTOMS OF PROSTATISM

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Mantle cell lymphoma(MCL) is a mature B-cell neoplasm. It constitues 6% of non hodgkin lenfomas.In this report we present a case with the diagnosis of mantle cell lymphoma complaining of prostatism.

Case: 80-year-old male patient was admitted to urology department because of complaints of difficulty with urination for two months.

Transurethral Resection has been done with the diagnosis of benign prostatic hypertrophy.Pathological analysis showed that CD20,CD5,and cyclin D1 positive, CD23 and CD10-negative staining atypic lymphoid cells infiltrating prostate tissue(figure 1a 1b).The patient was referred to Hematology department.The patient had no complaint of B symptoms and any other systemic disease in his history.On physicsal examination there was 1x1.5 cm left axillary,1x1.5 cm left inguinal and 1x1cm right inguinal lymphadenopaty.Laboratory results showed

Hb:9.1(13.6-17.2)gr/dl,WBC:9100(4.3-10.3)10x3/ul Plt:290.000(156-373)bin/ul,lymphocyte 3800(1300-3500)bin/ul,neutrophil:5000,(2100-6100),B2 mikroglobulin:3359(604-2286)ng/ml,erythrocyte sedimentation rate:64(0-10) mm/hour.In peripheral blood smear there were,atypical lymphocytes with the immature character of the core 1-1.5 times the size of a normal peripheral blood lymphocyte(Figure 2).In bone marrow biopsy CD5,CD20,Cyclin D1-positive stained tumor formation of lymphoid cells was observed.Computed tomography scan of the chest and abdomen showed common lymphadenopathies.Endoscopy and colonoscopy performed for ıron deficiency anemia and it showed common polypoid lesions of the stomach and the colon.Biopsy revealed CD20, CD5, cyclin D1, Bcl-2 positive,CD23,CD10 negative atypical cells.Based on these findings The patient was regarded as stage 4 MCL.We planned for total of 8 cycles Cyclophosphamide,Hydroxyldaunorubicin,Vincristine,Prednisone(CHOP).Till now,the patient has received 3 cycles of CHOP.

The prostate lymphoma is excessively rare.There are two types ;primary and secondary.In the primary prostate lymphoma tumor burden is in the prostate gland, and lymph nodes,liver and spleen involvement is not seen.In the secondary prostate lymphoma the prostate gland is enlarged and,lymph nodes and other organs are involved. In our patient since the symptoms depended on the size of the prostate lymphoma were classified as secondary. MCL is derived from mantle zone of lymphoid follicles.The general age at presentation is around 60 years.It is more common in men.Extranodal involvement of the bone marrow,spleen,liver,and gastrointestinal involvement are more prevalent.The prostate involvement is quite rare. Our patient had multiple lymphomatous polyposis lesions in the gastrointestinal tract.Immune phenotype was as CD19,CD20,CD5,CD43,cyclin D1positive,CD3,CD10, CD23 negative.Genetically(11.14) chromosomal translocation seen.In the literature,there were very few reported cases of MCL diagnosed with symptoms of prostatism.We find this case acceptable to present,because of not exiting lymphoma symptoms.

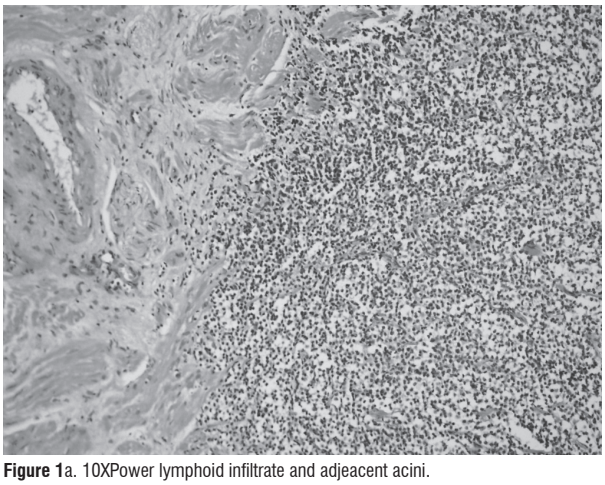

Figure 1a. 10XPower lymphoid infiltrate and adjeacent acini.

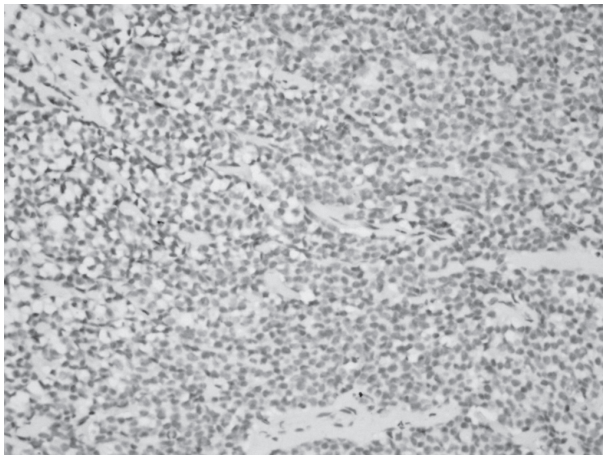

Figure 1b. cyclin D1 nuclear positivity

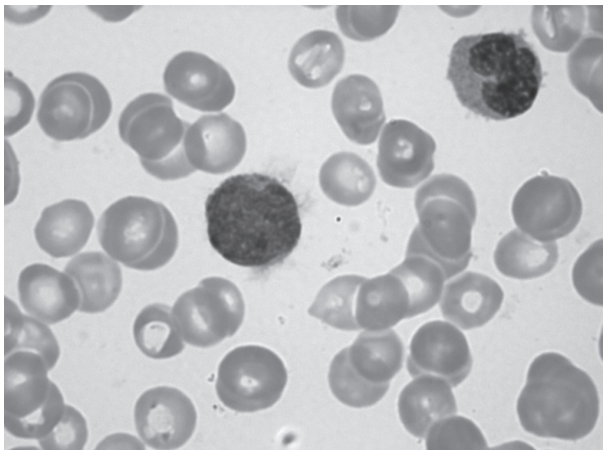

Figure 2. Atypical lymphocytes with the immature character of the core 1-1.5 times the size of a normal peripheral blood lymphocyte

ACUTE MYELOBLASTIC LEUKEMIA

P025 *ID: 47*

A RARE CASE REPORT:CYST HIDATIC DISEASE IN LIVER AND INTRAPERITONEAL CAVITY WITH ACUT MYELOID LEUKEMIA

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Echinococcosis is a zoonotic disease that is endemic worldwide. Humans are intermediate hosts of the Echinoccocus spp. Although any part of the body can be affected, liver and lungs are the most prominent sites of infestation. Radiology and serology both help the clinician while the definitive diagnosis depends on histopathology. Surgical excision is the most efficient therapy; where the operation cannot take place; pharmacological

therapy using Mebendasole or Albendasole is an acceptable option. 56 years of male patient with a history of Echinococcosis who had been operated for liver and abdominal cysts five years ago, came to our clinic complaining weakness and malaise for four months. He was using Albendasole for one year. He had stopped taking it one week ago. He was pale and a mass with a diameter of 5 cm. was palpable in left lumbar region. His hemogram was Hg: 6.8 gr/dl, Htc:23%, WBC: 12400/uL, Plt: 45000/uL. His peripheral blood smear showed atypical mononuclear cells with 2 nucleolus and marked thrombocytopenia. The bone marrow examination revealed a normocellular marrow. Myelopoiesis, erythropoiesis, megakaryopoezis were depressed, and atypical mononuclear cells were %80 in bone marrow. On flowcytometry CD13:%81.5, CD14:%0.3, CD33:%76.8, CD34:%70.8, CD45:%87.3, CD117:74.4 were found. On cytogenetic analysis t(8;21) was positive. On abdomen CT and USG, type two echinococcal cysts were found on segment six of liver which was 114x109 cm in diameter and also five more were found intraperitoneally which had different magnitudes (figure1,2,3). Echinococcus hemagglutination test was IgG 1/10000 positive. He was diagnosed as AML-M2 with Echinococcosis so Albendasole therapy began along side with Cytarabine-Idarubicine as he was not eligible for surgical therapy. He had also received Imipenem, Teicoplanin, Amikacin, Ciprofloxacin and Caspofungin for febrile neutropenia and during therapy; cysts were not associated with any clinical disorder. He successfully finished his remission-induction therapy and bone marrow examination showed remission. Only one case is found with Echinoccus infested patient with AML receiving chemotherapy therefore we want to represent our clinical experience in this rare clinical situation

HODGKIN'S LYMPHOMA

P026 *ID: 48*

HEMOPHAGOCYTIC SYNDROME ASSOCIATED WITH HODGKIN LYMPHOMA IN CHILDHOOD

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Hemophagocytic syndrome (HPS) is a clinically and pathologically well defined disease characterized by systemic activation of benign macrophages showing extensive phagocytosis of hematopoetic cells. It is occasionally associated with malignant lymphomas but its association with Hodgkin's disease has been rarely reported.

A 12-year-old boy was admitted to our hospital with a seven-day high grade fever, pancytopenia (Hb 8.4 gr/dL, Hematocrit 26%, leucocyte 3300/mm^3, thrombocyte 139000/mm^3), left cervical lympadenomegaly, splenomegaly and scrotal edema. Based on findings in bone marrow aspirates he was diagnosed as HPS, also supported hyperferritinemia (828 ng/mL) and hypertrigliseridemia (311 mg/dL). Radiological studies revealed supraclavicular, intrathoracic and intraabdominal multiple lymphadenomegaly. Mixed celluler Hodgkin Lymphoma was diagnosed after cervical lymph node biopsy evaluation and treated with combination chemotherapy containing cyclophosphamide, vincristine, procarbazine, prednisone, adriamisin, bleomisin and vinblastine.

We report a rare case of Hodgkin's disease associated with HPS. Rapid diagnosis of HPS and underlying lymphoma is mandatory for achieving cure in these patients.

ACUTE MYELOBLASTIC LEUKEMIA

P027 *ID: 49*

AZACITIDINE HAS LIMITED ACTIVITY IN REAL LIFE PATIENTS WITH MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Objectives: Azacitidine has been reported to result in comparably higher response rates and improved survival than other treatment strategies in Myelodysplastic Syndromes (MDS). In this retrospective study we report the results on 25 'real life' patients with MDS, CMML or AML treated with azacitidine between 2005 and 2009.

Methods: Patients fulfilled the WHO criteria for MDS and AML. No eligibility criteria other than diagnosis were considered. We terminated the treatment in our patients after 4 to 8 cycles of treatment if objective response was not achieved. This was mainly associated with financial problems and the reimbursement policy in our country

Results: Complete response (CR) rate was observed in three of the 25 'real life' patients(12%) with a median duration of CR of 5 months (4-6 months). 7 patients (28%) had mono- or bi-lineage hematologic improvement and 15 patients (60%) showed neither morphologic nor hematologic response. Among 17 non-AML patients, the median time from onset of Aza-C treatment to AML transformation was 10 months(4-15 months). Overall death rate was 72%. All of the eight AML patients died. The death rate under Aza-C among non-AML patients was 59%.

Conclusion: In clinical trials, it has been shown that treatment with Aza-C compared to supportive care, improves quality of life, prolongs median survival and decreases the rate of leukemic transformation. Clinical trials, however, are usually designed to test a drug in a certain group of patients with predefined qualifications. Thus, the results obtained in a clinical trial are somewhat "artificial" since they only represent the findings in an eligible group of patients. In daily practice physicians generally face with patients that are far more different than those treated in clinical studies. These "real-life" patients

are usually beyond the age limits of the trials, have comorbidities or organ dysfunctions, are heavily pretreated or show a worse performance status. Thus, applying the data obtained in the trials to "real-life" patients and trying to treat them accordingly sometimes becomes a real dilemma.

Unlike the results of the clinical trials, our data shows that Aza-C has a limited activity in "real-life" patients with MDS and AML. It is obvious that Aza-C can induce complete or partial responses in a considerable number of MDS patients but responses are usually not durable as we observed in our patients.

Table 1

Table 1: Aza C Patient Details		All	MDS			CMML-I	AML
			RCMD	RAEB-I	RAEB-II		
No of patients (M:F)		25 (20:5)	3 (3:0)	5 (4:1)	4 (4:0)	5 (3:2)	8 (6:2)
Median age		70 (53-85)	64 (56-76)	65 (55-81)	66 (57-85)	74 (53-80)	75 (61-82)
Median follow-up		13 (5-43)	16 (5-19)	14 (12-28)	9 (8-19)	23 (14-43)	8 (5-16)
ECOG	0-1	18	2	5	3	4	4
	2-3	7	1	0	1	1	4
IPSS	Low-INT I	10	2	3	0	5	
	INT II-High	7	1	2	4	0	
Karyotype	Normal	16	1	3	2	5	5
	Complex	6	1	1	2	------	2
	del7	2	1	1	------	------	------
	del5q	1	------	------	------	------	1
Median number of cycles (range)		8 (3-15)	5 (5-8)	8 (6-8)	5 (4-8)	8 (8-15)	6 (3-9)
Response	CR (duration of response - month)	3	------	1€ (4 mths)	1€ (6 mths)	1Ω (5 mths)	------
	PR (duration of response - month)	3	------	1¶ (17 mths)	------	1€ (4 mths)	1 (7 mths)
	SD (duration of response - month)	11	2 (16+, 19+ mths)	3 (3,5€, 14+, 28+ mths)	1δ (3 mths)	3	3
	PD	8	1€	------	2€	------	4
Hematologic Improvement	Tri-lineage	3	------	1	1	1	------
	Bi-lineage	2	------	------	------	------	2(HI-P&E ; HI-P&N)
	Mono-lineage	5	------	1 (HI-E)	1 (HI-E)	2 (HI-E)	1 (HI-P)
	No improvement	15	3	3	2	2	5
No of patients progressed to AML (time from the end of treatment to AML transformation -mths)		7	1 (under treatment)	2 (3.5 and 4 mths)	3 (6 mths and 2 pts under treatment)	1 (4 mths)	
No of patients died (time from the diagnosis to death-mths)		18	1 (5 mths)	3 (12, 13, 17 mths)	4 (8, 9, 9, 19 mths)	2 (23, 29 mths)	8 (5, 5, 6, 7, 9, 10, 11, 16 mths)
No of patients alive (survival; time from first dose of Aza C to study entry -mths)		7	2 (16+, 19+ mths)	2 (14+, 28+ mths)	------	3 (14+, 21+, 43+ mths)	------

CR: Complete remission, **PR**: Partial remission, **SD**: Stable disease, **PD**: Progressive disease
HI-E: Hematologic improvemen - erythroid, **HI-P:** Hematologic improvement - platelet,
HI-N: Hematologic improvement - neutrophil
€: Patient progressed to AML
¶: Patient died at 17th month after achieving PR due to congestive heart failure
Ω: Patient relapsed and re-treated with Aza C
δ: Patient died at 3rd month of response due to multiple organ failure

ACUTE LYMPHOBLASTIC LEUKEMIA

P028 *ID: 50*

TOLL-LIKE 4 (TLR-4), NOD2, DECTIN-1 POLYMORPHISMS AND SUSCEPTIBILITY TO INFECTIONS, RELAPSE AND OTHER COMPLICATIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Objective: Toll-like receptor (TLR) family regulates both innate and adaptive immune responses in humans. Polymorphisms within TLR genes result in an altered susceptibility to infectious or inflammatory disease. Nod1 and Nod2 are proteins involved in innate immune defense, especially necessary for clearance of infecting pathogens from the host. Dectin-1 and dectin-2 elicit protective immunity against fungal infections. They are prominently situated at portals of pathogen entry and best known for their ability to recognize fungal b-glucans. We aimed to investigate the association between single nucleotide polymorphisms (SNPs) of TLR 4, NOD2 and Dectin-1 in children with leukemia and their susceptibility to infections, relapse and other complications of treatment and disease. Methods: SNPs of TLR 4 Arg299Gly, TLR 4 Thr399IIe, NOD2 Leu1007fsinsC, NOD2 Arg702Trp and Dectin-1 were assessed in 96 children treated for acute lymphoblastic leukemia and 103 controls. Results: The mean age of the patients was 5,9 years old (±3,7 years), 54 (%56) were male. The TLR 4 Arg299Gly variant allele was found in 5 patients as heterozygous. The TLR 4 Thr399IIe variant allele was found in 8 patients, of 5 of whom TLR 4 Arg299Gly variant allele was also detected. Five of 8 patients who were carriers of 399IIe variant allele relapsed after treatment. Sixty-three percent of the patients who had 399IIe variant allele relapsed compared to 11% who do not have this allele ($p<0.05$). The 702Trp variant allele of the NOD2 gene was detected in only one patient who had no severe infection during therapy. The other NOD2 polymorphism (Leu1007fsinsC) was also heterozygous in 1 other case, this patient also had no severe infection during leukemia treatment. Dectin-1 mutation was detected in 16 patients. Five of 16 patient were relapsed patients, there was no statistical difference according to relapse between patients who had Dectin 1 mutation or not. The infections of the mutant Dectin patients were not different from the other ALL patients, however other rare complication of therapy were seen in this group. There was one patient who had secondary brain tumour and another boy who had avasculer necrosis; both of them had Dectin 1 mutation. Furthermore 4 patients had VOD during ALL treatment, 3 had dectin 1 mutation. Conclusions: Here, we tried to review the roles of each of these receptor polymorphisms in the host immune response, and their association with infections and other complications during treatment. There was a small number of patients with TLR4, NOD mutations so a definitive result could not be concluded in risk of patients with these mutations to infections. No relation between febrile neutropenia and dectin 1 mutation was found. However, the patients with TLR4 Thr399IIe variant allele were found to have a risk for disease recurrence. Patients with dectin 1 mutation may have a risk of VOD and secondary malignancy and avascular necrosis.

