2nd International Congress on Leukemia – Lymphoma – Myeloma

May 21 – 24, 2009 • Istanbul, Turkey

Proceedings & Abstract Book

Turkish Society of Hematology

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Dear Colleagues and Friends,

It gives us great pleasure to host the 2nd International Congress on Leukemia-Myeloma-Lymphoma 2009 (ICLLM 2009) in Istanbul, Turkey.

Since the introduction of the concept of blood circulation in 1628 to the present, numerous advances have been made in the field of hematology that have significantly improved the lives of patients with hematological disorders and blazed a trail for advances in other fields. In the last 50 years alone, substantial strides have been made in the research, treatment, and prevention of both hemato-oncological malignancies. Even some of the most basic research underway today has the potential to lead to promising life-saving treatments in the future. Targeted therapies, biological molecules and RNAi gene therapies are all revolutionary new studies in the treatment of hematological malignancies.

Large populations with centralized health care systems; clinicians motivated to participate in clinical trials in order to attain access to cutting-edge research, thereby furthering their professional qualifications and enhancing their prestige among colleagues; better-informed patients; and regulatory frameworks like the Good Clinical Practice (GCP) guidelines all serve to generate high-quality clinical trial data due to motivated investigators, good patient compliance, and well-qualified clinical research associates.

In this midst of this exciting new era, the 2nd ICLLM Congress provides a unique forum for scientists and medical professionals gathered from around the world to meet and exchange ideas and information in the fields of hematology and oncology. The scientific program of the ICLLM Congress boasts most of the hematology masters who aim to provide a perfect balance between clinical education and news of the latest scientific developments. These remarkable individuals, whom I refer to as our scientific stars, will be the light on our road to as of now unimaginable future successes.

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

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

The Istanbul Wow Convention Center, located near the airport and easily accessible by public transport, offers excellent facilities, including all the necessary infrastructure and professionalism to successfully host a medical convention of this import. Participants from 35 countries are registered, and the Congress has been accredited by both the European Hematology Association (EHA) and the Turkish Medical Association.

Dear colleagues, I extend to you a most warm welcome to Istanbul ICLLM 2009.

Muhit Özcan
Congress President

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2nd International Congress on Leukemia – Lymphoma – Myeloma

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SCIENTIFIC PROGRAM

May 21, 2009, Thursday

08:30-10:00 **Follicular Lymphoma**

Chairs: Robert E. Marcus *(King's College Hospital, UK)* – Mustafa Çetin *(Erciyes University, Turkey)*

- The management of Follicular Lymphoma in 2009
  Robert E. Marcus, King's College Hospital, UK
- The molecular pathogenesis of Follicular Lymphomas
  Finbarr Cotter, Barts and the London School of Medicine, UK
- How Scientific Insights Can Lead to New Therapy for Follicular NHL
  Jane Winter, Feinberg School of Medicine, Northwestern University , USA

10:00-10:30 *Coffee Break*

10:30-12:00 **Myelodysplastic Syndromes**

Chairs: H. Joachim Deeg *(Fred Hutchinson Cancer Research Center, USA)* – Ayşen Timurağaoğlu *(Akdeniz University, Turkey)*

- Classification of MDS and Its Relevance for Treatment
  Luca Malcovati, University of Pavia, Italy
- Molecular Biology of MDS - Does It Make a Difference?
  Ziyi Lim, King's College Hospital, UK
- MDS: Disease Control or Curative Therapy?
  H. Joachim Deeg, Fred Hutchinson Cancer Research Center, USA

12:00-12:15 *Lunch*

14:00-15:30 **Acute Myeloblastic Leukemia**

Chairs: Jacob M. Rowe *(Rambam Medical Center, Israel)*– Zafer Gülbaş *(Eskişehir Osmangazi University, Turkey)*

- Induction and Non-transplant Consolidation in AML
  Jacob M. Rowe, Rambam Medical Center, Israel
- Allogeneic Transplantation in AML
  Anthony Goldstone, University College Hospital, London, UK
- Autologous Transplantation in AML
  Charles Linker, University of California, USA

15:30-16:00 *Coffee Break*

16:00-17:30 **Multiple Myeloma**

Chairs: Bart Barlogie *(Myeloma Institute for Research and Therapy, USA)* – Levent Ündar *(Akdeniz University, Turkey)*

- Prospects for Cure in Multiple Myeloma
  Bart Barlogie, Myeloma Institute for Research and Therapy, USA
- Genomics Identify Myeloma Entities with Different Clinical Manifestations and Outcomes
  John D. Shaughnessy Jr., Myeloma Institute for Research and Therapy, USA
- Combining Genotoxic and Novel Agents Toward Optimizing Myeloma Outcomes
  Philippe Moreau, University Hospital Nantes, France

May 22, 2009, Friday

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

Chairs: Robin Foa *(La Sapienza University, Italy)* – Mehmet Ertem *(Ankara University, Turkey)*

- Targeted Therapies in ALL
  Robin Foa, La Sapienza University, Italy
- New Advancements in the Genetic Characterization of ALL
  Roberta La Starza, University of Perugia, Italy ?????????????
- Management of ALL in Adolescents and Young Adults
  Jean Pierre Marie, Hospital Hotel Dieu, France

10:00-10:30 *Coffee Break*

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

Chairs: Andreas Josting *(Evangelisches Krankenhaus Lippstadt, Germany)*– Bülent Ündar *(Dokuz Eylül University, Turkey)*

- Treatment of Advanced and Relapsed Hodgkin`s Disease
  Andreas Josting, Evangelisches Krankenhaus Lippstadt, Germany
- Treatment Strategies in Early and Intermediate Stages Hodgkin's Disease
  Houchingue Eghbali, Regional Cancer Centre Bordeaux Cedex, France
- Long Term Sequelae of Hodgkin's Disease and Its Treatment
  Jens-Ulrich Rueffer, University of Köln, Germany

12:00-12:15 *Lunch*

13:30-15:00 **Chronic Myeloproliferative Disorders**

Chairs: Ayalew Tefferi *(Mayo Clinic, USA)* – Zahit Bolaman *(Adnan Menderes University, Turkey)*

- Classification and Modern Diagnostic Approaches in Myeloproliferative Neoplasms
  Ayalew Tefferi, Mayo Clinic, USA
- JAK2 Inhibitor Therapy in Myelofibrosis: Preclinical and Clinical Update
  Srdan Verstovsek, MD Anderson Cancer Center, USA
- The Genetics of Clonal Evolution in Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis
  Radek Skoda, University of Basel, Switzerland

15:00-15:30 *Coffee Break*

15:30-17:00 **Chronic Lymphocytic Leukemia**

Chairs: Peter Dreger *(University of Heidelberg, Germany)*– Osman İ. Özcebe *(Hacettepe University, Turkey)*

- CLL: State of the Art of Treatment and Its Indications
  Emili Montserrat, University of Barcelona, Spain
- Perspectives of New Drugs and Strategies for CLL
  Eva Kimby, Karolinska Institute Huddinge University, Sweden
- Stem Cell Transplantation in CLL
  Peter Dreger, University of Heidelberg, Germany

May 23, 2009, Saturday

08:30-10:00 **Other Aggressive Lymphomas**

Chairs: Koen van Besien *(University of Chicago, USA)*– Önder Arslan *(Ankara University, Turkey)*

- CNS Lymphoma: Diagnosis and Management
  Koen van Besien, University of Chicago, USA
- Diagnosis and management of Burkitt Lymphoma
  Wyndham Wilson, National Cancer Institute, USA
- Mantle Cell Lymphoma
  Owen O'Connor, Columbia University, USA

10:00-10:30 *Coffee Break*

10:30-12:00 **Diffuse Large B Cell Lymphomas**

Chairs: Anna Sureda *(Hospital de la Santa Creu i Sant Pau, Spain)* – Muhit Özcan *(Ankara University, Turkey)*

- The Role of Allogeneic Stem Cell Transplantation in Patients with DLBCL
  Anna Sureda, Hospital de la Santa Creu i Sant Pau, Spain
- Treatment of DLBCL Patients in the Era of Monoclonal Antibodies
  Norbert Schmitz, Asklepios Klinik St. Georg, Germany
- The Use of Pet/Scan for Risk Adapted Therapeutic Strategies in DLBCL
  Corinne Haioun, CHU Henri Mondor, France

12:00-12:15 *Lunch*

13:30-15:30 **Chronic Myeloid Leukemia**

Chairs: Elias Jabbour *(MD Anderson Cancer Center, USA)*– Teoman Soysal *(Istanbul University, Turkey)*

- Treatment of CML Post Imatinib Failure
  Elias jabbour, MD Anderson Cancer Center, USA
- Monitoring of CML and Mechanisms of Resistance
  Andreas Hochhaus, University of Heidelberg, Germany
- CML History and Update of Imatinib Experience
  Guiseppe Saglio, University of Turin, Italy
- Update of Allogeneic Stem Cell Transplant in CML
  Richard Champlin, MD Anderson Cancer Center, USA

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PROCEEDINGS

Follicular Lymphoma

The last five years has seen the greatest change in the management of this condition for a generation. The introduction of monoclonal antibodies, specifically the anti-CD20 antibody rituximab has led to a major prolongations in progression free survival . We have also seen how the application of molecular biological techniques have yielded new insights into pathogenesis that can be used as the basis for innovative therapies

In this session Dr Robert Marcus will discuss the current management of follicular NHL, Dr Finbar Cotter will present data on the molecular pathogenesis of this condition and Dr Jane Winter will discuss how these insights may give rise to new scientifically based therapies

Dr. Robert Marcus

Dr. Robert Marcus, MA, FRCP, FRCPath, is Consultant Haematologist at Kings College Hospital London, UK

He qualified in medicine and pursued postgraduate studies in haematology at University College Hospital in London, subsequently becoming a Research Fellow at the MRC Leukaemia Unit at the Hammersmith Hospital, London. He then completed his training in haematology at the Royal Free Hospital in London and was appointed Consultant Haematologist at Addenbrookes Hospital in Cambridge in 1987 . He participated in the first clinical studies in monoclonal antibody therapy for lymphoma with the "CAMPATH" series of antibodies. He subsequently developed a particular interest in the development of novel therapies for lymphoma and has been chief investigator in a large number of practice changing phase 2 and 3 studies of chemotherapy and immunotherapy in lymphoma. He established stem cell transplantation in Cambridge and was, until recently, lead cancer clinician for Addenbrookes Hospital. He has published many papers and reviews on lymphoma and related topics in peer-reviewed journals and is the senior editor and contributor to the textbook, "Lymphoma – pathology, diagnosis and treatment," published by Cambridge University Press in 2007. He is currently Chairman of the NCRI low-grade lymphoma subgroup . He relocated to a position as Consultant Haematologist at Kings College Hospital in February 2008 where he is now lead cancer clinician and Chair of the KCH chemotherapy committee

The Management of Follicular NHL 2009

Dr. Robert Marcus

Kings College Hospital, London

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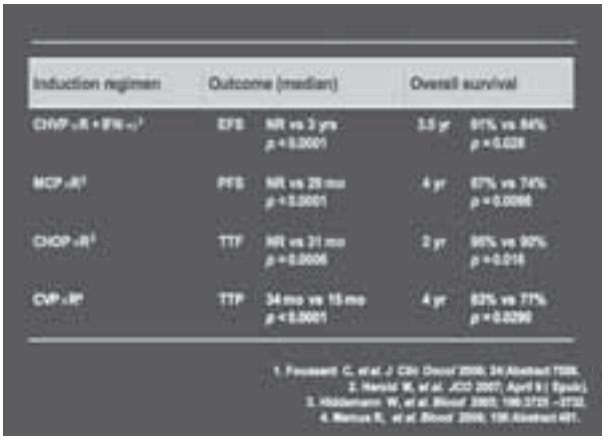
Introduction

In the pre antibody era the therapeutic options for patients with follicular lymphoma were more straightforward than they are in 2009: patients relapsing within, say, two years of first line chlorambucil could receive anthracycline or fludarabine second line chemotherapy with the expectation of responses lasting between 50 and 65% of previous remissions. Those relapsing late could receive akylating agents again and, in a small number of innovative centres, patients, usually under the age of 60 could receive high dose therapy with either autologous or allogeneic stem cell support.In the past five years we have see major innovation in the management of this condition: first the incorporation of the monoclonal antibody rituximab into first and second line therapy, secondly the increasing use of allogeneic stem cell transplantation with reduced intensity conditioning in a wider age range of relapsed patients

In advanced stage follicular lymphoma the critical initial question remains not which therapy should be offered to such patents but whether any treatment is required at all. The introduction of monoclonal antibodies therapy has not altered this. There is as yet no evidence that any therapy, however non-toxic, given to asymptomatic patients confers any long therm benefit and the criteria for therapy remain, in my view, unchanged:

What as yet we are unable to do is to identify by clinical or biological criteria those patients with slow tempo or low volume disease who have a poor long term prognosis.