NON-HODGKIN'S LYMPHOMA

P029 *ID: 51*

THE ASSOCIATION OF TOLL-LIKE 4 (TLR-4) AND NOD2 POLYMORPHISMS AND FEBRILE NEUTROPENIA IN CHILDREN WITH BURKITT LYMPHOMA

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Introduction: Toll-like receptor (TLR) family regulates both innate and adaptive immune responses in humans. The function of TLRs have been investigated comparing the incidence of disease among individuals with different polymorphisms participating in TLR signalling. The first identified TLR polymorphism encodes an Asp299Gly amino acid substitution in TLR4. This polymorphism is associated with decreased signalling response to bacterial LPS. Previous studies have demonstrated that Asp299Gly polymorphism causes an increased risk of gram-negative infections. NOD2 is a member of a superfamily of genes which are involved in intracellular reconginition of pathogens and expressed in intestinal epithelium, macrophages and dendritic cells. The two most common NOD2 variants are Arg702Trp and Gly908Arg. In the present study the associations between TLR4 (Asp299Gly and Thr399Ile), NOD2 (Arg702Trp and Gly908Arg) mutations and the risk of febrile neutropenia (FN) is investigated in children with Burkitt lymphoma.Patients and Method: Between September 1995 to December 2007; 27 children with Burkitt lymphoma were collected. Patients with immunodeficiency, anaplastic large cell lymphoma, MALT lymphoma and patients previously treated for any form of cancer or by transplantation were excluded. Patients were treated according to the BFM NHL-95 protocol. The number and duration of FN episodes during treatment were recorded. TLR4 (Asp299Gly and Thr399Ile), NOD2 (Arg702Trp and Gly908Arg) genotypes were analyzed using melting curve analysis on the LightCycler. Results: Four of 27 childrens (6 female, 21 male) with Burkitt lymphoma were heterozygous for the TLR4 Asp299Gly (n:1) and Thr399Ile (n:2) and NOD2 Gly908Arg (n:1) polymorphisms. One patient is heterozygous for both Asp299Gly and Thr399Ile polymorphism. There was no statistical difference in the prevalance of polymorphisms between patients and controls. Of the 6 blocks of chemotherapy, 54 FN attacks were detected. The patient with carriage of the Gly299 allele died after the 1. FN episode due to sepsis and this was the only patient who expired due to infection. The patient with Thr399Ile allele carrier had FN after 5/6 blocks of chemotherapy and had severe mucositis in every episode. Klebsiella was isolated in 2 throat cultures of this patient. The patient with heterozygote carrier of the Asp299Gly and Thr399Ile genotype also had FN in 5/6 blocks of therapy and severe mucositis. Candida albicans was isolated in one of the throat cultures of this patient. Discussion: The polymorphisms in TLR4 and NOD may give a clue on individual risk factors of certain patients to FN and toxic effects of therapy and potentially identify novel therapeutic approaches. This is the apreliminary results of our study, we planned to evaluate these correlations in larger groups of patients

ACUTE LYMPHOBLASTIC LEUKEMIA

P030 *ID: 52*

RENAL TUBULAR ACIDOSIS AS A COMPLICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA

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A 18-year-old girl was admitted to hematology ward of Çukurova University Hospital with anemia and thrombocytopenia. A bone marrow examination revealed precursor B cell acute lymphoblastic leukemia. We have observed persistent hypokalemia during hospitalisation period without any other reason for hypokalemia. There was a normal anion gap hyperchloremic metabolic acidosis. Urinary and arterial blood gas analysis demonstrated proximal renal tubular acidosis. A hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen resulted in complete remission. Interestingly metabolic acidosis also resolved after institution of chemotherapy. Temporal relation between hematologic recovery and resolution of metabolic acidosis made us think that defect in proximal bicarbonate reclamation in this case was most likely attributable to leukemic infiltration of renal tubules.

P031 *ID: 54*

SUCCESSFUL TREATMENT OF EARLY RELAPSE WITH ICE–RITUXIMAB CHEMOTHERAPY AND SUBSEQUENT BONE MARROW TRANSPLANTATION IN A PATIENT WITH BURKITT LEUKEMIA AND INVERTED DUPLICATION OF 1Q

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Although childhood acute lymphoblastic leukemias are of good prognosis than leukemias of adulthood, some chromosomal abnormalities may have negative effects on their prognosis. Inverted duplication (1q) is a chromosomal abnormality with negative effect on outcome of Burkitt leukemia and lymphomas. We report a case of CD20+ Burkitt leukemia with inverted duplication (1q) mutation, who had an early relaps during NHL-BFM 95 treatment. Two courses of ICE-rituximab treatment were administered after relaps and a successful HLA-full match bone marrow transplantation was carried out. He is in follow-up for 18 months without any problems after bone marrow transplantation. We suggest the usage of ICE protocol combined with rituximab in childhood CD20+ Burkitt leukemia with poor prognostic criteria such as inverted duplication (1q) mutation.

MULTIPLE MYELOMA

P032 *ID: 59*

PLASMA CELL LEUKEMIA WITH SKIN INVOLVEMENT

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Plasma cell leukemia (PCL) is a rare hematologic malignancy. There are two forms of disease, including primary (60%) and secondary (secondary to myeloma, 40%). Diagnosis can be made if plasma cells ratio in peripheral blood cells are at least 20% or plasma cell count in peripheral blood is above 2000/mm^3. Prognosis is poor and mean survival is 6-8 weeks and 7 months in untreated cases and with conventional therapy, respectively. 45-years old male patient referred to our clinic in January 2008 due to complaints of fatigue for 20 days and pain localized in right inferior section of chest for 3 days. The patient has been receiving antibiotherapy due to frequent pulmonary infection. In physical examination, he was pale, he had 5-cm ecchymosis in both hypochondriac region which had occurred from a massage session due to his pain and liver was 3-cm palpable below rib cage. His hemogram was Hb:7,4 g/dl, WBC:16000/uL, Plt:28000/uL, Sedimentation:89 mm/h, Creatinin:1,2mg/dl, Uric acid:14,4mg/dl, AST:222U/L, LDH:3891U/L, T.Protein:9,1g/dL, Albumin:4,0g/dl, Ca:13,6 mg/dl. In peripheral blood smear, findings of rouleaux formation in erythrocytes and blast (40%) were observed. In the bone marrow aspiration, blast rate was 50% and in the bone marrow biopsy, large, round and Cappa and CD138(+) neoplastic cells, which caused diffuse infiltration and were largely consisted of marked nucleolus, were observed (Figure1,2,3). In immunfixation, monoclonal IgG cappa was found. β2 microglobulin was 3,90 mg/L, IgG was 3417 mg/dl. In craniography, focal lytic lesions bone were seen. The patient was started VAD therapy based on diagnosis of Plasma Cell Leukemia. After VAD therapy Hg was 12g/dl and Plt was 30000/uL so bone marrow aspiration performed and he was considered as refractory; no donor could be found for the patient who had no sibling so treatment with bortezomid-cyclophosphamide–dexamethasone was started. Following 2 cycles of BCD, Hb was 12,3g/dl, WBC was 7400/uL, PLT was 160000/uL and bone marrow blast rate was found as below 5 percent. Four months after treatment, blast rate was found over 50% in peripheral blood smear. Biopsies obtained from mobile subcutaneous nodules, which occurred in anterior chest wall and upper extremities 15 days ago and CD138 and Cappa positive tumoral involvement was observed. Patient was started Dexamethasone-Thalidomid-Cisplatin-Doxorobucin-Cyclophsopahmid-Etoposid therapy but he was relapsed and his general status declined and he expired despite adequate care.

Similar to cases in the literature, we found organomegalia, severe anemia and thrombocytopenia, bone involvement and increase in IgG cappa monoclonal in our case in addition to increased LDH and calcium levels and lytic lesion in bones. Moreover, our case also had skin involvement. Our patient lived 5 months following chemotherapy. Due to poor prognosis and response to chemotherapy, survey can be slightly increase

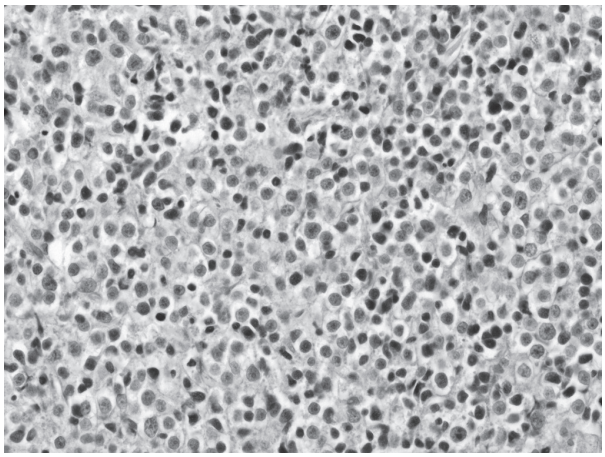

Figure 1. Bone marrow biopsy

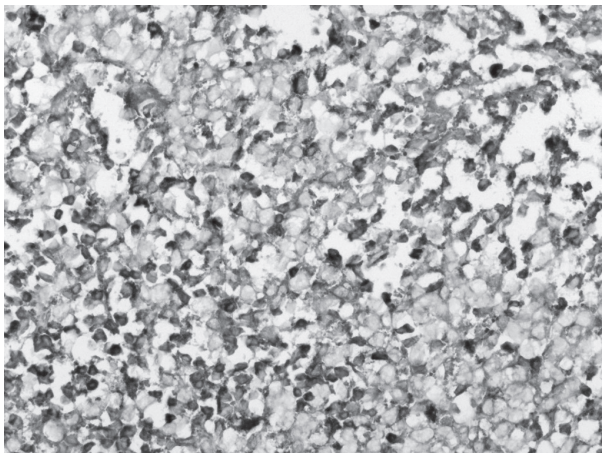

Figure 2. Cappa positivity in bone marrow

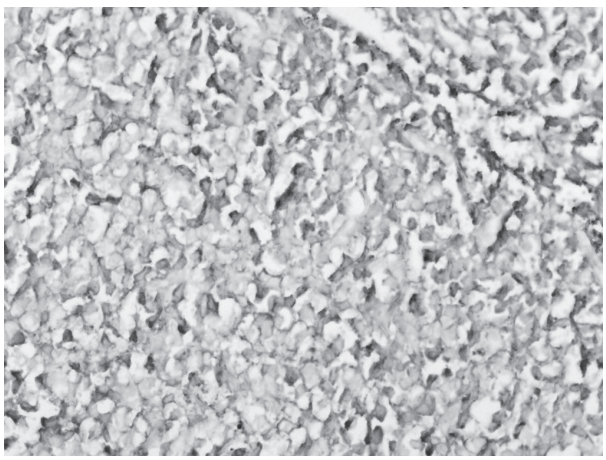

Figure 2. CD138 positivity in bone marrow

CHRONIC MYELOID LEUKEMIA

P033 *ID: 60*

TOXIC DERMATITIS RELATED TO IMATINIB

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Imatinib mesylate is the first line therapy for Chronic Myeloid Leukemia (CML) and it selectively inhibits bcr/abl. Imatinib is generally well tolerated but non-haematological side-effects occur in <10% of patients, including nausea, vomiting, oedema, weight gain, muscle cramps, diarrhoea and cutaneous reactions. A 47 year old woman came to our clinic complaining of fatigue. She had 10 cm of splenomegaly in her physical examination and her hemogram was Hg: 11.4 gr/dl, WBC: 143000/µL and Plt: 536000/µL. She was diagnosed as CML with a 98.5% positivity of t (9; 22) and was started Imatinib 400 mg daily. She had achieved haematological response in 3 months but developed grade 3 itchy maculopapular lesions (figure 1 and 2) and mild respiratory distress so Imatinib stopped for two months. After the lesions resolved, Imatinib 300 mg/day was restarted but the lesions appeared again. We stopped her therapy once again and performed cutaneous biopsy which revealed toxic dermatitis related to Imatinib so we switched her therapy to Dasatinib. She achieved complete molecular remission after 12 months. She suffered pericardial effusion 13 months after the therapy but managed with low dose steroid therapy and now she is followed in remission without any signs or symptoms of toxicity. Imatinib is usually associated dermatologic effects such as dermatitis, hypopigmentation, Sweet syndrome, pityriasis rosea-like eruption, erosive oral lichenoid reaction, erythema multiforme, acute generalized exanthematous pustilosis and Stevens - Johnson syndrome. Most skin reaction occurs in the first 12 weeks of therapy, are usually mild, self-limiting, do not require dose interruption and generally respond to topical steroids, emollients and antihistamines, but may occasionally require oral steroids. More severe cases may require dose reduction or interruption until the rash improve to grade I, and re-challenge of Imatinib at a lower dose (50-100mg/day) with steroid cover and gradual escalation is needed. In cases of severe, grade 4 skin rash, re-challenge is not recommended. Our patient had grade 3 dermatitis so a rechallenge was tried but it was not successful so we switched her therapy to Dasatinib. Imatinib is usually well tolerated, although cutaneous skin reactions occur frequently, it is usually self limited and manageable. Less frequently, serious adverse reactions can occur, which can be managed with reinstitution of a different drug therapy.

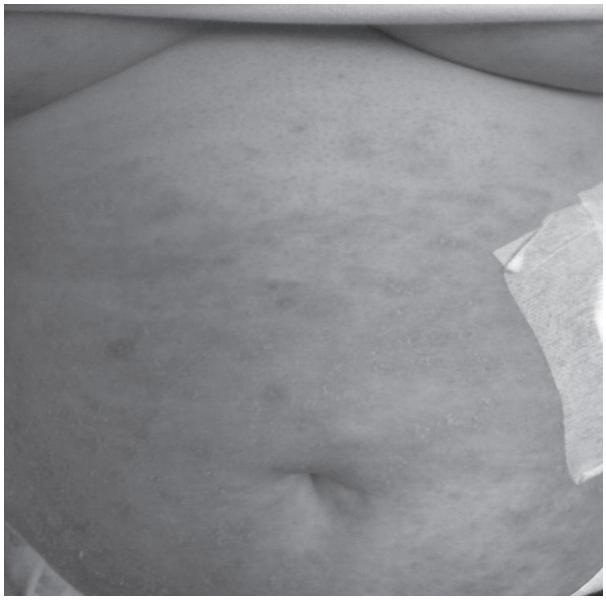

Figure 1.

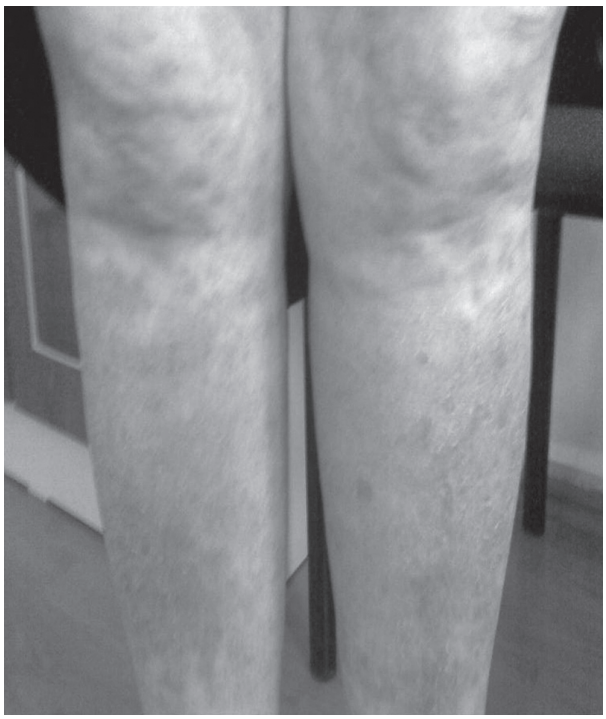

Figure 2.

NON-HODGKIN'S LYMPHOMA

P034 *ID: 61*

PRIMARY GASTROINTESINAL NON-HODGKIN LYMPHOMA IN A RENAL TRANSPLANT RECIPIENT CHILD

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Introduction: Increased cancer risks are well documented in adult organ transplant recipients. However, the risk in the pediatric organ transplantation is less well described. Nearly 7% of pediatric solid organ recipients develop a premalignant or malignant tumour during follow-up. Non-Hodgkin lymphoma (NHL) typically appear during childhood and deserve shortterm attention. Here we present a girl who developed EBV associated NHL after renal transplant. Problems related to managing a child with transplant and cancer are discussed.

Case: A 9 year old girl was diagnosed as chronic renal failure secondary to vesicourethral reflux and was put on peritoneal dialysis 4 years ago. She was transplanted from her mother 2 years later and was on immunosuppressive treatment (prednisolone, MMF and tacrolimus). Three months after her transplant, she was admitted to hospital because of weight loss. Ultrasonography showed intestinal wall thickening and lymphadenopathy. While she was investigated, she developed severe abdominal pain and was operated because of gastric and colon perforation. Gastric resection, gastrostomy, colon resection, ileostomy and parsial omentectomy was perfomed emergently. Pathology showed EBV positive diffuse peripheral B cell NHL. NHL-BFM 95 protocol was given consequently, but after first course as she developed severe febrile neutropenic period resulting near death, rituximab therapy (6 courses, dose: 375 mg/m2) and intravenous immunoglobulin therapy were treatment of choice thereafter. During chemotherapy, she had no renal problem, while infection and tissue defect around gastrostomy area were the main complications. She is in full remission for 2 years now.

Conclusion: NHL risk is greatly increased after renal transplantation. Two mechanisms of lymphogenesis are suspected; one is related to primary EBV infection in the context of intense immunosuppression and another dysregulated lymphoid proliferation in prolonged immunosuppression. This case emphasizes the need for clinical awareness of increased risk of NHL in renal tranplant recipients.

MULTIPLE MYELOMA

P035 *ID: 62*

CARDIAC TAMPONADE: AN UNUSUAL PRESENTATION OF MULTIPLE MYELOMA

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Introduction: Multiple myeloma is a neoplastic disorder arising from plasma cells. Pericardial involvement is a rare complication of the terminal stage disease and is caused by amyloidosis, infections, bleeding abnormalities or plasma cell infiltration.

Case: A 52 years old female was admitted to our hospital with a history of fatigue and progressive dyspnea. Atrial fibrillation was determined and echocardiogram showed pericardial effusion of 2.2 cm near by the posterior wall of left ventricul (figure 1 and 2). Because of progressive respiratory distress, a percutaneous drain was placed echocardiographically. Initially 1200 mL exudative, hemorrhagic fluid was removed. At the admission, laboratory tests were as: WBC: 7570 /mm^3, Hb: 10.5 gr/dL, MCV: 88, Plt: 153000 /mm^3, creatinine: 1.33 mg/dL, albumin: 3.99 g/dL, Ca: 11.2 mg/dL, P: 5.4 mg/dL, globulin: 1.5 gr/dL. On cytological examination of pericardial fluid, degenerated blood elements were seen. No tuberculosis bacillus was determined. The ADA was 94 IU/L. A few days later, thrombocytopenia developed and the patient was consultated to our hematology department. Bone marrow aspiration was performed and 40% plasma cell infiltration was seen on bone marrow examination. Serum immunofixation electrophoresis was performed; IgG: 1.9 g/L, IgM: <0.2 g/L, IgA: 0.3 g/L, kappa light chain: 39 mg/dL, lambda light chain: 240 mg/dL. At urine immunofixation electrophoresis; kappa light chain: 0.7 mg/dL, lambda light chain: 517 mg/dL. Beta-2 microglobulin level was 25.915 ng/mL. Lytic lesions were detected in cranial and vertebral bones. ECOG was 4.

In the light of these findings, the patient was diagnosed as lambda light chain myeloma. VAD (vincristine, adriamycin, dexamethasone) chemotherapy protocol was started. Pamidronate were given for bone lesions and hypercalcemia. Her atrial fibrillation was recovered, since no more pericardial fluid was drained, percutaneous drain was pulled out. Creatinine and calcium levels improved. The patient got better, ECOG score was 2 and she discharged from hospital. Two weeks later, no cardiac arrhythmia or pericardial effusion was determined on her cardiac examination. But 1 week later, it was learned that sudden death of unknown cause was emerged.

Discussion: Pericardial effusion is a rare complication of myeloma (less than 1% of cases) and may occur at any time during the course of the disease. This condition is usually fatal and optimal treatment modalities are not known. Cytological examination of aspirated pericardial fluid usually confirms the diagnosis, but pericardial biopsy can be essential. A high ADA activity in effusions of these cases can be observed and can be misdiagnosed as tuberculosis. Cardiac tamponade in these patients requires immediate therapeutic intervention with pericardial drainage.

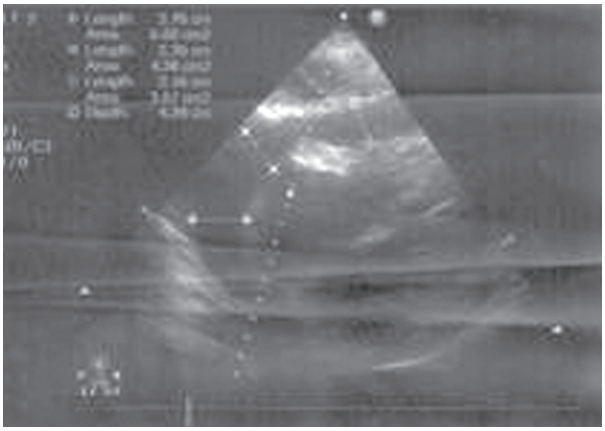

Figure 1.