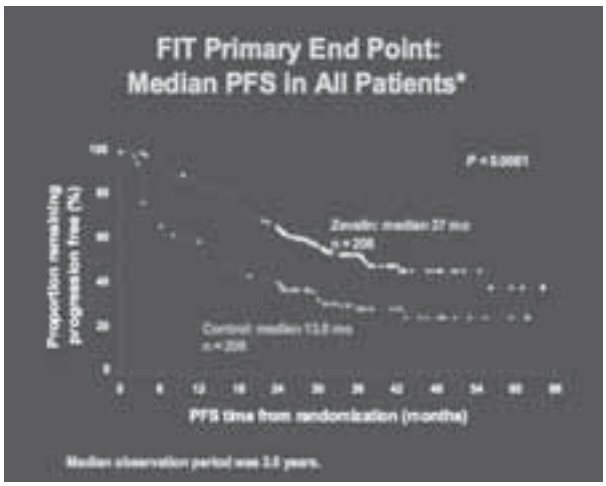
The effectiveness of the incorporation of Rituximab into first line chemotherapy for follicular lymphoma has now been supported by 4 large scale randomised trials: the first of these added rituximab to CVP with a more than doubling of PFS from 15 to 34 months (1) the other three added rituximab to CHOP or CHOP like therapies (CHVP, MCP) with the addition of alpha interferon maintenance. These also demonstrated marked improvements in PFS. Whether these more intensive regimens confer additional benefit over and above what is conferred by the addition of rituximab to CVP alone remains to be seen.



If they do it is also not certain whether it is the anthracycline or the interferon or both that improve such increases in freedom from disease. We also do not know whether the early use of anthracyclines will compromise the long term outlook of patients relapsing either with follicular NHL or transformed disease . A rediscovery of an old agent, bendamustine, may solve this dilemma: in a recently presented study the combination of bendamustine with rituximab was shown to yield equivalent results to R-CHOP (2) and novel trials are now being designed to establish the role of this agent in first line and subsequent therapies.

The alternative approach has been to utilise rituximab as maintenance therapy after standard CVP induction. Here too a more than doubling of PFS has been observed (3) It is not clear we can conclude that maintenance added to rituximab based induction regimens will increase the PFS further and the results of the now completed PRIMA trial that sets out to answer this study are awaited.

A parallel approach has been to use radiolabelled antibodies as consolidation therapy after induction. There have been a number of phase II studies utilising both131 Iodine and 90 Yttrium labelled anti –CD20 antibodies but only one prospective RCT that demonstrates the benefit of adding radioimmunotherapy to chemotherapy with an increase in PFS form 14 to 37months. (4)

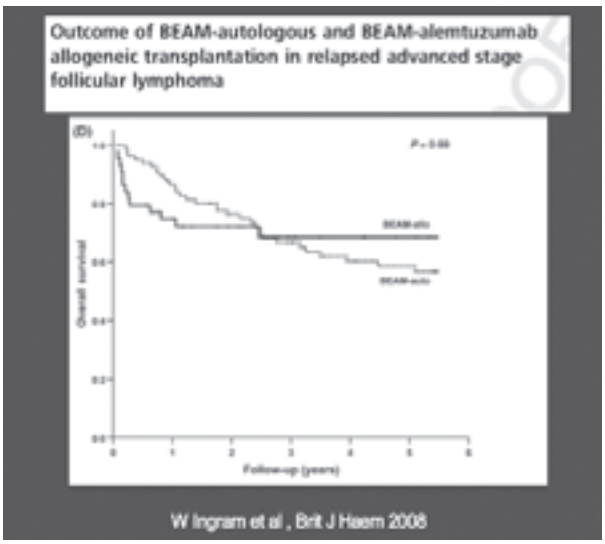


Unfortunately too few patient in this study were treated with rituximab containing regimens to assess whether radioimmunotherapy confers additional benefit over what is achieved with immunochemotherapy alone.

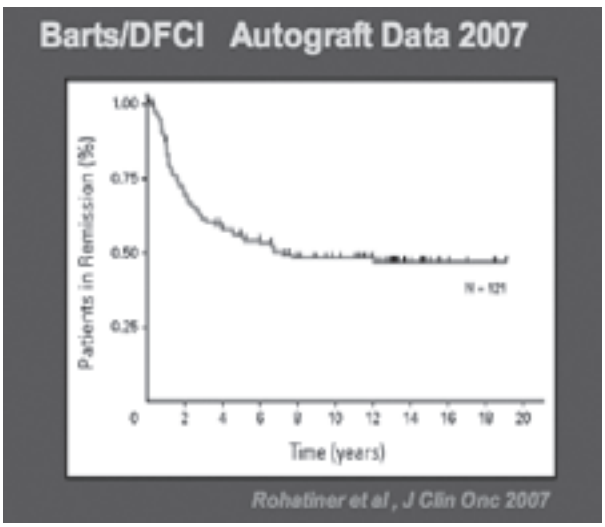
The widespread use of rituximab in first line therapy has called into question some of the optimistic data from studies of second line rituximab use : the data from the EORTC demonstrating substantial prolongation of progression free survival when rituximab is incorporated into induction and as maintenance can only apply to those patients who have not received this antibody before , nor any anthracycline (5) Since the majority of patients world wide now receive both, and many, despite the absence of randomised trial data maintenance rituximab too, the value of repeated use of this antibody at recurrence will, inevitably, be more limited, but it is likely that patients who relapse more than 2 years after a rituximab based induction therapies will benefit form re-treatment with an identical or similar regimen.

Conversely the reduced mortality of allografting with reduced intensity conditioning has led many

centres to offer patients this approach at first or second recurrence especially where first remissions have been short lived. (6) Other groups have persisted with high dose therapy with autologous stem cell support in this context. No randomised trials have been performed to address the question as the possible superiority of one technique over the other. A non randomised comparison suggests, as expected, that the relapse risk is significantly higher in patients who receive autologous stem cells balanced by the considerably lower transplant related mortality.(7)



There is also limited evidence of a true plateau in the allografted groups not seen in the autografted patients , although other groups data suggest long term disease free survival can be achieved without the additional risk of allogeneic stem cells.



These remain procedures carrying considerable short and medium term risk from infection and graft versus host disease, and non transplant approaches will continue to be required for patients whose disease relapses especially in patients too frail or elderly to withstand the rigours of high dose treatment . These include the use of novel antibodies: there are some encouraging preliminary data on the use of Ofatumomab in relapsed patients (8) who have previously received rituximab and a studies with another novel anti-CD20 antibody (GA-101) are about to commence.

The past five years have seen major improvements in the management of follicular lymphoma yet the majority of patients will still relapse and die form their disease. We can hope that a greater understanding of the biology of this disease will, described by Dr Cotter, will lead directly to some of the improvements in patient care that you will hear from Dr Winter.

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Dr. Finbarr E Cotter

Clinical Lead for Molecular Pathology and Chair of Experiemtal Haematology
Dept of Medical Oncology
Barts and the London Medical School of Medicine

I graduated in medicine from the University of London in 1978, trained in Haematology at the Royal London Hospital and in Oncology at St Bartholomew's Hospital, London.

In 1986 I obtained a PhD molecular biology of lymphoid malignancies, while working for the ICRF.

In 1992 I moved to the Inst of Child Health (University College London) as a senior lecturer and then as a reader in molecular haematology and oncology, where I continued my molecular research into haematological malignancies as part of the Leukaemia Research Fund centre.

My particular emphasis has been on the application of molecular understanding and therapy for malignancy. In 1999, I moved my research group to Barts and the Royal London School of Medicine to continue my work on molecular therapy and to take up the Cair of Experimental Haematology.

I am currently Editor in Chief for the British Journal of Haematology and the www.bloodmed.com website. I have numerous peer reviewed publications in the field of haematological malignancy and participate in a nubmer of national committees in the field of cancer genetics. I am currently the President elect of the British Society for Haematology. In my spare time I like to play the trumpet, both classical and jazz.

My current resarch interests remain focused on all aspects of B-cell malignancies, including Zebrafish models and molecular therapy. One of my other main aims is to bring through young haematologists to be our researchers for the future.

Molecular Pathology of Follicular Lymphoma

Dr. Finbarr E Cotter

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Follicular lymphoma (FL) remains one of the commonest of B-cell malignancies representing 20% of all lymphomas. The median age for presentation is 60years and males predominate by nearly 2:1 and the incidence varies geographically being less common in Asia suggesting genetic predisposition. It is often referred to as an indolent lymphoma as it can run a chronic course of chemotherapy induced remissions which may be quite prolonged followed by eventual relapse and subsequent shorter remissions. The median survival is well beyond a decade and with the advent of monoclonal antibody treatment with anti CD20 may now increase considerably more. However, it remains incurable and ultimately will transform into diffuse large cell lymphoma. While the majority of patients survive for many years unpredictably some patients develop a much more aggressive disease with a greatly shortened time to death. FL is characterised at the cytogenetic level with a characteristic t(14;18) chromosomal translocation in the majority of patients. Not only is this useful diagnostically it also provides some insight into the pathogesesis of the disease.

Follicular Lymphoma Pathology

Histologically it is characterised by Follicular centre B-cells from the germinal centre (both centrocytes and the larger transformed centroblasts) with a partially follicular pattern. Where the lymphoma has transformed into a diffuse pattern with more than 15 centroblasts per high power field it is now defined by the latest WHO classification as Diffuse large B Cell Lymphoma, whereas in the past it would have been described as a Grade 3 FL (See Table 1 below). Grading of FL has been important in many classifications but now can be simplified by predictive utility. Grade 1 and 2 appear to behave in a more indolent manner than Grade 3.

Grading	Definition
Grade 1-2 (low grade)	0-15 centroblast per high power field (hpf)
1	0-5 centroblasts per hpf
2	6-15 centroblasts per hpf
Grade 3	>15 centroblasts per hpf
3A	Centrocytes present
3B	Solid sheets of centroblasts

Table 3: Grading of Follicular Lymphoma. Diffuse areas containing more than 15 cetroblast per hpf are now defined as Diffuse large B-cell Lymphomas with Follicular lymphoma (including the grade for the FL element).

Clinical aspects

The predominant presentation symptom of Fl is lymphadenopathy both central (Abdominal and thoracic) and peripheral and splenic enlargement. In the presence of extensive nodal disease extranodal involvement of the GI tract may occur. Very occasionally the primary presentation is extranodal with the duodenum, ocular adnexa, breast and testis being favoured sites. In 40-70 % of presenting patients the bone marrow is involved making these patients Stage 4 disease. Relatively localised grade 1 and 2 disease is less common and in many respects the lymphoma grading system is less useful FL. However, despite extensive disease the patients are often systemically well making FL the archetypal indolent disease providing the histology is Grade 1 or 2 (75% approx). The clinical course of the disease is that of clinical responsiveness to chemotherapy initially with fludarabine containing regimens, followed by eventual relapse and further responsiveness to additional chemotherapy usually containing an anthracycline and the anti CD20 monoclonal antibody (Rituximnab). Further relapses will occur usually with shorter periods of remission. Autologous transplantation is remission has been used to good effect in prolonging the time to relapse. Allogeneoic bone marrow transplantation is rarely an option due to the age of the patient.