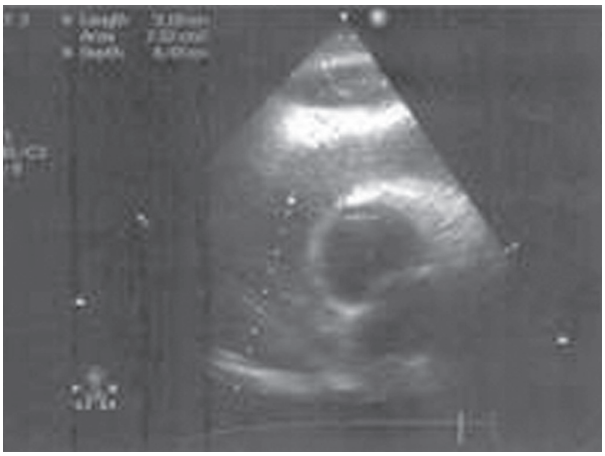

Figure 2.

CHRONIC MYELOID LEUKEMIA

P036 *ID: 63*

CHRONIC MYELOID LEUKEMIA AND MYELOFIBROSIS AS A SEPARATE ENTITY IN A PATIENT WHOSE FIBROSIS IMPROVED DESPITE NOT ACHIEVING A CYTOGENETIC RESPONSE

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Chronic Myeloid Leukemia (CML) is a chronic myeloproliferative disease that represents 15-20% of leukemias and the molecular hallmark of the disease is bcr/abl fusion oncogene. Tyrosine kinases selectively inhibit bcr/abl and other non-specific tyrosine kinases, such as c-kit and platelet derived growth factor receptor and they are now the first line therapy for CML. Myelofibrosis is a well known negative prognostic factor which affects approximately half of patients with CML; it disappears as the patient achieves remission with therapy. CML and myelofibrosis as a separate entity in a patient, is a very rare but well defined finding in recent years and it is usually associated with Janus Kinase-2 mutations alongside with bcr/abl although mutations such as MPL W515L/K and Jak-2 exon 12 mutations can also play a role. A 38 year old female patient had attained to a hematology department complaining abdominal pain, night sweats, weight loss of 6 kg in one month. Her physical exam had revealed splenomegaly which had been 205 mm on USG. Her hemogram had been as follows; Hg: 10 gr/dl, Htc: 29%, WBC: 47200 Plt: 274000/µL. Bone marrow had been aspirated after many attempts and had revealed dominance of myeloid cells. Cytogenetic analysis had shown 100% of t (9; 22) so Imatinib 400 mg/day had began. She had used for 15 days and after that she had come to our clinic for intractable vaginal bleeding for 3 days. Her Hg: 8.6 gr/dl, Htc: 27.7%, WBC: 21630/µL and Plt: 56000/µL. Her bone marrow aspiration and biopsy were hypocellular; dominance of myeloid series and grade 4 myelofibrosis had been found. We had given thrombocyte suspensions and stopped Imatinib. As soon as the bleeding stopped, Imatinib was restarted 100 mg/day and slowly increased dose to 400 mg/day over months, but the patient could not tolerate the drug because of frequent infections and marked pancytopenia. She also had not accepted transplantation. She could not achieve an acceptable molecular response and two years after the beginning of treatment she lost haematological response; we therefore began Dasatinib therapy. As she could not tolerate 70 mg/day due to neutropenia, 50 mg/day were used. 9 months after therapy, she achieved haematological response but t (9; 22) was 79% positive. So one year ago, her therapy increased to 70 mg supported with G-CSF 30 MIU every other day. JAK-2 mutation was found to be negative in the patient. At first, she had minor cytogenetic response (57%) but now although reticulin fiber is now grade 2, t (9; 22) is 92% positive and 4 months after the loss of cytogenetic response, she is still in haematological remission. Therefore we choose to continue Dasatinib as fibrosis is improved and transplantation is not a therapy option due to patient's preferences. Here we report a patient who had both CML and myelofibrosis and who did not achieve remission from CML but had her fibrosis significantly improved with tyrosine kinase inhibitor therapy.

CHRONIC LYMPHOCYTIC LEUKEMIA

P037 *ID: 64*

CHLORAMBUCIL-INDUCED INAPPROPRIATE ANTIDIURESIS IN A MAN WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH) is based on the evidence of improper urinary concentration with normal renal function and elevated urinary sodium excretion despite decreased plasma osmolality, after discarding other causes of euvolemic hypo-osmolality, such as hypothyroidism, hypocortisolism. Its etiology comprises broncogenic carcinoma, central nervous system (CNS) disorders, pulmonary diseases, and drugs. We describe a case associated with treatment of chlorambucil.Case: A 61 years old male admitted to our hospital with a history of fever, involuntary movements of the joints, aphasia and loss of consciousness. He had been diagnosed with chronic lymphocytic leukemia (CLL) 2 years prior to admission and 6 cures R-CHOP chemotherapy protocol

had been given at the time of diagnosis (last cure of R-CHOP had been given at February, 2009).He had also a history of Parkinson's disease and hypertension, for which he was receiving ramipril plus hydrochlorothiazide, levodopa, pramipexole, and amantadine sulfate. At 27th of September 2010, chlorambucil treatment was started at a dosage of 6 mg/m^2/day, because of increasing lymphocytosis with a lymphocyte doubling time less than six months. At the beginning of the treatment, laboratory tests were as: WBC: 116.000 /mm^3, lymphocyte: 105.000 /mm^3, Hb: 12.5 gr/dL, MCV: 77, Plt: 259.000 /mm^3, creatinine: 0.95 mg/dL, albumin: 4.5 g/dL, LDH: 138 U/L, Na: 133 mEq/L, K: 3.5 mEq/L. At this admission which is the 20th day of chlorambucil treatment, laboratory tests were as: WBC: 53.000 /mm^3, lymphocyte: 43.000 /mm^3, Hb: 12.2 gr/dL, Plt: 246.000 /mm^3, creatinine: 1.1 mg/dL, Na: 118 mEq/L, K: 2.85 mEq/L, urine density: 1013, spot urine Na: 93mmol/L, thyroid function tests: normal range, cortisol: 298 nmol/L. Because of symptomatic hyponatremia, sodium replacement therapy was begun with 3% NaCl solution but, few days later, the patient was still hyponatremic. Then, chlorambucil-induced SIADH was thought and water restriction (1.5 l/day) was begun. His anti-hypertensive drug was stopped. The dosages of anti-Parkinson's drugs were increased. After water restriction, serum Na increased gradually and reached 133 mEq/L on the 7th hospital day. Simultaneously, the neurological symptoms were regressed and the patient was discharged.Discussion:Hyponatremia is common in hospitalized patients, and sodium levels below 120 mEq/L are associated with increased morbidity and mortality. Therefore, diagnostic evaluation and treatment are mandatory. CLL have been described as the cause of SIADH, but only when the CNS is involved. On the other hand, some antineoplastic drugs such as vincristine may cause SIADH. Our patient was symptomatic after chlorambucil treatment and all his symptoms resolved after the discontinuation of the drug and water restriction. Easy control of the disorder after the medication was discontinued and water restriction support its causal role in SIADH.

NON-HODGKIN'S LYMPHOMA

P038 *ID: 65*

BURKITT LYMPHOMA ORIGINATING FROM THE SPHENOID SINUS

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Introduction: Burkitt lymphoma is a common craniofacial malignancy in childhood. The endemic form seen primarily in young children and presents with jaw and facial bone involvement. The sporadic form usually manifests as an abdominal mass and rarely involve paranasal sinuses. Here we report a case of Burkitt lymphoma that originated from the sphenoid sinus in a child.

Case: A 5 year old boy was admitted to the hospital because of vomiting, headache and vision loss. On physical examination his blood pressure (140/100) was high and he was investigated with initial diagnosis of hypertension. Cranial imaging revealed a destructive mass in the sphenoid sinus that spreaded into the cavernous sinus and optic foramen. An endoscopic biopsy was performed and showed CD20(+) diffuse peripheral B-cell Burkitt lymphoma. Bone marrow aspiration and biopsy were normal. The patient underwent NHL-BFM 95 protocol and additional triple intrathecal therapy consequently. After 2 cycles of chemotherapy he gained some vision in his left eye. Radiation therapy was omitted because of possible adverse effects on vision. After 14 months of systemic and intrathecal chemotherapy, follow-up imaging showed a rest tissue however there was no tumour on biopsy. He is followed-up in remisson for 1,5 years now.

Conclusion: This case is one of the few reported cases of Burkitt lymphoma originating from the sphenoid sinus. Blindness is a major morbity associated with this disease. Diagnosis, treatment and follow up strategies should be further studied to manage patients with paranasal lymphoma.

MYELOPROFILERATIVE DISORDERS

P039 *ID: 68*

''MEAN PLATELET VOLUME'' IN DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOSIS

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Background: The differential diagnosis of thrombocytosis is usually very diffucult, perhaps the reason why is that there are so many different etiological factors lies beneath it. Reactive thrombocytosis or secondary thrombocytosis should be distinguished from autonomous thrombocytosis in which the normal pathways and order of platelets synthesis can no longer be functioning properly. Reactive thrombocytosis or secondary thrombocytosis can be seen in patients with splenectomy, neoplasm, infectious, inflammatory diseases and anemia. Thus the maximum platelet count can differ in these two different groups, in primary thrombocytosis,thrombohemorragic complications are more likely to occur because of platelet disfunction. In this article we compared the mean platelet volume (MPV; 7-12 fL) levels in both primary and secondary thrombocytosis.

Methods: In this retrospective study we separated patients into two groups as primary thrombocytosis and secondary thrombocytosis that we have chosen patients with higher platelet counts(>450,000/μL). We used WHO Diagnostic Criteria of Myeloproliferative Neoplasms 2008, for the diagnosis of essential thrombocythemia. In the second group, we evaluated the patient results that the patients who have iron deficiency anemia and haven't taken any kind of treatment. At the end of the study we observed that after adequate iron treatment, platelet counts of the second group has returned to normal.

Results: 23 patients included in first group (age: 19-87; mean:65) and 26 patients included in the second group (age: 16-80; mean:43,5). Patient statistics are as shown at the table. In the first group it has been significantly found that the platelet count is more than the second group (995,000/μL - 548,959/μL; p=0.000).

However in the first group it has been significantly found that the mean platelet volume is more than the second group (8,819-7,607; p=0,007).

Discussion: Finally in myeloproliferative diseases including essential thrombocythemia; membrane and nucleotide structures are disfunctional as well as ADP, ephinephrine and collagen aggregation tests are inaccurate. We think that based on our early findings; increased MPV in the first group is a reflection of platelet membrane and nucleotide disfunction as well as thrombopoiesis dysregulation. In addition, contrary to other clinical researchs, higher platelet count is corralated with higher MPV. To sum up we can say that it is stil early to predict the diagnosis and the etiology of thrombocytosis judging by MPV results, we can suggest that higher MPV could point us towards the direction of primary disease.

Table 1.

	Primary Thrombocytosis	*Secondary (Reactive) Thrombocytosis*
Platelet Count	995 x 109/L	549 x 109/L
MPV	8,819 fL	7,607 fL
Hemoglobin	13,50 g/dL	9,18 g/dL
Ferritin	24 ng/mL	4,9 ng/mL
CRP	1,7 mg/L	3,3 mg/L
White Blood Cell Count	8480 x 109/L	8330 x 109/L

MULTIPLE MYELOMA

P040 *ID: 69*

HLA-DRB1*13 AND *15 ARE ASSOCIATED WITH RESPONSE TO THALIDOMIDE IN PATIENTS WITH MULTIPLE MYELOMA

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Thalidomide (T) has been approved for treatment of myeloma. There is no generally accepted predictor for response. The aim of this study was to analyze the impact of HLA antigens on response to T. Patients and methods: Patients (n=46) who received T either as monotherapy (n=36) or combination therapy with dexamethasone (n=10) were retrospectively analyzed. Patient characteristics were: median age 50 (31-73), male/female 31/15, IgG/IgA/IgM/light chain 33/6/1/6 and ISS-I/II/III 21/10/11. Numbers of patients given T for induction/consolidation/relapse were 2/18/26. Patients were given T at doses 50-400 mg for a median duration of 10 (2-72) months. Thalidomide was stopped whenever disease progression or side effects grade≥3 occurred. Response to T was classified as responders ≥ partial remission (PR) or non-responders (disease progression on T). Results: 16 patients had response, 18 patients had disease progression and 12 patients had stable disease on T. Parameters which may have contributed to response to T were compared between responders and non-responders (Table 1-2). There were no statistically significant difference between the responders and non-responders in terms of age, sex, paraprotein, prognostic subgroup or the number of previous chemotherapy cycles. The only significant differences were the number of previous chemotherapy lines and the HLA frequencies. In a recent study (Beksac et al 2008), it was demonstrated that HLA-DRB1*15, HLA-DRB1*13 and HLA-DRB1*11 were observed 7.2%, 18.2% and 21.1% in MM population, respectively. In this study, the percentage of response to T in HLA-DRB1*15 positive and HLA-DRB1*13 positive patients were 55.5% and 66.6%, respectively. There were 4 patients who were HLA-DRB1*15/*13 and all of them responded to T. On the other hand, HLA-DRB1*11 was associated with refractoriness to T (11% response, p=0.01). Conclusion: Host related factors such as HLA may have impact on response to T similar to that observed in aplastic anemia-immunosupression-HLA-DRB1*15.

Table 1.

	T responders	*T non-responders*	*p*
N=46	16 (35%)	30 (65%)	
Age (median,range)	50 (35-73)	50 (31-64)	0.38
Sex (M/F)	8/8	23/7	0.1
Paraprotein IgG Non-IgG	 11 5	 22 8	0.74
Prognosis ISS-I ISS-II or III	 6 10	 15 11	0.34
Number of previous CT cycles (median, range)	6 (0-9)	6 (1-13)	0.31
Number of previous CT lines (median, range)	1 (0-3)	2 (1-3)	0.02
Previous ASCT Present Absent	 9 7	 25 5	0.07
Del13q Positive Negative	 7 0	 8 6	0.06
p53 Positive Negative	 1 1	 7 2	0.42

Table 2.

	T Responders	*T non-responders*	*p*
HLA-DRB1*15 Positive Negative	 5 11	 4 26	0.24
HLA-DRB1*13 Positive Negative	 8 7	 4 25	0.01
HLA-DRB1*11 Positive Negative	 2 13	 16 13	0.01

ACUTE MYELOBLASTIC LEUKEMIA

P041 *ID: 70*

COEXISTING LYMPHOMA AND LEUKEMIA IN THE BONE MARROW TREPHINE BIOPSY: A CASE REPORT

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Background: Low grade lymphoma and acute leukemia are two different disease entities with contrasting indolent and aggressive behaviour. Blastic trasformation of a low grade lymphoma into a high grade one is well documented in the literature. In most cases of transformation it is an evolution of the same clone of cells that acquires additional genetic abnormalities, which gives it a growth advantage and becomes much more aggressive. But in a few instances, it appears to be the emergence of a second lymphoma that is unrelated to the first, but that is less common. To the best of our knowledge, coincidence of low grade lymphoma and acute myeloid leukemia or myeloperoxidase positive blastic transformation of an indolent lymphoma has not been previously reported in the literature.

Case Presentation: A 68-year-old man with a complaint of fatigue and weight loss of one year duration presented with increased severity of his complaints. Physical examination revealed pallor and 2cm splenomegaly. Laboratory examination revealed WBC: 9.50 $X10^9$/L, Hb: 7 g/dl, and Plt: $70X10^9$/L. Peripheral blood smear showed 10% atypical lymphocytes, 55% lymphocytes, 6% monocytes, 20% PNLs and decreased trombocytes. LDH was 217 U/l. Computed tomography of the cervical and thoracic region was normal, while abdominal CT revealed 19cm splenomegaly. Bone marrow aspiration showed atypical lymphocytes and blastic cells. Bone marrow trephine biopsy was infiltrated by two different population of neoplastic cells. Clusters of atypical lymphoid cells were neighbouring groups of blastic cells. Neoplastic lymhoid cells were small lymphoid cells with a non-paratrabecular and paratrabecular nodular, patchy and intrasinusoidal infiltration pattern. The neoplastic lymphoid cells were CD20+, CD79a+, IgM+, Bcl2+, CD23-,CD43-, CD5-, CD10-, IgD-, CD3-, and Cyclin D1-. Blastic cells were Myeloperoxidase+, CD34+, CD10-, CD20-, CD79a-, and TdT-. The morphologic and antigenic features were consistent with coexisting low grade lymphomatous infiltration of the bone marrow and acute myeloid leukemia. An intrasinusoidal pattern of lymphomatous bone marrow involvement by small lymphocytes associated with splenomegaly, and thrombocytopenia has been considered as a 'possible hallmark of bone marrow infiltration by splenic lymphoma, but splenectomy was not performed. The patient was treated with Cyterabine 40mg/day.Last hemogram revealed WBC: 3.50 $X10^9$/L, Hb: 11.4 g/dl, and Plt:$420X10^9$/L.The patient didn't need any transfusions following the therapy until current presentation.

Conclusion: We present a unique case of collision tumor consisting of lymphoma and acute myeloid leukemia. Blasts with Myeloperoxidase positivity can be explained by two hypothesis: One being the rarest form of blastic transformation of a low grade lymphoma, and the other, being the more probable one, the coincidence of two unrelated different neoplastic populations. Unfortunately, we couldn't perform clonality studies.

NON-HODGKIN'S LYMPHOMA

P042 *ID: 71*

EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA, NASAL TYPE : A CASE REPORT

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Background: Mature or peripheral NK/T cell lymphomas account for only 10-15% of non-Hodgkin's lymphomas. Amongst them, the most common and well-characterized ones are the 'nasal' and 'nasal type' NK/T cell lymphomas. Their characteristic histological feature is an angiocentric/angiodestructive growth pattern with zonal necrosis. Early diagnosis of extranodal NK/T-cell lymphoma (ENKTCL) is essential as disease will spread to adjacent sites and compromise local function. In addition, as the disease becomes more widespread, the clinical response to therapy falls greatly. Because of the anatomy of the nose, it may not be easy to obtain adequately sized specimens for histopathological examination, and hence multiple biopsies may be required. An additional difficulty is that the tissue may be friable in view of its often necrotic nature, indeed the necrosis may lead the need for repeated biopsies.

Case Presentation: A 16-year-old male presented with a 2-months history of progressive swelling of the lateral wall of the nose and nasal obstruction. There was no bloody discharge. On physical examination, left nasal wall was hyperemic and endurated. Endoscopic examination revealed irregular mucosal surface and intranasally protruding mass extending from the vestibule to the medial choncha. Paranasal sinus CT and MR revealed a mass of 3cm in dimension at the lateral wall of the left nasal cavity extending into subcutaneous tissues. The biopsy of the nasal mass showed a diffuse infiltrate of medium-sized lymphoid cells, with slightly irregular nuclei and moderate polymorphism. The immunophenotype of tumor cells was CD3+ (cytoplasmic), Granzyme B+, Perforin+, CD56+, CD20-,CD79a-, CD4-,and CD8-. The diagnosis of the case was ENKTCL, nasal type. There was not disseminated disease in the extent studies.

Conclusion: ENKTCL, nasal type, is an extranodal lymphoma, usually with an NK-cell phenotype, with a broad morphologic spectrum, frequent necrosis and angioinvasion, and most commonly presenting in the midfacial region. This is a case presentation in which the histopathologic and immunohistochemical properties of ENKTCL, nasal type are discussed, diagnostic difficulties are emphasized, and the literature is rewieved.

Key Words: NK/T-cell, lymphoma, nasal

CHRONIC LYMPHOCYTIC LEUKEMIA

P043 *ID: 72*

CHRONIC LYMPHOCYTIC LEUKEMIA/ PROLYMPHOCYTIC LEUKEMIA WITH SKIN INVOLVEMENT: A CASE REPORT

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Background: B-cell chronic lymphocytic leukemia (CLL) is a malignant disease characterized by the accumulation of mature monoclonal B cells in blood, lymph nodes, spleen, liver, and bone marrow. However, skin infiltration with B-lymphocyte CLL is rare and far less common when compared with T-cell leukemias or lymphomas. Skin involvement manifests as solitary grouped or generalized papules, plaques, nodules, or large tumors. Rarely encountered clinical manifestations include erythoderma, chronic paronychia, and palmar plaques. Some cases of CLL show atypical morphology. An increased proportion (>10%) of prolymphocytes identifies a clinically aggressive variant designated CLL/PL.

Case Presentation: A 65 year-old male presented with skin eruptions on his legs. Physical examination revealed multiple erythematous papules and plaques on his legs. He had been diagnosed as CLL/PL five years ago. The disease was stage IV at the time of diagnosis. He developed autoimmune hemolytic anemia on Fludarabine treatment and the drug had to be stopped. He couldn't get an appropriate therapy for the illness. He had been followed up with steroids at the begining, and than without any medication. A punch biopsy from the cutaneous lesions showed dermal and subcutaneous infiltration of small lymphoid cells with diffuse infiltration pattern. Neoplastic cells were CD20+, CD23+, CD43+, CD5+, CD3-, CD10-, and Cyclin D1-. Histopathologic diagnosis was cutaneous infiltration of CLL. The patient is given Chlorambucil therapy at the present time.

Conclusion: Cutaneous involvement in patients with CLL are rare. However, skin changes occur in up to 25% of patients with CLL. Any questionable skin lesions should be excised or biopsied and histologically investigated. Neoplastic lymphoid involvements should be carefully discriminated from the nonneoplastic ones by using wide panels of antibodies. We present a case of CLL/PL with cutaneous involvement and highlight the differential diagnosis of small cell lymphoid infiltrates of the skin.

Key Words: Chronic lymphocytic leukemia, prolymphocytic leukemia, cutaneous involvement

MULTIPLE MYELOMA

P044 *ID: 73*

PLASMA CELL MYELOMA LACKING CD138 AND CD38 EXPRESSION: A CASE REPORT

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Introduction: The WHO immunophenotype for plasma cell myeloma is deletion of CD19 and CD20, usual expression of CD38, CD138 and CD56, and occasional expression of CD10. CD138, also known as Syndecan1, is expressed by both nonneoplastic and neoplastic plasma cells. Although most myeloma cells are negative for the majority of B cell markers, the literature indicates that CD138 is an exception in that it is expressed regularly by both normal and myelomatous plasma cells. CD38 is considered to be plasma cell marker as both normal and malignant plasma cells have been demonstrated to be present in fractions which are strongly positive for CD38 such that identification of plasma cells depends in part upon the presence of CD38 at high intensities. Similarly to CD138, CD38 is unusual in that it is expressed by both normal and myelomatous plasma cells which is not the case with the majority of B cell markers. Lack of CD38 and CD138 expression on myelomatous plasma cells is extremely rare.

Case report: A 61-year-old man presented with backpain and head-ache. Thoracal MRI revealed an extradural mass of 3x3x2cm. at Th8 region having a dumbbell appearance resembling Schwannoma. Pathologic examination of the resected specimen revealed monotypic plasma cell infiltration consistent with plasmacytoma. Further investigations of the patient demonstrated a peak in the serum and urine protein electrophoresis representing an increase of Lambda light chain. There were no lytic lesions on skeletal survey.

Bone marrow trephine biopsy demonstrated a monotypic (Lambda positive) plasma cell infiltration. Plasma cells were negative for CD138, CD38, CD20, CD79a, Kappa, CD30, CK, ALK-1, CD3; and positive only for EMA and Lambda antibodies. The patient was clinically accepted as Multiple Myeloma, and was treated with VAD protocol.

Conclusion: Lack of CD38 and CD 138 expression on myelomatous plasma cells is a very rare occurence and represents diagnostic difficulty. We report an unusual case of plasma cell myeloma lacking CD38 and CD138 expression, and discuss diagnostic difficulties when abnormalities of immunoexpression are met.

HODGKIN'S LYMPHOMA

P045 *ID: 74*

A CASE REPORT:MARKED HIPEREOSINOPHILIA IN HODGKIN'S DISEASE

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A 40-year-old male patient presented to our department with marked leukocytosis and intermittent fever, weight loss, fatigue, pruritis of three months duration. Physical examination findings included generalized lymphadenopathy, hepatomegaly, abdominal mass and erythematous rash. There had been no pulmonary complaints. Laboratory results were hemoglobin of 12.7 g/dl, platelets of $208x10^9$/l, white blood cell count of $222x10^9$/l of which 90% were eosinophils. ESR was 12 mm/h and normal renal and liver function. Periferal blood smear showed markedly eosinophilia. The bone marrow examination indicated hypercellular marrow with eosinophilic proliferation. The abdominal computed tomography showed multiple large intraabdominal

lymphadenopathy and hepatomegaly, no splenomegaly. BCR/ABL and FIP1L1/PDGFRA fusion genes were negative. Lymph node biopsy and immunohistochemical study presented Hodgkin Disease(HD)-mixed cellularity. We initiated ABVD chemotherapy. During therapy anaphylactic reaction appeared. We thought it was due to cytokines. Supportive therapy decreased symptoms in a short time. After chemotherapy white blood cell and eosinophil count became normal range. During other therapies we didn't observe anaphylactic reaction.

We presented a case who was diagnosed to have HD and hypereosinophilia.

Blood eosinophilia may be either a primary or a secondary circumstance. Primary eosinophilia is classified into 2 categories: idiopathic and clonal. Genetic mutations involving the platelet-derived growth factor receptor genes (PDGFR-α and PDGFR-β) have been pathogenetically related to clonal eosinophilia. The most common cause of secondary eosinophilia is tissue-invasive parasitosis. Noninfectious causes of secondary eosinophilia include drugs, toxins, allergic disorders, idiopathic/autoimmune inflammatory conditions, malignancies, endocrinopathies. Secondary eosinophilia in inflammatory and malignant situations is mediated by tissue-derived or tumor-derived eosinophilogenic cytokines. The incidence of eosinophilia in HD is approximately 15%. The mechanism of eosinophilia remains unknown though various mediators like Interleukin 5(IL-5) and GM-CSF have been implicated. IL-5 is a Th2 cytokine essential for the growth and differentiation of eosinophils. IL-5 is expressed by Reed Sternberg(RS) cell lines and has been identified in primary RS cells from tumors with tissue eosinophilia. Tıssues containing HD of the nodular sclerosis and mixed cellularity subtypes frequently are extensively infiltrated by eosinophils. One possible explanation is provided by the observation that RS cells of HD contain messenger RNA (mRNA) coding for IL-5. Also other cytokines and chemokines contribute to the pathogenesis of HD.

Even though the occurrence of eosinophilia with malignancy is rare, patients who have no apparent cause should be screened for malignancy.

ACUTE LYMPHOBLASTIC LEUKEMIA

P046 *ID: 75*

THE LONG TERM RESULTS OF CHILDHOOD ALL AT TWO CENTERS FROM TURKEY: 15 YEARS OF EXPERIENCE WITH ALL-BFM 95 PROTOCOL

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Objectives: We evaluted the treatment results of ALL-BFM 95 protocol used between 1995 and 2009 in pediatric hematology departments of two hospitals. Methods: A retrospective analysis of 343 newly diagnosed children as ALL (M/F:200/143, mean age: 6.7±4.2;1-17.5 years)was performed. The overall (OS) and event free survival (EFS) according to age, sex, initial leucocyte count, chemotherapy responses on day 8th, 15th and 33rd and risk groups were analysed by Kaplan Meier survival analysis. Results: Median follow-up time was 6.4±4.02 years. Complete remission was achieved in 98.5% of children. The gender did not have a significant effect on EFS and OS (p>0.05). Children with good response to prednisolone on day 8th achieved significantly better OS and EFS (p=0.001). Children in the standart (95%)and the medium risk groups (83%) obtained higher EFS comparing to high risk group (56%)(p=0.001). EFS for B- and T-cell ALL were 81% and 66%, respectively. Adolescents achieved 65% of EFS. Five years EFS and OS were found 78% and 80%,respectively. Relaps rate was 15%. The median relapse time from diagnosis was 23.21±13.16 months. Death occured in 69 out of 343 patients (20%). The major causes of death were infection and relapse. None died of drug related toxicity. Conclusions: ALL-BFM 95 protocol was applied successfully in these two centers. In developing countries in which MRD could not be performed, this protocol could be still used with high survival rates.

P047 ID: 76

ASSESSMENT OF ENDOCRINOLOGIC AND CARDIOLOGIC LATE EFFECTS AMONG SURVIVORS OF CHILDHOOD LEUKEMIA

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Objectives: Survival rates for childhood acute leukemia have significantly improved and late effects of therapy have been important in follow-up of survivors. The objective of this study is to identify the endocrinologic and cardiologic late effects of acute leukemia patients treated in our pediatric hematology unit. Methods: Patients treated for leukemia with BFM protocols after at least five years of diagnosis were included in the study. Endocrinologic late effecs (growth failure, obesity, insulin resistance, dyslipidemia, thyroid gland disorders such as hypothyroidism, osteopenia/osteoporosis, pubertal disorders) and cardiologic late effects (cardiac toxicity, hypertension) were evaluated. The study group was evaluated with anthropometric measurements, body mass index, laboratory testing of fasting glucose, insulin, serum lipids and thyroid functions. Pubertal stage was determined by using the Tanner criteria. Bone mineral densities were measured by DEXA (dual-energy X-ray absorptiometry). Blood pressures were noted. Evaluation of cardiac systolic and diastolic functions were performed using standard M-mode echocardiography and tissue doppler imaging. Results: Of 43 acute leukemia survivors with a median age of 15 (range; 7-30 years), 23 (54%) were females and 20 (46%) were males. Five (12%) of the patients had acute myeloid leukemia and 38 (88%) of them had acute lymphoblastic leukemia. They had been off therapy for an average of eight years (range; 5-17 years, SD 3.4 years). At least one adverse event occured in 25 (58%) of the 43 survivors, with 10 of them (23%) having multiple problems. Six (14%) of the survivors were obese and 10 (23%) of them were overweight. Subjects who were overweigth or obese at the time of diagnosis and at the end of therapy were more likely to be overweight or obese at last follow-up. Overweight and obesity were more frequently determined in patients who were younger than six years of age at the the time of diagnosis. Insulin resistance was observed in nine (20%) subjects. Insulin resistance was more frequently seen in

subjects who are overweight or obese and who have family history of type 2 DM. Hyperlipidemia was detected in eight (18%) of the 43 survivors. Premature telarche was detected in one (2%) subject. None of the patients had short stature. Hypothyroidism was observed in one (2%) survivor. Two (5%) survivors had osteopenia. Avascular necrosis of femur head occurred in two (5%) survivors. Cardiovascular abnormalities occurred in one (2%) of the subjects with hypertension and cardiac diastolic dysfunction. No statistically significant difference was determined for the distribution of late effects between subjects who received cranial radiotherapy or not. Conclusions: In our study at least one adverse event occured in most of the cases. Acute leukemia survivors should be followed up for the endocrinologic and cardiologic late effects with concerning sex, age at diagnosis and contents of the therapy.

P048 *ID: 77*

A RARE COMPLICATION OF INTRATHECAL METHOTREXATE

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Objectives: Methotrexate (MTX) is an essential component of chemotherapy for childhood acute lymphoblastic leukemia (ALL). Both intravenous and most commonly intrathecal routes of MTX have been implicated in acute, subacute and chronic neurotoxicity syndromes. Herein we describe the clinical and typical neuroimaging features of a child with ALL who presented with subacute MTX neurotoxicity that rapidly progressed to a severe clinical condition in a few hours but eventually resolved completely with dexamethasone and folinic acid. Case presentation: On 43th day of ALL-BFM 2000 treatment, 8 days after third IT MTX (12 mg) administration, an 11-years-old female patient with pre-B ALL suffered from a severe headache on her frontal region awakening her from sleep. Her neurological examination was normal. Due to persisting headache and accompanying vomiting, computed tomography of brain was performed and showed normal result with no hemorrhage. Thereafter her headache was disappeared. On the 52th day of Protocol I (8 days after last intrathecal treatment) she was hospitalized with fever, severe headache, and vomiting. Neurological examination and vital signs were normal; computed tomography of the brain revealed normal results. The other day she developed sudden dysarthria and blurred vision, her otherwise neurological examination was normal. Immediate magnetic resonance and diffusion magnetic resonance imaging of the brain revealed symmetrical diffusion restriction in frontoparietal regions of the brain in keeping with MTX induced neurotoxicity. At the night of the same day she developed sudden hemiparesis with 4/5 muscle strength in right upper and lower extremities. The other day she gained her full strength in upper extremity but developed a confusional state. She lost cooperation and orientation, became agressive, had urine and stool incontinence. She was sedated with intravenous diazepam. Folinic acid with a dose of 50 mg per 8 hours was started and continued till complete resolution of her symptoms. As she had areas of cytotoxic edema on her MRI intravenous dexamethason was started for its antiedematous property and continued for 5 days. She was unconscious and had no cooperation and orientation for 10 hours. Thereafter she gained her consciousness, had a fluent speech and full orientation and cooperation. She didn't receive the remaining subsequent doses of IT methotrexate in consolidation, she received intravenous MTX at a dose of 1g/m2 instead of 5 g/m2. As she couldn't receive the required doses of intrathecal MTX, she received 12Gy of prophylactic cranial irradiation for prevention. Conclusions:Subacute MTX neurotoxicity leading to transient neurological dysfunction should be considered in patients presenting with similar symptoms. Discontinuation of subsequent IT MTX therapies should be considered in severe cases and treatment with dexamethasone and folinic acid may help to resolve the acute symptoms.

CHRONIC MYELOID LEUKEMIA

P049 *ID: 78*

PLEURAL AND PERICARDIAL EFFUSIONS IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS DURING LOW DOSE DASATINIB TREATMENT

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Introduction: Dasatinib is a second generation tyrosine-kinase inhibitor (TKI) which can be used for treatment of BCR-ABL positive chronic myeloid leukemia (CML). Although dasatinib is effective, patients are also subject to various adverse effects. Dasatinib-related pleural effusion is a relatively common adverse event. In this paper we discuss chronic phase CML patients who were treated with low-dose dasatinib and developed pleural and pericardial effusions during the course of their diseases.

Patients and methods: 23 chronic phase CML patients who receive low dose dasatinib (50-100 mg daily) due to resistance or intolerance to imatinib were enrolled. 10 of them (9 patients with pleural effusion and one patient had pericardial effusion) had pleural and pericardial effusions (43%). 8 patients were males and 2 were females, and the median age was 61.5 (range 44-69). Nine patients out of 10 were in late chronic phase who were switched to dasatinib because of imatinib resistance and only one patient was in early chronic phase since she started receiving dasatinib due to intolerance of imatinib. The median duration of dasatinib use was 26 months (range 13-33).

Results: All of the patients had grade I/II effusions. Only one patient had a known pulmonary disease. In 7 patients the maneuver was interrupting dasatinib with the initiation of furosemide+steroids and effusions totally resolved in 4 of them. Dasatinib was restarted in those 4 patients and effusions didn't occur again. The remaining 3 patients had just started receiving furosemide and steroids and are under follow up so we were unable to make a comment on the success of the treatment. In one patient we didn't stop dasatinib when he developed pleural effusion and we only added steroids and the effusion had improved. In the other 2 patients no other intervention was made other than interrupting dasatinib treatment and the pleural effusions were improved. After

we restarted dasatinib in those 2 patients, one of them developed pleural effusion which was then managed with furosemide and steroids as well as discontinuing dasatinib treatment and he fully recovered afterwards.

Discussion: 10 patients developed effusions and they were all grade I or II. Pleural effusions occurring during dasatinib are managed by treatment interruption as well as supportive therapy. One of our patients had chronic obstructive pulmonary disease and received dasatinib because nilotinib wasn't at the market in Turkey at that time. Since the effusion formation is showed to be directly correlated with dasatinib response, the relation between pleural effusion formation and response to dasatinib therapy in our patients will be discussed at the time of presentation. We agree that effusions may occur with relatively lower doses of dasatinib and screeningfor any possible co-morbidities and potential risk factors before starting dasatinib is mandatory and all the patients should be followed up closely.

CHRONIC LYMPHOCYTIC LEUKEMIA

P050 *ID: 79*

CUT OFF VALUE FOR CD38 EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS

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Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemi. Some patients will have an excellent prognosis and never require treatment, while in other patients the clinical course is more aggressive with a very short life span. Although Rai and Binet clinical staging systems offer important prognostic clues at the time of CLL diagnosis, they fail to provide indications about disease heterogeneity and treatment requirements. Over the last few years, technological advancements have led to identify important biological and genetic parameters related to the clinical course of CLL. Ig VH mutuation, ß2 microglobin, cytogenetical analysis, thimidine kinase activation, ZAP 70, CD38 are identifed and the therapy leaded in this way. There are different studies on the litretature for the assesment of CD38 cut-off value, as flow cytometry. There is no absolute consensus, yet.

We investigated research about the CD38 positive, in flow cytometry as analysing the immunephenotypical and with different cut off values(%7, %12,%20) according to different RAI stages, on 124 untreated patients (ages 40-87 (avg 68,0±10,4), 39 Women(%31.5), 85 Men(%68,5)), who diagnosed as CLL. The diagnosis criteria is taken as existance of clonal lymphocyte more than 5000/mm³ in peripheric blood and more than 30% in bone marrow. CD38 positive was analysed in the peripeheric blood, for CD5+CD19+CD23+,Anti- Kappa or Anti-Lambda +, CD22- cells with 4 colored flow cytometry (a panel consists of CD5, CD11c, CD19, CD20, CD22, CD23, CD25, CD38, CD79b, FMC7, Anti Kappa, Anti Lambda, Anti HLADR) The clinical phasing is constructed according to th RAI staging. The distrubution on the patients according to stage is listed below.

Stage 0: 50 cases (40,3%), Stage I : 21 cases (16,9%), Satge II: 11 cases (8.9%), Stage III: 24 cases (19,4%) Stage IV: 18 cases (14,5%)

The cut-off values are taken 7%, 12%, 20% and age, sex, RAI staging, tretmant free survival hemoglobin, thrombocyte and number of lymphocyte are evaluated. When, the cut-off value is taken as 12%, sensitivity is found as 85,7% and specifity is found as 74,4%, in compare with the cut-off values 7% and 20%. This study indicates a CD38 expression 12% is an important parameter for the identification of early CLL patients with more aggressive disease.