The t(14;18)(q32;q21) chromosome translocation

The additional characteristic in 80% of FL is the presence of the t(14;18) translocation that places the Immunoglobulin Heavy chain enhancer region alongside the anti apoptosis gene B-cell lymphoma/leukaemia 2 (Bcl-2) proto-oncogene with resulting over expression of the Bcl-2 protein. This protein is normally expressed in resting B cells and in perifollicular mantle zone and in post follicular B cells as well as memory B cells. The role is to prevent apoptosis of immunologically useful B cells. However within the germinal centre (GC) B cells that have not undergone class switching to be come functional immunoglobulin expressing cells they lack this survival signal and apoptose. Only if stimulated to leave the GC as functional B cells will the survival protein normally be turned on. In FL the GC B cells all express high levels of Bcl-2 protein and with a prolonged life span permit the development of lymphoma. The translocation is readily detected by DNA PCR and may be used to monitor the presence or absence of disease. In addition, the t(14;18) translocation has been shown to be present at very low levels occasionally in healthy individuals who do not go on to develop lymphoma and in only 10% of FL is the translocation the sole cytogenetic abnormality. It has also been shown in transgenic mice over expressing Bcl-2 do not develop lymphoma without the presence of additional genetic mutations. All of this suggests that the t(14;18) translocation is an early permissive event in a multistep process for the development of FL.

It would appear that the one common feature of FL is the presence of excessive Bcl-2 protein and in the majority of cases this is brought about by the t(14;18) translocation. Rarely variants of the t(14;18) translocation occur in the form of t(2;18) and t(18;22) where the Bcl-2 gene is juxtaposed alongside the kappa and lambda immunoglobulin light chain genes. The result is the same unopposed Bcl-2 protein expression. Even in the t(14;18) negative patients high levels of Bcl-2 protein are present in the lymphoma cells sometimes associated with an additional chromosome 18. Bcl-2 protein negative FL occurs in 10% of cases and it is presumed that other anti apoptosis genes of the same Bcl-2 family are over expressed. It is clear that FL is a progressive disease accumulating additional consisted cytogenetic abnormalities and with progression the t(14;18) chromosome translocation may be lost with the transformation to a grade 3 FL.

Additonal FL chromosome alterations

In addition to the t(14;18) translocation found in the majority of FL loss of chromosomes 1p, 6q, 10q and 17p and gains of chromosomes 1, 6p, 7, 8, 12q, X and 18q duplication occur and increase in number with the progression of the disease from follicular to diffuse centroblastic translocation which increases with time from diagnosis and treatment relapses. The presence of deletions in the long arm of chromosome 1 and 6 and the short arm of chromosome 17 (containing TP53) are notable poor prognostic markers. Of particular mention is the detection of the t(8;14) chromosome translocation, the MYC gene rearrangement found in Burkitt's lymphoma as this denotes a more rapidly progressive disease and sometimes the transformation into a Burkitt like morphological appearance.

Bcl-2 negative FL

In this 10% subgroup of FL half are t(14;18) translocation positive and the apparent Bcl-2 protein negativity is due to poor protein epitope recognition by the antibodies used diagnositically. In the remainder there are some explanations. Bcl-XL another potent anti apoptosis gene may be up regulated, or the presence of the t(3;14)(q27;q32) chromosome translocation leading to increased Bcl-6 protein expression rather than Bcl-2 may be detected. It is however clear that both t(14;18) positive and negative FL should be viewed as a single entity with divergent oncological pathways leading to the same morphological, immunophenotypic disease and molecular features.

Microenvironment and FL

The tumour microenvironment is becoming of increased interest. The interaction of T cells with the neoplastic B cells may be dysfunctional in FL. It has been reported that an interfollicular infiltrate of FoxP3-positive T cells and CD68-positive macrophages were good prognostic findings for treatment with CVP but poor prognostic markers for Fludarabine treated patients. Gene expression profiling defined two signatures termed immune response signatures 1 (IR1-good response) and 2 (IR2-poor response) at the time of diagnosis. These signatures are generated from both tumour cells and microenvironment cells. While the interaction with the microenvironment is not yet well understood it is an important factor .

Summary

FL is a complex and common disorder in the field of B cell malignancies. While it shares some common factors in the majority of patients such as the t(14;18) translocation involving Bcl-2 protein over expression it is a disease that will progress with an underlying picture of genetically unstable tumour cells interacting abnormally with their microenvironment. Understanding this process more fully will provide the window for better therapy and maybe the possibility of cure sometime in the not so distant future.

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Committee Service:
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American Board of Internal Medicine
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American Society of Hematology
- Co-chair, Educational Program, American Society Hematology, 2007 meeting.
- Co-chair, ASH Highlights 2008,
- Co-chair, Best of ASH, ASH Annual Meeting, 2007
- Educational Affairs Committee, 2006-present.
- Program Committee, 2006-2008.
- Clinical Research Training Institute Study Section - 2007.
- ASH/ABIM Task Force, Hematology Board Exam Committee, 2005-2007.
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Eastern Cooperative Oncology Group
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- Chairman, Review Committee for BMT Center Designation, 1993- 2000.
- Toxicity chair for Bone Marrow Transplant Committee, 1996-2000.

American Society for Blood and Marrow Transplantation
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American College of Radiology, "Hodgkin's Disease Working Group." Panel to establish and maintain "Appropriateness Criteria" for evaluation and treatment of Hodgkin lymphoma, 2004-2008.

American Society for Clinical Oncology
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Autologous Blood and Marrow Transplant Registry (CIBMTR)
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Cancer Therapy Evaluation Program- External reviewer for new concepts. Jan. 2005- present.

National Comprehensive Cancer Network
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Special Liaison to the Breast Committee re: High-dose chemotherapy, 1996.
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Israel Cancer Research Fund
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University
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Medical School

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Member, Scientific Advisory Committee of the General Clinical Research Center, 1990-1993.
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Member, Women Physicians Organization, Executive Committee, 1997-1998.
Member, Cancer Committee 1990-1997.
Member, Venous Access Device Committee, Northwestern Memorial Hospital, 1992-1994.
Member, Radiation Emergency Coordination Committee, 1985-1997.
Member, Infection Control Focus Group, NMH Redevelopment Project, 1994-1995.
Member, Northwestern Memorial Hospital Thorson-Goodall Diagnostic Molecular Oncology Laboratory Steering Committee, 1994-1995.
Member, Combined Northwestern Memorial Hospital and VA Lakeside Medical Center Research Committee, 1984-1987.