ACUTE MYELOBLASTIC LEUKEMIA

P051 *ID: 81*

STANDARD DOSE OF CYTARABINE-INDUCED SINUSAL BRADICARDIA IN AML PATIENT

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A 43 year-old woman admitted to our hospital. and diagnosed with acute myeloid leukemia (AML-M1) Induction treatment (7/3) of standard dose cytarabine (200 mg/m²/day intravenous infusion) and idarubicin (12 mg/m²/day) was started. Fourth day of treatment, she developed sinusal bradicardia rate of 38 beats /min. The electrocardiograpy showed normal atri- and intraventricular conduction. Serum electrolyte levels and cardiac injury biomarkers were normal. Echocardiography was any abnormality. In literature, intermediate and high dose cytarabine-induced bradicardia is mentioned. However, Standard dose of cytarabine-induced cardiac rhythm abnormality is not available.

HODGKIN'S LYMPHOMA

P052 *ID: 82*

THE RELATIONSHIP BETWEEN INHIBIN B, PUBERTY AND SECONDARY SEX CHARACTERISTICS IN CHILDHOOD CANCER PATIENTS AFTER GONADOTOXIC TREATMENT AND HAVE PROVIDED CURE

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Objectives:The prognosis in children with childhood cancer has dramatically improved with the use

of intensive and multi-agent treatment regimens. With improved survival, concerns and issues related to long-term toxicities and quality of life of the survivors have become a crucial point of interest. In this study, we have evaluated gonadal functions, onset of puberty and secondary sex characteristics of survivors enrolled in treatment of childhood cancers, including potential gonadotoxic agents.

Patients and Method:Gonadal functions were studied in 33maleand 22female survivors of Hodgkin's Lymphoma,Non-Hodgkin's Lymphoma,Acute Leukemia, Osteosarcoma and Rhabdomyosarcoma.The follow-up period time off-treatment ranged 1-10 years, median 4.5 years.All patients were post pubertal and were older than 15 years of age at the time of the study.All patients were taken gonadotoxic chemotherapy regimens, eight of them had received radiotherapy to abdomen and 9 patient had prophylactic cranial radiotherapy.The patients history were taken and they underwent a clinical evaluation of pubertal development and secondary sexual characteristics.Serum follicle stimulating hormone (FSH), leuteinizing hormone (LH), Inhibin B and sex steroids were measured.Results compared with 13 male 20 female age-matched healty controls.

Results: In female patients, there was no significant difference in secondary sex characteristics and the pubertal timing, compared with control group. Although,female patients had borderline elevated basal follicle stimulating hormone (FSH) levels than control group(P:0.025), their pubertal timing was normal, median menarche age was 12 and none had delayed puberty or amenorrhea. Inhibin B levels were normal and Inhibin B did not seem to be a superior and reliable marker to show the gonadal toxicity compared to FSH in our female patients. In our male patients, pubertal timing and pubertal development for age were normal but adult-type hair growth was significantly delayed when compared to control group.(P:0.002) While the serum FSH levels in males did not differ, the levels of inhibin B were found to be significantly lower compared to control group(P:0.022) We found diminished Inhibin B as the only marker of gonadal dysfunction in our male patients, considering this finding, we could not demonstrate significant correlation with age at diagnosis, time elapsed off-treatment, malignant disease type, given gonadotoxic agent and radiation therapy below the diaphragm. As the number of patients receiving radiotherapy below the diaphragm is inadequate that, a comment can not be done about the contribution of radiotherapy in gonadal toxicity.

Conclusion:Detection of diminished Inhinin B levels compared to age matched control group in our male patients, while normal pubertal timing/progression with normal levels of FSH and testesteron levels, considered that this parametr is an early and sensitive marker of gonadal toxicity.

P053 *ID: 84*

RETROSPECTIVE ANALYSIS OF HL PATIENTS FROM A SINGLE INSTUTITION

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Objective: Hodgkin Lymphoma (HL) is a curable disease both in pediatric and adult population. Response to initial treatment is closely related to the outcome. Herein, we retrospectively evaluated HL patients received chemotherapy followed by radiotherapy (RT) between 2003-2010 at Ankara Oncology Hospital.

Materials and Method: A total of 31 patients (17 men, 14 women), ranged from 5 to 73 years (median 39) were analyzed. Classic HL was 89% (Noduler sclerosing type was 46.5%,mixed cellularity type was 25% and lymphocyte rich type was 18%) and lymphocyte predominance HL was 11%. Stage distrubition of the diseases were stage 1 (13.8%), stage 2 (58.6%), stage 3 (20.7%) and stage 4 (6.9%). ABVD was the most common (81.3%) chemotherapy (CT) regimen given in 3 to 8 cycles to a median of 6. Bulky disease was observed in 35% of cohorts. Radiotherapy was given as an adjunct to chemotherapy mostly as an involved field radiotherapy (92%) to a dose of 24 to 40 Gy.

Results: Follow-up time was 6 to 72 (median: 24) months. During the period of follow-up there was no death. Relaps was observed in 6 (2 of them were stage 3 and 4 of them were stage 2) patients. Two patients who did not initially receive RT were successfully salvaged with a combination of RT and CT and they were disease free at the time of last follow-up.

Conclusion: This study shows us that CT and RT combination is effective in management of HL and RT is essential and must not be omitted in advanced stages also.

ACUTE MYELOBLASTIC LEUKEMIA

P054 *ID: 85*

SINGLE CENTER EXPERIENCE: IDA-FLAG TREATMENT IN PATIENTS WITH RELAPS/REFRACTORY ACUTE LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA.

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Abstract: The optimal treatment of relapse/refractory acute leukemias is still unclear. Complete response rates are reported between 20-80% in different patient series. However, remission duration is very short. Most common chemotherapy regimen administered in these patients is idarubicin, high dose cytosine arabinoside, fludarabin and G-CSF combination (IDA-FLAG) and is accepted as an effective treatment in these patients.

Method: In this study, we reported retrospective data of fourteen relapse refractory patients with acute lymphoblastic lymphoma (N: 4), acute myeloblastic leukemia (N: 9) and B-cell lymphoblastic lymphoma (N: 1) treated between 2006 and 2010.

Results: Characteristics of 14 patients including disease status, cytogenetic properties and WHO/ ECOG performance score are summarized in table 1. Ten of the patients were male. Median age was 43.5 years (range 21-61 years). Nine patients had relapsed and five patients had refractory disease. Four patients with ALL and one patient with B-cell lymphoblastic lymphoma had relapsed disease. Five of the patients with AML were treated for refractory disease. Cytogenetic analyses were available in ten patients. Except for one patient with complex

caryotyping anomaly, nine of the patients had normal caryotype.

Three patients had hypertension and diabetes mellitus.

Prior therapies were cytarabine and idarubicin combination (7+3) in nine patients and Hyper-CVAD in five patients. Three of the patients were relapsed after autologous hematopoietic stem cell transplantation and one relapsed after allogeneic hematopoietic stem cell transplantation.

IDA-FLAG regimen revealed complete hematological response in three patients. One of three patients with complete hematological response underwent allogeneic stem cell transplantation.

Eleven patients died. Mortality causes of eleven patients were sepsis (N: 7), disease progression (N: 2), bleeding (N: 1) and type l respiratory insufficiency (N: 1).

Overall median survival was 12.9 months (range: 6-25).

Non-hematologic toxic events associated with IDA –FLAG regimen are indicated in table 2. Four patients experienced grade l-ll infection while ten patients had grade lll-lV infection. Lungs were source of infection in four patients. One patien had oropharyngeal candidiasis. In nine patients, infection was multifocal. Isolated fungal pathogens were aspergillus fumigatus in four and candida albicans in one patient. We detected herpes simplex type l infection in four patients.

Discussion: This retrospective analyses including limited number of patients indicates that IDA-FLAG regimen is a highly toxic regimen and the rate of complete hematological remission is low. There is a great demand for alternative salvage therapeutic approaches.

Table 1.

	Gender	*Age*	*Diagnosis*	*Status*	*Cytogenetics*	*ECOG Performance score*
1	M	24	ALL	Relapse	normal	0
2	M	48	AML	Refractory	normal	0
3	M	47	AML	Relapse	NA	1
4	M	22	BLL	Relapse	NA	0
5	F	61	AML	Relapse	unfavorable	2
6	M	50	AML	Relapse	NA	2
7	F	21	ALL	Relapse	normal	1
8	F	57	AML	Relapse	normal	2
9	M	61	AML	Refractory	normal	1
10	M	34	ALL	Relapse	normal	0
11	F	47	ALL	Relapse	normal	2
12	M	36	AML	Refractory	NA	0
13	M	48	AML	Refractory	normal	1
14	M	53	AML	Refractory	normal	2

Table 2.

WHO grade	*I/II*	*III/IV*
ınfection	4 (28.6%)	10 (71.4%)
Diarrhea	4 28.6%)	
Nausea/vomiting	11 78.6%)	
Mucositis	3 (21.4%)	5 (35.7%)
Bilirubin	5 (35.7%)	
AST/ALT	5 (35.7%)	
Bleeding	2 (14.3%)	2 (14.3%)
Skin	2 (14.3%)	
Renal	4 (28.6%)	
Neuroxicity	1 (7.1%)	

NON-HODGKIN'S LYMPHOMA

P055 *ID: 86*

RADIOTHERAPY RESULTS FOR 36 ADULT NONHODGKIN LYMPHOMA PATIENTS

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Introduction: Although non-hodgkin's lymphoma (NHL) is very heterogeneous group of lymphoid system malignancies, our knowledge and ability is increasing dramatically to treat these patients for the last decade. To see our treatment results for adult patinets with NHL, we retrospectively reviewed our records of radiotherapy.

Methods: The results of treatment in 36 consecutive patients with NHL clinical stage I to IV were analysed. 24 (67%) male and 12 (33%) female patients with the median age at diagnosis 50 years-old (range;23-79) was evaluated. Pathological analysis had concluded that of 36 patients, 70% were diffuse large B cell lymphoma, 10% were marginal zone lymphoma, 7% were anaplastic large cell lymphoma, 7% were follicular lymphoma, 3% were lymphoplasmocytic lymphoma and 3% were small lymphocytic lymphoma. Totally 9% was Tcell and 91% was B cell lymphoma.According to Ann Arbour Staging System 24% of the patients had stage I, 39,4% had stage II, 18,2% had stage III and 18,2% had stage IV disease. 14 (39%) patients had bulky sites (cervikal,axillary, inguinal, mediastinal, abdominal lymph nodes and massive splen involvement)initially.14 (39%) patients had extranodal involvement (5 had bone involvement, others were: 2 thyroid, 2 nasopharynx,1 orbita, 1 chest wall, 1 liver, 1 gastric,1 testis and lung).

31 (86%) patients received 2 to 9 (median 6) cures chemotherapy.26 patients' chemoterapy regimens had included rituximab.Most common regimen was R-CHOP. All of the patients received involved field radiotherapy between April 2005 an November 2010. Radiotherapy was given either to bulky site or residual disease after chemotherapy or as a primary therapy. Median radiotherapy dose was 36 Gy (range;20-44 Gy).

Results:Median follow up time was 23 months (range; 2 to 72 months).22 (61%) patients were evaluated as disease free and alive for the last control.3 years over-

all and disease free survival rates were 89,7% and 63,5%,respectively.

Conclusion: Our results were similar with literature. Rituximab had been included 84% of the chemotherapy regimens and all patients had involved field radiotherapy which is less toxic than extended field.So we think these can lead to better results than past decades.

P056 *ID: 87*

SHORT TERM RADIOTHERAPY OUTCOMES FOR PATIENTS WITH GASTRIC MUCOSA ASSOCIATED LYMPHOID TISSUE LYMPHOMA

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Introduction:Marginal zone lymphoma is now recognized as a different subtype of non-hodgkin's lymphoma(NHL) in the WHO classification,accounting for 10% of NHL cases.The most common site of mucosa associated lymhoid tissue lymhoma is the stomach and localised gatric MALT lymphoma generally has a favorable prognoses.Over the last two decades the therapeutic approach to gastric MALT lymphoma has completely changed in favour of stomach preserving therapies like Helicobacter pylori eradication therapies and radiation rather than surgery.To investigate our treatment outcome of gastric MALT lymphoma cases we retrospectively reviewed the radiotherapy or chemotherapy plus radiotherapy outcomes of 7 patients.

Methods: Between December 2005 and February 2010, 9 patients with gastric MALT lymphoma were given radiotherapy with therapeutic aim in our institution. Because we have not follow up records of two, this report focuses on seven patients.

Results: 4 men and 3 women with stage IE to 4 (IE:3 patients; 2E:2 patients; 3E:1 patient; 4:1 patient) were analyzed.All of them received 3600 cGy (range; 3000-4600 cGy) raditherapy to gastric site and most surrounding lymphatics.Conformal treatment planning were used for 3 of them. Also one patient with paraaortic nodal involvement and other one with splenic and upper mediastinal involvement received involved field radiotherapy to these sites.

Radiation therapy alone was conducted as a second line therapy after antibiotics for 1 patient; after CHOP (Cyclophosphamide, doxorubicine, vincristine and prednisone) chemotherapy for 4 patients; and as a sole treatment for 2.Median chemotherapy cure was 6 cycles (range;5 to 8) and 2 of them received rituximab (6 and 8 cures) in addition to CHOP.

While five patients were followed up with regular endoscopy in addition to computed tomography (CT), remaining two were followed with CT and ultrasonography.The median follow up period was 15 months (range; 6-57 months). All of the patients achieved complete response clinically and alive at the last control with no serious acute (only grade I - II upper gastrointestinal) or chronic side effects reported.

Conclusion: Patients with gastric MALT lymphoma have excellent clinical outcome after radiotherapy for organ preserving approach as described with previous studies.

CHRONIC LYMPHOCYTIC LEUKEMIA

P057 *ID: 88*

A CASE OF AGRESSIVE T-CELL CHRONIC LYMPOCYTIC LEUKEMIA PRESENTING WITH SKIN INVOLVEMENT

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Cuteneosus T-cell lymphomas are suspected if skin involvement is extensive. Differentiation from CLL is made by identifying the convoluted nuclei and hepler T cells (with immunohistochemistry and flow cytometry) that are characteristic of this disease.

We report a case of rare in the literature and on August 2009 Department of Hematology Clinic, T-CLL in the course of the clinical features of skin involvement was to identify.

Case Report: 51 year-old, woman in face and neck redness and swelling at the external audits carried out during the application was referred to Clinic Department of Hematology white blood cell count. The first evaluation of patients admitted to our center, didn' t weight loss, night sweats, decreased appetite, fever, such as B symptoms. In the history of the patient with diabetes mellitus (DM), hypertension, osteoporosis, epilepsy, facial paralysis after surgery had a history of meningioma. Family history of DM in the mother, the father had heart failure. Physical examination revealed widespread over the entire body, thick scaly, erythematous, hard-edged, itchy skin lesions there and didn't hepatosplenomegaly or lymphadenopathy (LAP). In laboratory tests, WBC: 82900/mm^3, neutrophil: 12500/mm^3, lymphocyte: 43800/mm^3, Hgb: 13.9 g / dl, MCV: 84fL, Plt: 381.000/mm^3. Biochemical findings of examinations of liver and kidney function tests normal, lactate dehydrogenase (LDH): 582 U / L, the result is high, the viral markers were negative. The patient's peripheral blood smear lymphocytes: 80%, neutrophils: 15%, atipical lymphocytes: 4%, band: 1%, basket cells (+), platelet aggregation normal and normocytic, normochromic. The bone marrow aspiration as a result of looking mature lymphocytic cell infiltration were observed in favor of mild hypercellular bone marrow. In addition, flow cytometry of CD3: 95.6%, CD4: 94.1%, CD8: 2.9%, while CD5: 95.7%, CD19: 4%, CD20: 3.3%, CD23: CD5 positivity of 0.2% despite B-cell markers were negative. Tumor debridement of the pathological examination; atypical lymphoid cell infiltration, ulceration and granulation tissue were detected. As a result of immunohistochemical staining of the LCA, diffuse and strongly positive with CD3, CD2, CD5, CD43 and diffuse positive, CD8 sparse and scattered, the small number of cells staining with CD20 was observed. The neck tomography; 2A zone on the left at approximately 6-7 mm short axis of reaching a large number of lymph nodes was observed. The patient T-cell chronic lymphocytic leukemia (T-CLL) and T-CLL of the skin involvement was diagnosed. The patient was allopurinol and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), chemotherapy planned. The patient 3 cycles of CHOP before creating chemotherapy died.

MULTIPLE MYELOMA

P058 *ID: 89*

PRIMARY DIAGNOSE OF A MULTIPLE MYELOMA IN MANDIBLE: A CASE REPORT

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Multiple myeloma (MM) is a monoclonal malignant proliferation of plasma cells that causes osteolytic lesions in the vertebrae, ribs, pelvic bone, skull and jaw that is characterized by an almost exclusive accumulation in the bone marrow, secretion of monoclonal immunoglobulin, and a suppression of normal immunoglobulin production and hematopoiesis, especially that of the erythroid lineage.Another important clinical feature of MM is a marked stimulation of osteoclastic bone resorption, which causes the most debilitating clinical symptoms including intractable bone pain, disabling multiple fractures, and hypercalcemia. It develops mainly in men aged 50 to 80 years, with a mean of 60 years.In this study we present a rare case such as MM was first diagnosed from the mandible lesion.64 year-old man referred to our clinic with a chief complaint of swelling on his left cheek area. Intraoral examinations revealed an expantion in left molar region of mandibula. In radiological examinations, at the same region a well-defined, unilokular radiolucent lesion was seen. After biopsy, the histopathological result was plasmocytoma. According to the histopathological features of the lesion further diagnostic investigations were done. Screening of the serum electrophoresis was performed. Additionally some other lesions was detected on skull film. The final diagnosis had been established as multiple myeloma. After removal of all teeth which have a risk of causing focal infection chemotheraphy and radiotheraphy were performed to control the disease.

NON-HODGKIN'S LYMPHOMA

P059 *ID: 90*

PRIMARY B CELL LYMPHOMA WITH BONE MARROW INVOLVEMENT ACCOMPANIED BY HEMOPHAGOCYTOSIS

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Secondary involvement of malignant lymphomas in bone marrow is relatively common. However, primary occurrence of lymphomas in bone marrow is quite rare, except in chronic lymphocytic leukemia or small cell lymphoma. Large cell lymphoma with primary bone marrow involvement is exceptional, although secondary involvement is sometimes observed. Murase et al. reported the Asian variant of intravascular large B-cell lymphoma (AIVL) in which bone marrow involvement of large B lymphoma cells was frequently observed. They proposed criteria for AIVL, including clinical and laboratory criteria and histologic criteria. The former include cytopenia, hepatomegaly and/or splenomegaly, and absence of overt lymphadenopathy and tumor formation. The latter include erythrocyte hemophagocytosis, immunophenotypic evidence of neoplastic B cells, and pathologic findings of intravascular proliferation of lymphoma cells.

We are presenting a case of B-cell lymphoma manifesting itself primarily in the bone marrow with hemophagocytic syndrome.

Our patient was a 17 year-old male attended with the complaints of diffuse leg and back pain, fever, dyspnea and inability to walk. He had an history of trauma 3 months ago and after that his back pain had begun. He had become unable to walk progressively. He had diffuse myalgia and bone pain. Before attending to our hospital, he had severe dyspnea and fever. At his first visit he was septic and cachectic. He had signs of heart failure with tachypnea, tachycardia and hepatomegaly of 4 cm below costal margin. He was unable to move and extend his legs due to the severity of pain. He had pancytopenia and his biochemical findings were pointing out to hemophagocytic syndrome. There was 3% of immature cells in the bone marrow aspiration. For holding down hemophagocytosis pulse steroid and cyclosporin therapy was introduced. He had clinical improvement. Multiple lytic lesions were present at all his vertebral corpi, sternum, iliac bones and sacrum in the radiological evaluation. With repeated bone marrow aspirations and biopsy, he was diagnosed as primary lymphoma of the bone marrow by immunophenotypic and histochemical stainings. His chemothreapy protocol was planned and he was sent to his home town for getting rest of his therapy. We find our case interesting due to its being a rare disease and its having clinical similarities with intravascular large-B cell lymphoma with accompanying hemophagocytosis.

P060 *ID: 91*

PRIMARY RENAL LYMPHOMA IN A CHILD

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Primary renal lymphoma (PRL) is a rare lymphoma which usually presents with hematuria, flank pain, abdominal mass, and weight loss. It is more diagnosed in adults than children. Renal involvement is frequently seen in patients with lymphoma. However, the entity PRL is controversial and rare. The term PRL is applied when the disease is localized to the kidney without any sign of other organ involvement or in whom renal involvement is the presenting manifestation. We describe a child who presented with weakness, anorexia and mild abdominal pain and was subsequently diagnosed with primary renal lymphoma.

A fourteen year old boy presented to our Pediatric Hematology-Oncology Unit, with a 4-month history of weakness and anorexia. He had mild abdominal pain. Physical examination revealed no significant abdominal

or systemic findings. Initial laboratory testing showed high erythrocyte sedimentation rate (50 mm/h), high renal function tests (urea 134.5 mg/dL, creatinine 4.27 mg/dL) and normal urine examination. An abdominal ultrasonograhy revealed an increase in bilateral kidney sizes. Abdomen computed tomography (CT) scan showed an increase in thickness of renal parenchyma with hypodense appearance and with bilateral mild ectasia in pelvicalyceal system. An ultrasonography guided renal biopsy demonstrated precursor B-cell lymphoblastic lymphoma. Hematoxylin and eosin section of these renal masses revealed neoplastic lymphoma cells with increased nuclear-cytoplasmic ratio, prominent nucleoli, and mitotic figures. The lymphoma cells stained positive for terminal deoxynucleotidyl transferase and B-lymphocyte marker CD10 and focal CD20 immunohistochemical stain. A staging bone marrow aspiration did not show evidence of involvement. Cervical, thoraks, pelvic CT scans and bone syntigraphy were unremarkable. He was diagnosed as non-Hodgkin's lymphoma (NHL), pre B-cell type and was treated with multidrug chemotherapy and prophylactic intrathecal methotrexate according to British-French-Munster (BFM) protocol. After the initial therapy, renal function tests were ameliorated rapidly and during consolidation and maintenance chemotherapy, they continued as normal. He is still in complete remission and was followed regularly in the second year after diagnosis.

It is difficult to diagnose primary renal lymphoma. Delayed diagnosis and the histological aggressive characteristics of this disease are responsible for the poor outcome. Early diagnosis and urgent therapy, with supporting therapy are necessary for good prognosis.

ACUTE LYMPHOBLASTIC LEUKEMIA

P061 *ID: 93*

THE DEVELOPMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH GAUCHER DISEASE AFTER ENZYME REPLACEMENT THERAPY

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Gaucher disease is a lysosomal storage disorder resulting because of the deficiency of an enzyme, glucoserebrocidase. The most prominent symptoms are those related to pancytopenia. Cytopenia is related to hypersplenism and/or infiltration of bone marrow with Gaucher cells. Here we present a case developing acute lymphoblastic leukemia after enzyme replacement therapy (ERT). A 37 year-old-female patient was admitted to the hospital with abdominal pain fourteen years ago. She had massive splenomegaly, pancytopenia and diagnosed as Gaucher's disease in our hospital. She could start to recombinant human Glu Cer enzyme therapy at the tenth year of her diagnosis. Pancytopenia was revealed and spleen size was reduced partially. At the follow up, she complained about nasal bleeding and weakness.Laboratory examination revealed trombocytopenia, anemia and lymphocytosis. On the peripheral blood smear, lymphoblasts were detected and after bone marrow examination the patient was diagnosed as pre-B ALL Her WBC at diagnosis was 7 x10e3/UL and conventional cytogenetic examination was 46 XX der (3)(1)/46 XX,t(1,19)(q23,p13)(2),/42-44 XX -10(3)/46 XX (13). The patient was treated with modified Linker protocol (J Clin Oncol 20:2464-2471) with six cycles. Because of persistant trombocytopenia and anemia bone marrow was examined; Gaucher was determined but ALL was in remission. Because of official problems she could not be treated with enzyme therapy again and she undergone a splenectomy operation 7 months after the last chemotherapy. We still follow the patient in hematological remission with a normal complete blood count.

Enzyme replacement therapy is the standard of treatment but it is unknown if it has a role in malignancy development.

NON-HODGKIN'S LYMPHOMA

P064 *ID: 98*

DISSEMINATED INTRAVASCULAR COAGULATION INT CELL LARGE GRANULAR LYMPHOMA AT DIAGNOSIS: A RARE PRESENTATION

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The WHO classification has three distinct disorders of large granular lymphocytes: T-cell large granular lymphocytic leukemia (T-LGL), chronic lymphoproliferative disorders of NK-cells (CLPD-NK) and agressive NK-cell leukemia. T-LGL leukemia is often asymptomatic and up to half of patients may not require therapy. Treatment is generally indicated for patients with symptomatic cytopenias. We here present a rare case with DIC prior to diagnosis of T-LGL. A 34 year-old-male patient was hospitalized in the emergency rooms of different hospitals with febrile neutropenia for three times in two years. He was admitted to our unit with fever and weakness. Complete blood count signified pancytopenia with lymphocytosis. Protrombin time, activated partial tromboplastine time were prolonged and D dimer was increased. Mature lymphocytosis and fragmented erytrocytes were determined on the peripheral blood smear. Antibiotic therapy and plasmapheresis was started with diagnosis of disseminated intravascular coagulation (DIC) Acinetobacter baumanii and Coagulase negative Staphilacoccus auereus was shown in blood stream cultures. Flow cytometric examination of his bone marrow (BM) aspiration was consistent with 90% infiltration of T cells, 41% of these cells were large granular cells with TCR alpha/beta positive in 97%. Diffuse interstitial T lymphoid cell infiltration (CD3-/CD4-/CD8+/CD16dim/CD56-/CD57+), grade 3 was determined in bone marrow biopsy. Cytogenetic and molecular examination of the BM revealed clonally abnormality, including t(2,7),der(3),der(10),der(16),der(17),der(21) and TCR beta clonally gene rearrangement. CHOP21 chemotherapy was initiated for treatment of T cell LGL. After the first cycle of chemotherapy the patient's clinical status and laboratory finding improved but recurred before the second cycle. Therefore, we gave CHOP14 therapy. The patient was treated with 3 more cycles of CHOP14, deteriorations of clinical and laboratory finding did not recur. Besides the clonally LGL infil-

tration significantly reduced after the 4th cycle of the chemotherapy.

Majority of patients with T-LGL have no symptoms at diagnosis. Systemic features are less common and less severe than NK-cell type. Therefore, approaches of treatment should be like those for aggressive form of high grade non-Hodgkin lymphoma.

HODGKIN'S LYMPHOMA

P065 *ID: 99*

FOLLICULAR HYPERPLASIA OF THE LYMPH NODE MISDIAGNOSED AS HODGKIN'S LYMPHOMA BY FINE NEEDLE ASPIRATION: A CASE REPORT

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Background: The cytodiagnosis of Hodgkin's lymphoma (HL) is based on demonstration of Hodgkin's cells or Reed-Sternberg (RS) cells, or both, among the appropriate reactive cellular components. Reactive components, such as eosinophils, plasma cells and benign histiocytes, are also present and may be misleading when making differential diagnosis. Overall diagnostic accuracy of fine needle aspiration (FNA) in cases of all types of lymphoma varies between 80% and 90%. False-positive and false-negative results can be encountered on FNA diagnosis of lymphadenopathy, and excisional biopsy of the lymph node from the appropriate site should be performed following the cytodiagnostic decision. FNA diagnosis of HL may be false-positive owing to the similarity of Hodgkin's reactive background with benign process. One should carefully look for RS cells to diagnose HL, and keep in mind that many nonneoplastic RS-like cells are present related with benign conditions.

Case Report: A 55 year-old female presented with cervical mass and a FNA was performed resulting in the diagnosis of HL. Examination of the cytologic material revealed lymphoid cells at varying stages of maturation, plasma cells, histiocytes, and atypical cells consistent with Hodgkin's and RS cells. The patient underwent an excisional biopsy. Histologic examination of the biopsy material showed follicular hyperplasia with enlarged germinal centers. Paracortical hyperplasia was also prominent. Subcapsular and medullary sinuses were open. There was an area with fibrosis and capillary proliferation representing the prior FNA site. There were no RS cells and only scattered mononuclear centroblast-like cells were stained positive with CD30 antibody. CD15 staining was negative. There were plasma cells and a few eosinophils which could be the elements responsible for the misleading thought as an appropriate background consistent with HL on cytologic evaluation. The cytologic and histopathologic evaluation were first made at two different outside pathology laboratories, and then both of them were consulted to our pathology laboratory and the diagnosis of follicular hyperplasia was confirmed.

Result: FNA diagnosis of the lymph nodes can be misleading, and should always be accompanied by an excisional lymph node biopsy. FNA and histology are not competitive but complementary to each other in the diagnosis of a case of lymphadenopathy. FNA diagnosis alone may cause misdiagnosis of the patient especially when the clinical preliminary diagnosis is lymphoma. Even the experienced cytopathologists can make misdiagnoses and cytodiagnostic decision of lymphoma should suggest an excisional biopsy from an appropriate lymph node in order to confirm the diagnosis.

NON-HODGKIN'S LYMPHOMA

P066 *ID: 100*

HIGH GRADE PROSTATIC CARCINOMA METASTATIC TO CERVICAL LYMPH NODE MISDIAGNOSED AS LYMPHOMA: A CASE REPORT

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Background: Poorly differentiated carcinoma can easily be misdiagnosed as high grade lymphoma if the histologic examination is made solely on morphologic grounds without using immunohistochemistry. It is extremely probable if the lymphadenopathy is of cervical location, and the clinical preliminary diagnosis is lymphoma. Prostate carcinoma is one of the most frequent cancers in men. Cervical lymphadenopathy and metastasis are uncommon and signify advanced disease. Adenocarcinoma of the prostate can present with metastatic disease of unknown origin and in patients with a known primary prostatic carcinoma, metastases require confirmation of prostatic origin of poorly differentiated tumors. This is most often achieved by immunohistochemistry for Prostate Spesific Antigen (PSA), which is a sensitive and spesific marker of prostatic differentiation, and is positive in the big majority of prostatic adenocarcinomas. Lymphoid markers should also be included in the immunohistochemical panel if the tumor is poorly differentiated. Within the differential diagnosis of the cervical lymphadenopathy in adult men, prostatic carcinoma should be considered and immunohistochemical studies should be performed in order to avoid misdiagnoses like lymphoma in poorly differentiated cases.

Case report: A 78 year-old male patient with a 10 years previously diagnosed prostatic adenocarcinoma and treated by bilateral orchiectomy presented with cervical lymphadenopathy. Pathologic examination was performed at an outside pathology laboratory and the lymph node was diagnosed as having lymphoma infiltration consistent with diffuse large cell lymphoma. Then, a second opinion was obtained from another outside pathology laboratory and it was reported as malignant neoplasm in which neoplastic cells were negative with lymphoid and epithelial immunohistochemical markers. Finally, the paraffine blocks of the specimen was consulted to our pathology laboratory in need of third opinion, and a definitive diagnosis. Histologic examination of the consulted material revealed neoplastic epithelial tissue replacing the entire lymph node, with a solid and cribriform infiltrating pattern. Neoplastic cells showed Cytokeratin and PSA positivity, while EMA and LCA were negative. Final diagnosis was poorly differentiated prosttaic carcinoma metastatic to cervical lymph node.

Conclusion: Although metastases to the cervical lymph nodes are rare in prostate cancer, it should be

considered in the differential diagnosis of elderly men with cervical lymph node metastases, and distinguished from malignant lymphoma and other malignancies. The current report emphasises the need for a pathologic examination by an experienced pathologist. It also underlines the significant role of medical history and immunohistochemical studies including appropriate antibodies in the differential diagnosis of metastatic carcinoma of undetermined origin in cervical lymph nodes.

P067 *ID: 101*

PERIPHERAL T CELL LYMPHOMA MISDIAGNOSED AS LANGERHANS CELL HISTIOCYTOSIS: A CASE REPORT

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Background: Misdiagnosis of peripheral T cell lymphoma (PTCL) is frequently observed, because of the lesions' demonstrating marked heterogeneity. Generally, a spectrum of lymphoid cells is evident, and these lymphoid cells exhibit various degrees of nuclear complexity. Histiocytes, eosinophils, and plasma cells may be prominent. Langerhans Cell Histiocytosis (LCH) is not usually considered in the differential diagnosis of PTCL because of its characteristic morphology. The histologic hallmark of LCH is the presence of proliferating Langerhans cells in the appropriate cellular milieu. Careful examination of the H&E stained sections by experienced hematopathologists and using an appropriate set of antibodies for immunohistochemical studies are essential in making a correct diagnosis in neoplastic hematopathology.

Case Report: A 75 year-old male patient with a 7 years history of Non-Hodgkin's Lymphoma presented with right inguinal lymphadenopathy. He had been evaluated as stage IA and complete cure had been achieved by radiotheraphy. 2 years after the initial diagnosis, the patient underwent right hemicolectomy with the diagnosis of lymphoma involving ileocecal region, but neither the pathology report, nor the paraffin blocks of the specimen could be obtained. During the follow-up, he was healthy until a mass was encountered in the right inguinal region 5 years after the hemicolectomy. Excisional biopsy of the inguinal lymph node was first evaluated at an outside private pathology laboratory, but it was not diagnostic because of extensive necrosis. A second excisional biopsy was performed after 10 months and sent to another private pathology laboratory which resulted in the diagnosis of LCH. A second opinion was needed because of the discordance of the patient's primary lymphoma diagnosis, and the diagnosis given by that laboratory, so the paraffin blocks were consulted to our pathology laboratory. Sections from the consulted paraffin blocks revealed a neoplastic lymphoid tissue with polymorphic appearance and atypical cells with CD2 and CD3 positivity. Neoplastic cells were focally positive for CD43 and CD4, and negative for CD8, Granzyme B, CD20, CD79a, TdT, CD10, Bcl-6 and CD30. There were many histiocytes and eosinophilic leukocytes accompanying neoplastic cells. The histiocytes were positive with CD68, and negative with S-100 and CD1a. The final diagnosis was PTCL, not otherwise specified.

Result: The distiction between PTCL and LHH can be difficult in rare cases. Morphology remains the keystone of lymphoma diagnosis and the production of a well handled, high quality H&E section remains the single most important element of accurate lymphoma diagnosis. An immunohistochemical study including appropriate antibodies should accompany to morphologic evaluation. Biopsy of suspicious adenopathy should be reviewed by an experienced hematopathologist.

MOLECULAR HEMATOLOGY – CYTOGENETICS

P068 *ID: 102*

EXPRESSION OF CHEMOKINE RECEPTORS CCR1 AND CCR2 IN CD10+ B-CELL LINES AND IN CD10+ PERIPHERAL BLOOD B-CELLS OF PATIENTS WITH B-CELL LYMPHOPROLIFERATIVE DISORDERS

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Chemokines - chemokine receptors (CRs) signal transduction network controls the proper function of the immune system. Previously we have identified the cluster of CR genes that includes CCR1 and CCR2, on human 3p21.31 within the malignancy-related chromosome instability region (MCIR). Genes within MCIR are often silenced in cancer cells by DNA rearrangements and/or by epigenetic mechanisms (methylation). This 3p21.3 region was the most frequently deleted (LOH was detected in 83% of informative cases) in human solid tumors from different tissues (576 tumors from 10 tissues were analyzed) (Petursdottir et al., 2004). EBV is associated with endemic Burkitt's lymphoma (BL) and post-transplant lymphoproliferative disease. EBV infection leads to B-cell activation and transformation. Upon infection viral proteins induce interferon pathway, cell-surface adhesion molecules, activation antigens, chemokines and CRs (CCR6, CCR10, and CCR7).

The aim of this study was to examine expression of CCR1 and CCR2 in long-time cultivated CD10+ B-cell lines both, EBV-negative (EBV−) and EBV-positive (EBV+), and also in peripheral blood (PB) circulating CD10+ B-cell sub-population of primary patients (prior specified diagnosis and treatment) with B-cell lymphoproliferative disorder (LPD).

Methods. Twenty three B-cell lines (18 BLs (11 EBV+ and 7 EBV−), 3 PB B-cell lymphomas (BcL), and 2 diffuse histiocytic lymphomas (DHL)) were assayed by duplex RT-PCR for CRs (CCR1, CCR2, CCR5) from 3p21.31 region, CXCR4, CD markers (CD10, CD30, CD34, CD38, CD77), and EBV genes (EBNA1, EBNA2, LMP1) as well. Eleven cell lines (all BL) that transcribed CCR1 (among them 7 transcribed also CCR2), and PB of 8 patients were analyzed by polychromatic flow cytometry (FC) (by BD FACSAriaII), using monoclonal antibodies CD19-PerCP-Cy5.5, CD10-PE, CD191-Alexa-Fluor647 and CD192-Alexa-Fluor647.

Results. All cell lines were negative for CD34 and CCR5 transcripts, and were positive for CXCR4 transcript. In all 12 EBV− cell lines CCR2 transcript was not found, but CCR1 transcript was detected in two. On the contrary, among 11 EBV+ cell lines seven were CCR2-transcript positive and nine were CCR1-transcript positive. Notably that by polychromatic FC CCR2 was only found in about 10% of cells in 3 EBV+ cell lines, but CCR1 was present in the range of 4 – 36% in 9 out of the 11 EBV+ and in the range of 6 – 10% in two EBV− cell lines. In 8 samples of primary patients with CD10+ B-cell LPD CCR1 and CCR2 were observed on PB circulating CD10+ B-cell sub-population in the range of 98 – 100% and 76 – 99% respectively.

Conclusion. Our results tentatively suggest that the lack of CCR2 in PB circulating CD10+ B-cell sub-population might be associated with progression of immature B-cell malignancy. Obviously, further extensive studies are necessary for the verification of our hypothesis.

Petursdottir et al., Genes Chromosomes Cancer, 2004; 41:232-242.

MULTIPLE MYELOMA

P069 *ID: 106*

ZOLEDRONIC ACID (ZOL) AND THALIDOMIDE (THAL) COMBINATIONS IMPROVED OVERALL SURVIVAL (OS) AND BONE ENDPOINTS IN THE MRC MYELOMA IX TRIAL: OPTIMISING BISPHOSPHONATE (BP) AND ANTIMYELOMA THERAPIES

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Objectives: MRC Myeloma IX (N=1,960) included intensive and non-intensive pathways and 2 BPs (ZOL and clodronate [CLO]) in patients (pts) with newly diagnosed multiple myeloma (MM). Both OS and SREs were evaluated in the context of BPs and a Thal, alkylating agent, and steroid induction regimen; and maintenance Thal. We previously reported that ZOL significantly improves OS and PFS and reduces SREs (Morgan et al. Lancet. 2010), and Thal-containing induction regimens and maintenance are superior for OS (Morgan et al. ASH 2009, #352).