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Editorial/Review Service

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Medical Advisor: Bone Marrow Transplant Newsletter
Abstract Reviewer: American Society of Hematology, 1998
Protocol Reviewer: PDQ Database, National Cancer Institute, 1995-present
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Professional and scientific activity:

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How Scientific Insights can Lead to New Therapy for Follicular Lymphoma (FL)

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Anti-idiotype vaccines, monoclonal antibody therapy, and new targeted strategies have their roots in work that is decades old, but only now sufficiently mature to impact clinical outcomes. Examples of these new treatment strategies for FL are summarized below.

Vaccination Strategies

FL occasionally undergo spontaneous regression leading some investigators to speculate that they might be responsive to immune regulation. All cells in a lymphoid clone express the same idiotype – the variable region of the immunoglobulin molecule – making it a "tumor-specific antigen" and an ideal target for immunotherapy. Custom-made Id-specific monoclonal antibodies led to durable complete remissions in a subset of FL patients.[1] To provide a more long-lasting immune response to the lymphoma-associated idiotype, vaccination with case-specific idiotype was studied.[2] Patients who generated an immune response to vaccination were found to have a better survival than those who did not.2 Based on these encouraging results, a phase II clinical trial in previously untreated patients who were first cytoreduced with mutiagent chemotherapy was initiated.[3] Minimal residual disease detectable by PCR following chemotherapy was eliminated by vaccination in nine of twelve cases, providing evidence for an anti-tumor effect of vaccination. These results led to a phase III randomized trial comparing vaccination plus KLH (a nonspecific immunostimulant) in previously untreated patients who achieved a complete remission with combination chemotherapy to KLH alone (NCI/Biovest).[4] According to a recent press release, there is a statistically significant clinical benefit for vaccination. The details will be presented at the American Society of Clinical Oncology meetings, May 2009. In contrast, two other large phase III randomized trials of anti-idiotype vaccine have shown no benefit to vaccination.[5,6] Differences in study design are likely responsible for the differences in outcomes among the trials. New directions in vaccination include Id-pulsed dendritic cell and membrane proteolipsomal vaccines. Alternative immunologically based approaches are also in development.

Antibody Strategies

Novel antibody approaches to FL include new and improved anti-CD20's, antibodies that bind to alternative targets, and chemoimmuno- and radioimmunoconjugates.

Anti-CD20's

Whereas the mechanisms of resistance to rituximab are many, there are innumerable potential strategies for the development of new anti-CD20 reagents. Ofatumumab is a fully human antibody that targets a novel epitope of the CD20 molecule, and is reported to have stronger complement-dependent cytotoxicity than rituximab.[7] In cell lines, ofatumumab lyses rituximab resistant cell lines with low antigen density and high levels of complement-inhibitory proteins. GA101 is another novel anti-CD20 that was "glycoengineered" to enhance antibody-dependent cellular cytotoxicity (ADCC) through increased affinity to the ADCC receptor FCgRIIIA.[8] GA101 binds a type II epitope on CD20 with high affinity and has greater direct cellular cytotoxicity compared to type I antibodies. Complement-dependent cytotoxicity, however, is reduced. New anti-CD20's with enhanced binding affinity to the low affinity FcγRIIIa receptor include ocrelizumab, AME-133v and PRO131921.[9,10]

Other Targets

CD22 is a B-cell associated antigen expressed on the surface of mature B-cells. The humanized anti-CD22, epratuzumab, acts predominantly by ADCC, but some studies suggest that it acts, at least in part, by mechanisms different from rituximab. Whereas epratzumab and rituximab target different antigens and likely effect cell kill through different signaling pathways, the combination has been studied in relapsed or refractory low-grade, CD20-positive NHL.[11] This combination with extended dosing is currently under investigation.

CD80 is an immune-costimulatory molecule that is constituitively expressed on FL cells. In vitro,

Table 1. Novel strategies for the treatment of follicular lymphoma.

Vaccination
Anti-idiotype
Monoclonal Antibodies
New anti-CD20 monoclonal antibodies
New antigenic targets (CD22, CD80, CD74)
Conjugates
Targeted Therapies
Proteosome inhibition
Histone deacetylase inhibitors
mTOR inhibition
Bcl-2 family inhibitors

crosslinking of CD80 with anti-CD80 antibodies, inhibits cell proliferation, up-regulates proapoptotic molecules and induces ADCC.[12] As a single agent in a phase I trial in relapsed/refractory follicular lymphoma patients, the response rate was modest, but late and prolonged responses were observed leading to a study of the combination.[13,14] The extent to which the addition of galiximab to rituximab improves outcomes compared to rituximab alone remains to be seen.

CD74, the invariant chain of the MHC class II molecule is another attractive target for the treatment of FL. Milatuzumab, a humanized anti-CD74 monoclonal antibody, is rapidly internalized, and consequently has very limited capacity for ADCC or CDC, but may prove to be an ideal agent for conjugation with radioisotopes or cytotoxic agents.[15]

Conjugates

Like the antileukemia agent, gemtuzumab ozogamicin, inotuzumab ozogamicin (CMC-544) is composed of a humanized antibody conjugated to calicheamicin, a potent cytotoxic antitumor agent. This chemoimmunoconjugate targets the B-cell antigen CD22. Responses to CMC-544, alone and in combination with rituximab, have been seen in both FL and diffuse, large B-cell lymphoma.[16,17] A new immunoconjugate, SAR3419, consisting of the humanized anti-CD19 antibody, huB4, conjugated to an antimitotic agent has just entered clinical trial.

Targeted Agents

Not only is the list of potential pathways to be targeted expanding, but for each strategy, there is a growing list of potential agents, each with their own activity and toxicity profiles. Combinations of agents with other targeted therapies as well as chemotherapy are under investigation.