Methods: The intensive pathway randomized pts to CVAD (Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone [Dex]) or CTD (Cyclophosphamide, Thal, Dex) as induction, followed by high-dose Melphalan and ASCT. The non-intensive pathway randomized pts to Melphalan and Prednisolone (MP) or attenuated CTD (CTDa). Each group also was randomized to ZOL (4mg IV q3-4wk, dosed per renal function) or CLO (1600 mg/d) continued at least until disease progression. After induction in both pathways, a second randomisation to maintenance Thal or no maintenance was performed. Endpoints included progression-free survival (PFS), OS, and response. SREs include fractures, spinal cord compression, radiation or surgery to bone, and new osteolytic lesions. Time to 1st SRE was assessed using cumulative incidence function, and OS estimated by Kaplan-Meier. Cox analysis was used for hazard ratios (HR) and 95‰ CI for SRE risk, adjusting for regimen, minimisation factors, and SRE history at baseline.

Results: At 3.7 yr median follow-up, SRE risk was significantly reduced with ZOL vs CLO (HR=0.74, P=.0004) and with CTDa vs MP (HR=0.74, P=.021), but was similar for CTD vs CVAD (HR=1.03; P=.80). In the intensive pathway (n = 1,111; median age, 59), CR or VGPR was achieved by 43‰ of pts with CTD vs 28‰ with CVAD; OS and PFS were slightly better for ZOL vs CLO, although statistical power was low (OS: HR=0.84; 95% CI, 0.68-1.03; PFS: HR=0.90; 95‰ CI, 0.78-1.05; P>.05 for both). In both the CVAD and CTD arms, fewer ZOL- vs CLO-treated pts had SREs (28‰ vs 36‰; log-rank P=.034). In the nonintensive pathway (n = 849; median age, 73), pts randomized to CTDa had higher CR (13‰ vs 2‰; P<.0001) and CR/VGPR rates (30‰ vs 4‰; P<.0001) vs MP; ZOL had higher rates of CR/VGPR vs CLO (MP: 6‰ vs 2‰; CTDa: 34‰ vs 26‰, respectively; P=.03 overall), reduced risk of death by 17‰ (HR=0.83; P=.049), and prolonged time to first SRE vs CLO (P=.008, consistent in both MP and CTDa groups). Time to first SRE was also significantly longer for CTDa vs MP (P=.021). The impact of achieving a CR and of CTDa vs MP on SREs appeared to be correlated. In the maintenance randomization (n=820), ZOL also significantly reduced SREs vs CLO.

Conclusions: MM pts receiving regimens containing Thal and ZOL had better responses/survival and lower SRE risk.

NON-HODGKIN'S LYMPHOMA

P070 *ID: 107*

FOLLICULAR LYMPHOMA OF THE ORBIT PRESENTING WITH BILATERAL PTOSIS AND PROPTOSIS

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Introduction: Lymphomas constitute 10-15% of all tumors and 55% of malign tumors in the ocular region. An increase in the incidence of non-Hodgkin orbital lymphomas has been observed over the last three decades. Case: 72-year-old woman was admitted to our internal medicine department for bilateral ptosis, eyelid swelling and painless proptosis in June 2004 (Figure 1). She complained of eyelid swelling, which had been present for one year and progressed in the past few months despite non-specific therapy applied at another hospital. Physical examination of the patient revealed multiple cervical, inguinal and axillary lymphadenopathies. A previous USG of the patient had reported dense infiltrations of the conjunctivae, eyelids and retrobulbar portions of both orbits. An orbital NMR performed for further analysis was suggestive of orbital lymphoma or metastasis. Further studies revealed additional lymphadenopathies in the precarinal, aorticopulmonary and external iliac regions. Cervical ganglionic biopsy lead to the diagnosis of grade II follicular lymphoma with expression of CD20 and Bcl-2. With the diagnosis of stage IV follicular lymphoma, COP (cyclophosphamide, vincristine,

and prednisolone) chemotherapy protocol was initiated. Following two courses of chemotherapy, eyelid swelling disappeared to be followed by complete remission after completion of six courses. The patient has been stable and free of symptoms for the past six years.Conclusion: Lymphoma, the most common type of primary malignant orbital tumor,usually presents with extraorbital involvement. MALT is the most common type. The treatment is succesfull in most cases. The recognition of this highly prevalent and treatable neoplasm is crucial for the opthalmologist, often being the first physician to be confronted with these patients. Published series have demonstrated that a significant majority of orbital lymphomas (91%) initially present with ophthalmologic findings: pink conjunctival masses or hyperemia in 32% of patients, exophthalmos in 27%, palpable or orbitary mass in 19%, reduction in visual acuity and ptosis in 6% and diplopia in 2% of patients. There is a mean delay-interval of 4 to 6 months from the onset of symptoms to the time of actual diagnosis. In our case, this interval was one year. Lymphoid proliferations in the ocular region are more common in females than males (1.75/1) and can occur at any age, being more frequent in the fifth or seventh decade. Our patient was 72 at the time of diagnosis. 10-17% of patients with orbital lymphoma have bilateral orbital involvement, which presents simultaneuosly in 80% and subsequently in 20% of cases. Described herein is a case of follicular lymphoma presenting with bilateral ptosis, lid swelling and proptosis with concurrent extraorbital involvement. Recent studies have observed an increased prevalence of orbitary non-Hodgkin lymphomas and therefore it is important to identify this curable entity to avoid it going unnoticed.

The image of the patient with orbitary lymphoma

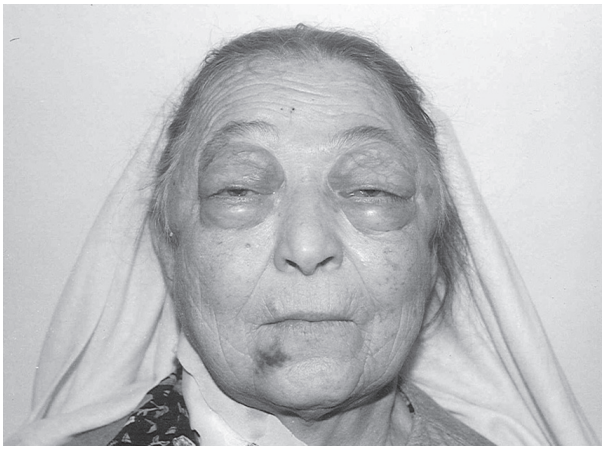

Figure 1. Bilateral ptosis, eyelid swelling and painless proptosis secondary to orbitary lymphoma.

P071 *ID: 109*

CLINICAL CHARACTHERISTICS AND TREATMENT RESULTS OF 173 NON-HODGKIN LYMPHOMA PATIENTS

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The demographic, clinical features and treatment modalities of one hundred seventy three consecutive patients with non-hodgkin lymphoma diagnosed between September 2004 and October 2010 in Izmir Ataturk Training and Research Hospital, Hematology clinic were evaluated retrospectively. The M/F ratio was 100/73 with a median age of 58 years. Median follow-up time was 29±22.5 months (1-122). 49.1% of all NHL was presented as extranodal form. The most common extranodal site was gastrointestinal tract (16.4%). At the diagnosis, 57 patients (32.9%) were in stage I, 39 patients (22.5%) in stage II, 28 patients (16.2%) in stage III and 49 patients (28.3%) in stage IV according to Ann Arbor staging system. The 5-year survival ratio was 71.5% for all type NHL patients. The relapsed free survival was 22±21.5 (1-122) months. The mean survival time for all type of NHL patients was 95.5 ±4.9 months (median OS time was not reached). The mostly seen histological form was diffuse large B cell lymphoma (DLBCL) (77.5%, n=134 patients). The median age of DLBCL patients was 58±16.2 with M/F ratio as 77/57. At the end of follow up time, 82% of patients were alive. The 5-year survival ratio was 83%. The overall survival rate of the patients with low and low-intermediate ınternational prognostic index was higher than others (p<0.0001).

The charactheristics of our NHL patients and treatment outcomes were similar with the literature.

ACUTE LYMPHOBLASTIC LEUKEMIA

P072 *ID: 111*

TREATMENT OF ADOLESCENTS AND YOUNG ADULTS WITH ALL: COG EXPERIENCE IN A SINGLE CENTER

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Background: The prognosis of acute lymphoblastic leukemia (ALL) in adolescents and young adults (AYA) is poorer than in children. Recently, there has been an increasing interest in the treatment of AYA with ALL because new reports show that these patients have a better outcome when treated with pediatric rather than adult therapeutic protocols. Here we present the treatment results of AYA with ALL in a pediatric center in Turkey.

Design and Methods: Thirteen patients (4 girls, 9 boys) aged 15–24 years (median 17.4 years) diagnosed with ALL and treated by AALL 0232 COG protocol during 2003-2010 were included. We characterized the biological subtypes, clinical features and outcome of these patients.

Results: In the whole group, 3 patients had T-cell ALL, 7 precursor B-cell and 3 had myeloid marker positive ALL. A translocation was not detected in any patient. Two patients presented after bone-marrow and testicular relapse (late relapse, more than 10 years). Four of 13 patients were SER (slow early responders). One patient relapsed on follow-up during maintenance but this patient had myeloid marker positive ALL and left treatment after delayed intensification. Most of the patients had toxicity due to treatment; 1 patient had hepatitis B infection and hemophagocytosis, 2 had severe pancreatitis and 1 of them required parsial pancreatetectomy, 2 had venous thrombosis, 2 had diabetes mellitus during induction period, 1 stayed in ICU due to severe invasive fungal infection for 2 weeks, 1 had convulsion due to hypertension and 1 had hepatitis related to chronic hepatitis B infection. One patient had PEG-asparaginase allergy. All patients are alive and treatment has been stopped in 6 of them who are in full remission of a

median time of 50 months (33-86 months). Four patients are on maintenance treatment and are in remission for a median of 15 months (8-24 months). Two patients are on interim maintenance and are also in full remission. Only 1 patient is still on reinduction treatment after relapse.

Conclusions: ALL in AYA is a rare disease and its biology is ill-defined. The survival rate of children with ALL has improved during the past decades however, the outcome of adult ALL

remains in the range of 35-50%. On the other hand, AYA patients have a good prognosis with Pediatric protocols. Progress in treatment of these patients may only be possible with decreased toxicity, increased efficacy and quality of cure and aftercare.

CHRONIC LYMPHOCYTIC LEUKEMIA

P073 *ID: 113*

THE REAPPEARANCE OF 11Q DELETION WITH COMPLEX KARYOTYPE IN A RARE CASE OF RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA MANIFESTING WITH EXTENSIVE NODAL INVOLVEMENT, LYTIC BONE LESIONS AND MALIGNANT HYPERCALCEMIA

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Introduction:In chronic lymphocytic leukemia (CLL),del(17p13) as a sole abnormality has a median survival 2 to 3 years compared to 6 to 7 years del(11q22),9 years for trisomy 12 or normal karyotype,and 11 years for del 13q14. More than 25% of patients acquire new cytogenetic abnormalities (ie, karyotype evolution).In presence of (17p13) or del(11q22),karyotype evolution is associated with short survival with a median of 1.3 years.Case:A 30-year-old woman referred with generalized peripheral lymphadenopathy, bulky intrathoracic and intraabdominal lymphadenopathies and massive splenomegaly in the presence of B symptoms.Bone marrow and cervical ganglionic biopsies were consistent with CLL. Blood counts revealed anemia,thrombocytopenia and a leukocyte count of 13100/mm^3 with 82% mature appearing lymphocytes.Because of aggressive presentation, the patient was treated as having blastic transformation with acute lymphoblastic leukemia remission induction regimen. BFM followed by hyper-CVAD achieved no response.Bone marrow cytogenetic analysis revealed del(11)(q13q23).The diagnosis was established as CLL (Rai stage IV). Chemoimmunotherapy with R-FC induced complete hematologic and cytogenetic remission and was completed to six courses. No matched related and unrelated donors were found. For follow-up monitoring, FISH analysis was performed on peripheral blood samples which remained negative until 27th month of initial diagnosis. At that time, the patient presented with severe back pain.Blood count was normal and there was severe hypercalcemia.MRI demonstrated reapperance of multiple intraabdominal lymphadenopathies and splenomegaly accompanied by multiple osteolytic lesions,the largest lesions on T9 vertebral body (picture 1)and right femur.Bone marrow examination was consistent with CLL and conventional karyogram detected a complex karyotype with 43-44,X,-X, der(8q),der(9p),-8,-9,-10,11q-,der(12q),der(12q),+mar cp(16).Reconstructive surgery was performed for the right intertrochanteric femoral fracture whose pathologic examination showed CLL infiltration; Richter transformation was excluded.Radiotherapy and bisphosphonate infusion were given followed by R-FC. Donor screening was updated.At present,the patient has stable disease state. Conclusion:11q deletion is characterized by advanced and progressive disease; younger patient age; extensive peripheral,abdominal,and mediastinal lymphadenopathy; shorter time from diagnosis to treatment; and shorter survival, at least in patients younger than 55 years.Described herein is a young CLL patient with 11q deletion,who had relapsed aggressively with reapperance of 11q deletion and karyotype evolution.Our case emphasizes the association of karyotype evolution in presence of 11q deletion in CLL with aggressive clinical progress and, poor prognosis. Further documentation of del(11q22) in CLL will enable a more accurate evaluation of the influence of this cytogenetic abnormality on clinical course of the disease.

Vertebrae-MRI.

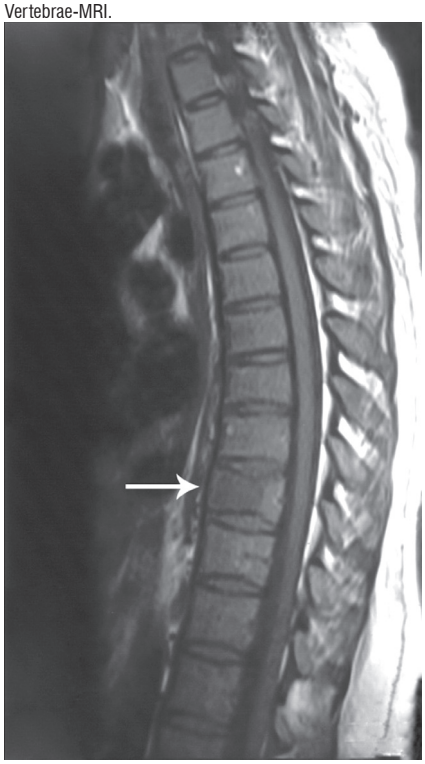

Figure 1. A lytic lesion on the T9 vertebral body *(marked with arrow).*

ACUTE LYMPHOBLASTIC LEUKEMIA

P074 *ID: 114*

COMPARISON OF TWO DIFFERENT INDUCTION REGIMENS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Despite therapeutic advances, there is no standart induction regimen in adult patient with Ph negative acute lymphoblastic leukemia (ALL). In this retrospective study, we aimed to compare two different induction regimens. Between June 2006-June 2010, we evaluated 25 patient (13 Females/12 Males) with pre-B ALL. Median age was 32 years (17-60 years). Fifteen patients received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) (Cancer. 2004 Dec 15;101(12):2788-801) and 10 patients were treated with Modified Linker regimen ((J Clin Oncol 20:2464-2471). The patients' age and gender were comparable (Table) Remission rate was higher in Linker group than HyperCVAD (p=0.125), but statistically not significant. The relapse ratio was similar between the groups (p=0.890). In hyperCVAD group, more patients underwent allogeneic hematopoetic cell transplantation (Allo-HCT) after first/second complete remission or refractory disease compared to Linker group (p=0.018). The probability of two-year disease-free survival (DFS) and overall survival (OS) were not affected by the induction regimens (Table). In conclusion, comparison of HyperCVAD with Modified Linker regimen, no superiority was found. Therefore, randomized prospective studies including large number of patient should be planned in treatment of adult ALL patients.

Table 1.

	HyperCVAD	*Linker*	*p*
Age, years (Range)	35 (17-60)	32 (18-56)	0.643
Gender, M/F	8/7	4/6	0.688
Remission rate	11/15 (73.3%)	10/10 (100%)	0.125
Relapse ratio	3/11 (27.3%)	3/10 (30%)	0.890
Allo-HCT	11/15 (73.3%)	3/10 (30%)	0.032
2-year DFS	33.3±12.2%	48.2±18.8%	0.200
2-year OS	40.0±12.6%	62.5±17.1%	0.329

MULTIPLE MYELOMA

P075 *ID: 115*

SKELETAL-RELATED EVENTS (SRES) IN THE MEDICAL RESEARCH COUNCIL (MRC) MYELOMA IX STUDY: ZOLEDRONIC ACID (ZOL) IS SUPERIOR TO CLODRONATE (CLO) IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (MM)

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Objectives: Use of bisphosphonates for the prevention of SREs is a standard of care in MM. Both ZOL and CLO are approved for the prevention of SREs in patients with bone lesions from breast cancer or MM in the UK. However, the relative efficacy of these agents in MM was previously unknown. The MRC Myeloma IX Study compared the efficacy and safety of ZOL vs CLO in patients with MM. The significant overall and progression-free survival benefits with ZOLvs CLO have been previously reported (Morgan et al. Lancet. 2010)

Methods: The MRC Myeloma IX Study randomized patients with newly diagnosed MM 1:1 to ZOL (n = 981; 4 mg IV q21-28d, dose-adjusted based on renal function) or CLO (n = 979; 1600 mg PO qd) plus intensive (eg, with ASCT) or non-intensive first-line antimyeloma therapy. ZOL and CLO continued at least until disease progression. SREs were defined as fractures (vertebral or non-vertebral), spinal cord compression, the requirement for radiation or surgery to bone, hypercalcaemia, and new osteolytic lesions. SRE data were collected until progression.

Results: At a median follow-up of 3.7 years, approximately 75‰ of 1960 evaluable patients remained on treatment until disease progression. As previously reported, ZOL reduced the risk of death vs CLO (HR=0.84; P=.012) and also significantly prolonged disease-free survival (HR=.88; P=.018). In addition, ZOL provided benefits beyond CLO in SRE-prevention endpoints including reductions in the proportion of patients with an SRE vs CLO (27.0‰ vs 35.3‰, respectively; P=.0004) and the total number of on-study SREs (419 vs 597 SREs, respectively). ZOL also produced reductions in each of the SRE types vs CLO, including vertebral fractures (5% vs 9%) and new osteolytic lesions (5‰ vs 10‰). Both ZOL and CLO were generally well tolerated, with no apparent differences in renal safety. Rates of confirmed osteonecrosis of the jaw (ZOL, 3.6‰; CLO, 0.3‰) compare favorably with previous reports in MM. Most events were mild to moderate in severity.

Conclusions: The MRC Myeloma IX Study revealed that, in addition to survival and progression-free survival benefits, ZOL is superior to CLO in preventing SREs in patients with newly diagnosed MM receiving first-line therapies. Both agents were generally well tolerated.