Bortezomib

In addition to its well established role in the treatment of mantle cell lymphoma, the novel proteosome inhibitor, bortezomib, is likely to become an important agent for the treatment of FL. By inhibiting the ubiquitin-proteosome pathway, bortezomib causes the accumulation of multiple proteins including the cyclin-dependent kinase inhibitors such as p27/p21, the tumor suppressor p53, and IκB, leading to cell death through multiple pathways. Response rates are high, and bortezomib is well-tolerated.[18]

HDAC-inhibitors

Many inhibitors of histone deacetylases are currently in clinical trial for the treatment of hematologic malignancies. Vorinostat, approved for clinical use in the US for the treatment of cutaneous T-cell lymphomas, has activity against class I and II deacetylases and activity in FL.[19] This class of agents is likely to be used in combination with others or as a maintenance therapy.

MTOR Inhibition

Inhibitors of the mammalian target of rapamycin (mTOR) have broad effects reflecting its central role as a key kinase, impacting cell growth, proliferation, and apoptotic cell death. Activity in FL has been reported in a phase II study of temsirolimus (CCI-779).[20] Further study in this histologic subtype is warranted.

BCL-2

Inhibition of anitapoptotic Bcl-2 and its family members by a variety of small molecules is under investigation in the malignant lymphomas. Thus far, there have been only minor responses in follicular lymphoma by ABT-263.[21] Other Bcl-2 inhibitors are under study.

Conclusions

As our understanding of the biology of FL grows, so too do the treatment options. The combination of rituximab and chemotherapy was the first step in improving survival for patients with FL. It is likely that new treatment strategies will further improve outcomes.

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Myelodysplastic Syndromes

The incidence of myelodysplastic syndromes (MDS) increases progressively with age, and the prevalence is expected to increase with the current aging of the population. Recent years have seen considerable developments in our understanding of the pathophysiology of MDS, and the interest has been further enhanced by the development of several drugs that are now approved for the treatment of MDS. This session will cover current classifications of MDS, including the recently proposed modifications by WHO and the incorporation of transfusion dependence into the scheme. There are also new data on the impact of cytogenetics on outcome, both with transplant and non-transplant therapy. Additional insights have been gained at the molecular level, showing chromosomal instability including uniparental disomy even in patients without cytogenetic abnormalities as determined by conventional methodology. These abnormalities are likely to affect prognosis and, in fact, may influence the selection of therapy. Hematopoietic cell transplantation, currently the only modality with proven curative potential, has undergone major changes in the form of reduced-intensity conditioning regimens and graft manipulation, allowing the use of transplantation, at least in subpopulations of patients, even in the seventh decade of life. Other non-transplant modalities are being developed. Thus, this session should update the audience on the state of the art of diagnosis, pathophysiology, and therapy of MDS.

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Curriculum studiorum

Luca Malcovati obtained his Medical Degree with honours at the University of Pavia Medical School, Pavia, Italy in 1996. From 1996 to 2000 he completed his training in Hematology at the Department of Hematology, University of Pavia Medical School & S. Matteo University Hospital, Pavia, Italy. From 2001 to 2006 he was awarded a postdoctoral fellowship at the same institution in the frame of a research program on "Novel stem cell transplantation procedures in myelodysplastic syndromes. Since 2006 he hold the position of Assistant Professor of Hematology at the Department of Hematology, University of Pavia Medical School, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

Scientific research

His primary area of clinical and research interest are the myelodysplastic syndromes, where he has been carrying out biological and clinical studies on genomic analysis and gene expression profiling of hematopoietic stem cell, on iron metabolism in refractory and sideroblastic anemias, on the effect of transfusion-dependency and secondary iron overload on survival of patients with myelodysplastic syndromes. Since 2006 he is member of the Advisory Board of the European MDS Registry.

Editorial activity

Since 2003 he is member of the Editorial Office of Haematologica / the Hematology Journal, Official Journal of the European Hematology Association. Since 2008 he acts as Deputy Editor.

Classification of MDS and Its Relevance for Treatment

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Myelodysplastic syndromes (MDS) are hematological disorders characterized by peripheral cytopenia and an increased risk of developing acute myeloid leukemia (AML). The impressive heterogeneity of the natural history of MDS complicates clinical decision-making regarding therapeutic modalities and timing of intervention.

In 1997 Greenberg and coworkers defined the International Prognostic Scoring System (IPSS), based on bone marrow blast percentage, number of peripheral cytopenias, and karyotype. The IPSS was validated in independent patient cohorts, and has become a benchmark for clinical trials and decision-making. In 2001, the WHO formulated a new classification of MDS based on uni- or multi-lineage dysplasia, bone marrow blast count and distinctive cytogenetic features. Among MDS patients without excess blasts, an isolated involvement of the erythroid lineage was found to be associated with a better prognosis compared with multi-lineage dysplasia. The IPSS retains significance within the WHO subgroups; however, the only variable adding prognostic information to WHO categories is cyto-

genetics. In addition, the IPSS included also subjects with 20-30% marrow blasts, now considered as having AML.

Within WHO subgroups the onset of a regular transfusion requirement was found to significantly affect survival of MDS patients. These observations are in agreement with the results of a recent study which showed that the severity of anemia at diagnosis is of additive prognostic value to IPSS in terms of survival.

Based on these observations, a WHO classification-based prognostic scoring system (WPSS) was defined, including WHO subgroups, karyotype abnormalities categorized according to the IPSS, and transfusion requirement. Patients are stratified into five distinct risk groups, showing different survival (median survival ranging from about 140 months to 10 months), and probability of leukemic evolution (2-year probabilities of leukemic progression ranging from 2 to over 80%).

The WPSS is based on a dynamic prognostic model that provides an accurate prediction of survival and risk of leukemic evolution in patients with MDS at any time during the course of the disease, and that may, therefore, be used for implementing risk-adapted treatment strategies. In particular, the dynamic WPSS was proven to significantly stratify the outcome of MDS patients receiving allogeneic stem cell transplantation.

Recently, the prognostic value of bone marrow histological abnormalities was refined in MDS patients classified according to WHO criteria. A moderate to severe bone marrow fibrosis was shown to be a significant independent prognostic factor in both low- and high risk patients. In prognostic terms, the increase in risk due to the presence of BM fibrosis sustains a one-step shift into a more advanced WPSS risk group.