STEM CELL TRANSPLANTATION

P076 *ID: 116*

LONG-TERM RESULTS OF HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOETIC STEM CELL RESCUE FOR HODGKIN'S LYMPHOMA: İSTANBUL MEDICAL FACULTY EXPERIENCE

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Objectives:In advanced Hodgkin's lymphoma (HL), conventional chemotherapy with/without radiotherapy provides complete remission(CR)rates over 80%. Yet, 30% to 50% either undergo disease progression or relapse.Progression-free survival(PFS)rates in these patients in only 20%.We report our single centre experience with autologous hematopoetic stem cell transplantation (AHSCT) in HL.Methods:Records of 33 patients, who had AHSCT for HL between June 1995 and August 2010,were reviewed retrospectively. Results:Patient characteristics and disease findings at diagnosis and prior to AHSCT are summarized in Tables 1 and 2.Following AHSCT,30 patients(90.9%)suffered from complications,with febrile neutropenia, infections, sepsis and mucositis being most common.11 patients (33.3%) relapsed and 20 patients(60.6%) died.Most common cause of mortality was primary lymphoma relapse (n=11; 55%) followed by transplant-related mortality(3 secondary malignancies, 2 acute myelogenous leukemia and 1 hypernephroma; 6 sepsis and multiorgan failure ; 45%).Median PFS and overall survival (OS) after AHSCT were 52 months (95% CI 22.4-81.6) and 52 months (95% CI 23-81), respectively. Rates of PFS at 16, 30, 34, 46, 52 and 56 months were 93.8%, 80.8%, 59.8%, 52.4%, 43.6% and 34.9%, respectively. Most relapses (81.8%)occurred within 12 months, and all relapses occurred within 48 months of AHSCT. OS at 16, 30, 34, 46, 52 and 56 months were 94.1%, 81.5%, 61.1%, 53.5%, 44.5% and 35.6%, respectively.Conclusions:In relapsed HL,AHSCT provides OS rates of 30–65% at 5 years. Similarly, OS rate at 56 months was 35,6% in our study. According to previous data,half of patients with PR REF disease undergoing AHSCT eventually relapse and die.Rates of relapse and death in our population were 33.3% and 60.6%, respectively.4 patients had PR REF disease at time of AHSCT. One died 9 months and another one 3 years after AHSCT due to disease relapse; cause of death in a third was sepsis.One patient has been in CR for 14 years.Our results support AHSCT represent an active salvage approach even in PR REF disease. Prior to AHSCT, our patients were either in at least second CR or in first PR or had PR REF disease and they all had received at least one salvage regimen. Since our patients were not given risk escalated dose chemotherapy, we could not assess the outcomes of AHSCT in patients having received risk adapted chemotherapy as first line treatment.Secondly, due to limited study population, outcomes of AHSCT at first relapse and after multiple relapses could not be compared. In conclusion, mortality rates related to relapse and transplant complications were similar (55% versus 45%).Being a country with insufficient number of transplantation centers and rapidly growing transplantation waiting lists, delay in transplantation results in development of advanced disease status at time of transplantation,which contributes to increased rates of transplantation complications in our patients.

Table 1.

Characteristic, at diagnosis	*Number of patients*	*Percent*
Total	33	100
Male/female	27/6	81.8/18.2%
Median age (years)	30 (range, 11–53)	
Histology		
Nodular sclerosis	16	48.5%
Mixed cellularity	16	48.5%
Lymphocyte-rich	1	3%
Stage, at diagnosis		
Stage I	1	3%
Stage II	7	21.2%
Stage III	13	39.4%
Stage IV	12	36.4%
First-line chemotherapy (n=31)		
ABVD	21	67.7%
MOPP	3	9.7%
Hybrid MOPP-ABV	3	9.7%
Hybrid MOPP-ABVD	1	3.2%
COPP	2	6.5%
Hybrid COPP-ABV	1	3.2%

Table 2.

Characteristic, at time of AHSCT	*Number of patients*	*Percent*
Total	33	100
Median age (years)	33 (range, 16-56)	
Disease status before AHSCT		
Primary refractory	4	12.1%
Chemosensitive relapse	14	42.4%
Complete remission	9	27.3%
Partial remission	6	18.2%
Stage, at time of AHSCT		
Complete remission	9	27.3%
Stage II	12	36.4%
Stage III	4	12.1%
Stage IV	8	24.2%
Radiotherapy before AHSCT	16	48.5%
Source of stem cells		
Peripheral blood	30	90.9%
Bone marrow	3	9.1%

MULTIPLE MYELOMA

P077 *ID: 118*

A CASE OF MULTIPLE MYELOMA WITH EXTRAMEDULLARY DISEASE OF STOMACH AND EVOLVING WITH SEROSAL INVOLVEMENT

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A fifty five year old female patient was diagnosed as multiple myeloma by bone marrow biopsy. Her initial presentation was epigastric pain and left hypocondriac dullness. Her past and familial medical history was not remarkable. She had anemia and thrombocytopenia with 9.4 gr/dl hemoglobin and 65000/mm^3 thrombocytes on blood count and high LDH levels in blod serum but no hypercalcemia, renal failure, or lytic bone lesions at initial work up. Her peripheral blood smear revealed leucoerythroblastosis and tear-drop erythrocytes. The bone marrow was infiltrated with plasma cells. The M protein was IgG kappa type and the urine immunfixation electophoresis was negative for clonal light chain. The immunphenotype of plasma cells were identified as CD38 and CD138 positive, and CD 20 and CD56 negative. She had high tumor burden represented by β2 micrglobulin level. No anomaly was detected on conventional cytogenetics and FISH was negative for 13 q. Imaging done as abdominal MRI, disclosed gastric wall thickening reaching 2.5 cm and a mass neigbouring spleen. Patient treated with VAD scheme. After two cycles of therapy ascites with plasma cells evolved. Upper endoscopy was done on second evaluation and large gastric and duedonal submucosal lesions protruding to the lumen was detected. Biopsy pathology was concordant with primary diagnosis. The treatment scheme was switched to bortezomib plus high dose dexamethasone. After short course of response, ascites progressed so cylophosphamide two weekly pulses was added to the treatment. There appeared no clear response on ascites but control biopsy of bone marrow was almost free of plasma cells and gastroscopy revealed no tumoral remnant. After 5 cycles of therapy the patient developed dyspnea bacause of left sided pleural effusion reaching to apex diagnosed as malign exudate. The patient moved to autologous bone marrow transplantation after stem cell collection with chemotherapy induced mobilisation. A short lasting good health followed by recurrence of symptomatic ascites. Short after patient died with progressive disease. Extra medullary (EM) disease can occur either at initial diagnosis of MM or later during the disease course. overall incidence is about %10. EM involvement commonly affects the pleura, lymph nodes, soft tissue, liver, skin, lungs, central nervous system (CNS), genitourinary system, breast, and pancreas, and involvement of multiple sites can occur. The presence of EM involvement in MM indicates aggressive disease with shorter overall survival and progression free survival. The presence of 13 q deletion, high levels of serum LDH, high tumor burden, leukemic picture are risk factors for EM disease.

ACUTE MYELOBLASTIC LEUKEMIA

P 078 *ID: 119*

AN ACUTE PROMYELOCYTIC LEUKEMIA CASE TREATED SUCCESFULLY DURING THE COURSE OF BREAST CANCER

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44 years old female patient had been diagnosed as invasive breast cancer in December 2007. Also bone marrow biopsy had showed carcinoma metastasis at time of diagnosis. While she was given chemotherapy regimen consisting of Anastrozol (Aromatase inhibitor) 1x1/day, Transtuzumab (Herceptin) 450mg/3weeks and Goserelin (GnRH anologue) 3,6mg/4weeks for invasive ductal carcinoma which is in stage-4, widespread ecchymotic lesions, epistaxis and gingival hemorrhage has occured in August 2010. In her first investigation Hb;9.6g/dl, Htc;28.8%, PLT; 20x109 /L and the WBC was 19.4x109 /L. In peripheral smear blastic cell ratio was %68. Bone marrow examination showed acute promyelocytic leukemia (APL) infiltration and carcinoma metastasis. PMLRARA t(15;17) was positive.She was successfully treated for APL by induction therapy with Ara-C- idarubicin and all-trans retinoic acid (ATRA).She was given maintenance therapy with ATRA 25mg/m2/day for 45 days. After treatment bone marrow aspiration showed no blastic infiltration but carcinoma metastasis persist. PMLRARA t(15;17) was negative Complete hematological remission has been maintained for six months in this patient.She is still on the treatment of breast cancer.

P079 *ID: 120*

MAY PERIPHERAL BLOOD WT1 MRNA EXPRESSION LEVELS PREDICT MINIMAL RESIDUAL DISEASE (MRD) IN PATIENTS WITH NEWLY DIAGNOSED ACUTE LEUKEMIA?

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Objectives and aim: Wilms tumour gene 1 (WT1) overexpression has been offered as a panleukaemic molecular marker because it has been demonstrated in many leukemia types including acute lymphoblastic and acute myeloid leukemias (ALL and AML), chronic myeloid leukaemia in blast crisis as well as in myelodysplastic syndromes.

The aim of the study was to evaluate peripheral blood WT1 mRNA expression status and availability of this method in determining minimal residual diasease (MRD) in acute leukemias as well.

Patients and Methods: This study was performed in Department of Hematology, Faculty of Medicine, Erciyes University, Kayseri, Turkey and Department of Hematology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey from May 2007 to August 2009. A total of 42 patients whom were newly diagnosed as acute leukemia according to the patients' history, physical examination, cytomorphology, immunophenotyping, immunohistochemistry, flow - cytometric analysis and biocemical findings approved by the same physicians and technicians also. The bone marrow (BM) and peripheral blood (PB) samples were obtained at the time of diagnosis, first remission and during post - treatment follow-up period via same intervals. samples - both PB and BM- were obtained during the study period and these samples were collected in Department of Hematology and Department of Medical Genetics in Erciyes University, Kayseri and Department of Hematology, Gaziantep University, Gaziantep. The control group was consisted of 20 healthy subjects. RNA isolation (PB) and Real-time quantitative PCR of WT1was performed by experts in Department of Medical Genetics. For this method, abl gene positive control sample was dilueted and was formed a standart data determining abl copies of all samples. Analysis of the data was performed using SPSS version 16.0 for Windows, 2001, SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered as statistically significant difference.

Results: A total of 42 patients newly diagnosed as acute leukemia were included in the study. 20 healthy subjects were chosen as control group. Of the patients, 28 (66.6%) of them were acute myeloid leukemia (AML) while 14 (33.4%) were acute lymphoblastic leukemia (ALL). A total of 92 PB and 42 BM samples were collected during the follow-up. The median peripheral blood WT1 mRNA expression level in control group was found 0.07 copy (0 - 0.134). The median PB WT1 mRNA expression levels in patients with AML was found 0.58 copy (median; 0.003 - 3.292) and this was statistically significant when compared with the control group ($p<0.05$).

CHRONIC MYELOID LEUKEMIA

P080 *ID: 121*

RETROSPECTIVE EVALUATION OF PATIENTS WITH IMATINIB RESISTANT OR INTOLERANT CHRONIC MYELOID LEUKEMIA

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In this retrospective study, 16 patients with imatinib resistant or intolerant chronic myeloid leukemia(CML) evaluated. 10 of the patients were male(67.5%) and 6 of patients were famele(37.5%). The median age of patients was 40.68 years (range, 18-56 years). Sokal scores were as follows: 43.75% low, 43.75% intermediate, and 12.50% high. Imatinib treatment duration range was 10-56 months. Before starting nilotinib or dasatinib treatment mutational analyses were performed, only one patient had T315I mutation. In intolerant patients, side effects such as grade3 anemia, grade4 neutropenia, nausea, myalgia were observed. Nilotinib and dasatinib treatment were initiated to 7 and 8 patients when resistance or intolerance appeared, treatment durations have been 4-40 months and 21-39 months, respectively. Imatinib treatment was continued to remaining one patient who had T315I mutation. The results were obteined as: 7 patients with complete molecular response, 3 patients with major molecular response, 1 patient with complete cytogenetic response, 1 patient with partial cytogenetic response, 1 patient without response so planned to allogenic stem cell transplation, 1 patient with T315I mutation still in heamatological response. 2 patients were dead.

MULTIPLE MYELOMA

P081 *ID: 122*

FIBRINOLYTIC SYSTEM ACTIVATOR AND INHIBITOR LEVELS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPL MYELOMA

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Objectives: Thrombotic and hemorrhagic events have been frequently observed in patients with multiple myeloma. A number of studies that have investigated fibrinolytic activity in multiple myeloma patients have shown conflicting results. In multiple myeloma both impaired and excessive fibrinolysis have been reported. Therefore in this study, we aimed to measure the levels of major fibrinolysis activator tissue-type plasminogen avtivator (t-PA), the major fibrinolysis inhibitors plasminogen activator inhibitor -1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI) in order to investigate the fibrinolytic system in multipl myeloma.

Methods: Forty-eight newly diagnosed patients with multiple myeloma who admitted in hematology clinic of Karaelmas University Medical School between August 2008 - August 2010 were enrolled into the study. As the control group, 20 age and sex matched healthy subjects without systemic diseases who admitted in internal medicine clinic for routine control included in the study.

Results: The mean plasma t-PA levels were 11.2 ± 6.4 ng/ml in the myeloma group and 13.3 ± 6.6 ng/ml in the control group and no statistically significant difference was found ($p = 0,221$). Plasma PAI-1 levels were 36.8 ± 17 ng/ml in the myeloma group and 47,3±26,4 ng / ml in the control group. The difference between the two groups was not significant ($p = 0,057$). Plasma TAFI level in the myeloma group (7.8 ± 3.0 mg/ml) was significantly lower than the level of control group (10.8 ± 2.7 mg/ml) ($p <0.001$).But there was no correlation between disease stage and TAFI levels. No statistically significant difference was found between plasma D-dimer levels of multiple myeloma patients and the control group ($p = 0,406$).

Conclusions: We suggested that low levels of TAFI without any change in t-PA and PAI-1 levels may be one possible mechanism that contributes hemorrhagic complications in patients with multiple myeloma.

HODGKIN'S LYMPHOMA

P082 *ID: 123*

CLINICAL FEATURES AND TREATMENT RESULTS OF PEDIATRIC HODGKIN LYMPHOMA: SINGLE CENTER EXPERIENCE

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The epidemiologic, clinical and histologic features of pediatric Hodgkin's Disease (HD) in developing countries are different from developed countries. The aim of this study was to evaluate the clinical characteristics and therapy results of the HD in childhood.

From 1990 to 2010, 82 children with newly diagnosed, untreated biopsy-proven stage I-IV HD were treated with chemotherapy (CT) and involved field radiotherapy. Treatment consisted of two cycles of ABVD chemotherapy for stages I and IIA, four cycles of ABVD for stages IIB and IIIA, six cycles of MOPP/ABV for stages IIIB and IV. All children received involved field radiotherapy of 15 Gy ≤5 years old, 20 Gy if 6-10 years old, 25 Gy if ≥11 years old. Overall (OS) and event-free survival (EFS) and factors associated with inferior OS and EFS were detected.

The 5-year EFS and OS for all patients were 80% and 85%, respectively with a median follow-up of 50 months (3-245 months). Male to female ratio was 3:1 and median age was 84 (30-193) months, 76% were younger than 10 years. Mixed cellularity was the predominant histologic subtype (42%). 7% was classified as stage I, 53% as stage II, 25% as stage III, 15% as stage IV. The 5 year overall survival was 100% for stages I and II, 90% for stages III and 78% for stages IV respectively. EFS was 98% for stages I and II, 84% for stages III and 68.5% for stages IV respectively.Factor associated with inferior EFS by univariate analysis was stage.

There is a predominance of mixed cellularity subtype, male sex and younger age in our study population. Results obtained with a combined modality therapy consisting of chemotherapy, modified according to stage, and low dose involved field radiotherapy are satisfactory.

NON-HODGKIN'S LYMPHOMA

P083 *ID: 127*

DOES THE FORMATION OF THE ABDOMINAL SKIN OF A REACTIVE LESION OCCURRING? / IS INDOLENT LYMPHOMA? LYMPHOMATOID PAPULOSIS TYPE A AND TYPE B CASES

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Introduction: Lymphomatoid papulosis (LyP) is a chronic, recurrent usually self-healing clonal T-cell disorder, on a continuum with CD30+ anaplastic T-cell lymphoma. It is characterized by recurrent crops of polymorphous erythematous-brown scaly papules and nodules that may crust and ulcerate. Three distinct histological subtypes exist. Type A comprises large, sometimes multinucleated CD30+ cells. Type B (fewer than 10% of cases) is characterized by cells with cerebriform nuclei, often an epidermotropic infiltrate and resembles MF. Type C compries complement sheets or large clusters of CD30+ cells suggisteve of anaplastic CD30+ large-cell lymphoma. Individuals with lymphomatoid papulosis are reported to have an approximately 5% chance of developing MF, large-cell lymphoma and/or Hodgkin lymphoma. The prognosis is generally excellent. We report two case that evaluated lymphomatoid papulosis type A and type B.

Lymphomatoid papulosis type A case report: Thirty-six-year-old woman patient.The first evaluation of the patient's not weight loss, night sweats, decreased appetite, fever, such as B symptoms. In the history of the patient and family history was unremarkable. The bone marrow biopsy and aspiration showed infiltration of lymphoma and bone marrow normosellüler findings were interpreted in favor. Morphological and antigenic characteristics of the excisional biopsy specimen re-examined the patient were compatible with lymphomatoid papulosis type A.

Lymphomatoid papulosis type B case report: Twenty-five-year-old woman patient.The bone marrow biopsy and aspiration showed'nt infiltration of lymphoma and bone marrow normosellüler findings were interpreted in favor. Excisional biopsy material found to be compatible morphological and antigenic characteristics of primary cutaneous CD 30 (+) with lymphomatoid papulosis type B.

Results: Whether LyP represents an indolent lymphoma or a reactive process is debatable. A more cohesive pathogenesis of LyP would combine both the reactive and neoplastic theories. Perhaps LyP is a reaction that, after persistent inflammation or in the right environment, can progress to malignancy. If the antigen is persistant, the immune system may continue to over-react and a malignant clone may develop, similar to the may in which helicobacter pylori infection can result in gastric cancer.

P084 *ID: 129*

BLASTIC TRANSFORMATION IN A PATIENT WITH PRIMARY GASTRIC LYMPHOMA

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Herein, we present a patient with gastric lymphoma in blastic transformation. A 26 years-old man presented to our clinic with dyspeptic symptoms in March 2010. Upper gastrointestinal tract endoscopy demonstrated diffuse large B-cell lymphoma. At the time of initial diagnosis the CT scans of thorax and abdomen revealed involvement of liver and lung. The patient was designated as having stage IVB diffuse large B-cell lymphoma. R-CHOP regimen was given. After the second course of chemotherapy, he was confirmed to have progression which was treated with salvage chemothrepy R-ICE regimen in April 2010. After two course of R-ICE no clinical response was observed, so in June 2010 the patient underwent hyper-CVAD regimen. During his treatment, peripheral blood smear examination showed full-blown blast cells in September 2010. Flow cytometric analysis of the blood revealed features of ALL. Two days after the diagnosis of blastic transformation, the patient was complicated with upper gastrointestinal bleeding. Despite appropriate therapeutic support the patient died on the seventh day. To our knowledge, this is the first report of blastic transformation developing in a primary gastric diffuse large B-cell lymphoma.

3rd International Congress on Leukemia – Lymphoma – Myeloma

May 11 – 14, 2011 • İstanbul, Turkey

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