Finally, it is known that extra-hematological comorbidity significantly limits the eligibility of MDS patients to intensive treatments as allogeneic stem cell transplantation and affect transplant-outcome. The hematopoietic cell transplantation-comorbidity index represents a useful tool estimate the comorbidity-related risk, and integrating MDS- and comorbidity-related risks allows to stratify more accurately the outcome of patients receiving stem cell transplantation. However, the presence of one or more comorbidities also affect the natural history of MDS, increasing non-leukemic-death. Therefore, an accurate evaluation of comorbidity must be part of the risk assessment in MDS patients.

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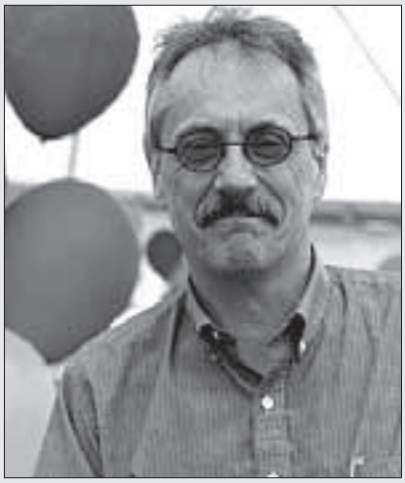

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Treatment of MDS: Disease Control or Curative Therapy?

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Myelodysplastic syndromes (MDS) comprise a spectrum of clonal marrow disorders with the potential of evolving into leukemia. However, the course is extremely varied, and life expectancies may be as long as a decade or two or as short as a few months. Recent years have seen considerable progress in our understanding of subgroups of patients with MDS, and we are beginning to develop a better understanding of the underlying pathophysiology. The best studied example may be that of patients with a deletion of part of the long arm of chromosome 5 [del(5q)] for which lenalidomide has become the first-line therapeutic strategy. It is also clear that more complex/high-risk clonal cytogenetic abnormalities and the need for regular red blood cell transfusion support are major risk factors for accelerated disease progression. What is not clear is what are the factors responsible for the manifestation of high-risk chromosomal abnormalities or for the need of regular transfusion support due to reduced production or increased destruction of red cells.

We and others have shown that patients who present early in the disease course or are clinically assessed as having "low-risk" disease often have increased rates of apoptosis of hematopoietic cells in the marrow, at least in part related to the upregulation of pro-inflammatory and pro-apoptotic cytokines such as TNFα. In fact, we have shown that treatment of those patients with a soluble TNF receptor, particularly when given in combination with immunosuppressive therapy with antithymocyte globulin (ATG), will lead to responses in as many as 60% of patients, in some of whom the responses persist unmaintained for years. Conceivably, this

success is achieved by "resetting the rheostat." Others have suggested factors such as the presence of HLA-DRB15 as a parameter that predicts a high probability of response to immunosuppression. Conceivably, those patients should receive immunosuppression as first-line therapy.

A considerable amount of work has been done on various mutations in hematopoietic cells and even whole genome analysis is being carried out in an attempt to identify predisposing factors. Some of our studies have focused on the interactions between hematopoietic cells and stroma and have yielded potentially relevant data as to why hematopoietic cells in the marrow of patients with MDS undergo apoptosis at an accelerated rate. These studies, including a characterization of the effects of interleukin-32, PYCARD, and p53, may also be relevant for the resistance to apoptosis observed in later stages of the disease. Thus, these and other studies emphasize the need for further investigations to characterize subgroups of patients with MDS for whom a particular type of therapy may be more likely to be successful than in other patients.

As of now, the only modality with proven potential to cure MDS is hematopoietic cell transplantation (HCT). Without going into details of various MDS classifications, available data suggest that patients who present with advanced or high-risk disease, as indicated by high-risk cytogenetics, increased proportions of marrow myeloblasts, and peripheral blood cytopenias or frequent transfusion needs, should be transplanted early in the disease course. However, even patients with otherwise low-grade disease who are, for example, severely neutropenic or transfusion-dependent, may gain an advantage and prolonged survival or even cure if transplanted earlier rather than later, by preventing transfusion-related problems and infectious complications. For patients with low-risk disease, i.e., for example, normal cytogenetics, low blast counts, and no transfusion need, some 75-80% are likely to become long-term survivors after allogeneic HCT either from a genotypically HLA-identical sibling or from an unrelated donor HLA-matched as determined by high resolution typing. We have recently shown that among patients with low blast counts, a subgroup with a high risk for post-transplant relapse can be identified on the basis of an aberrant phenotype of marrow cells prior to transplantation. Presumably, those patients should be subjected to more aggressive conditioning or preemptive post-transplant therapy. Among patients with advanced disease (for example, high risk by IPSS), the probability of long-term survival in remission after HCT may be only in the range of 25%. The major reason for this difference, as compared to patients with low-risk disease, is a significantly higher relapse rate. This applies also to patients with secondary or treatment-related MDS in whom the high frequency of high-risk cytogenetics determines the overall poor outcome. Common to all patients is, of course, the risk for GVHD and other transplant-related complications.

The relatively high complication rate has led to various efforts to modify the transplant regimen. Considerable effort has gone into the development of reduced-intensity conditioning regimens. It is clear from those studies that reducing the intensity of conditioning (for example, instead of using a combination of high-dose total body irradiation and cyclophosphamide, prepare the patient with fludarabine and low-dose TBI) can reduce the day-100 mortality to about 5%. There is evidence, however, that such an approach is associated with a somewhat higher relapse rate. In a recent report, the 3-year relapse-free survival for patients with de novo MDS was 22%. It is nevertheless of note that individual patients in their early 70s have been transplanted successfully. This is an important observation as the median age of patients at the time of diagnosis of MDS is 70-75 years. Currently, however, selection of patients for transplantation with MDS who are 65 years of age or older should occur on an individual basis, considering the patient's motivations, and, definitely, the underlying disease severity. These decisions should also consider the presence of co-morbid conditions, which have been shown to have a major negative impact on transplant outcome.

Currently ongoing investigations are examining whether pre-transplant debulking therapy, be it by induction chemotherapy as used for acute leukemia or approaches that use DNA methyltransferase inhibitors or other modalities, and post-transplant manipulations, such as reduction of immunosuppression, preemptive donor lymphocyte infusion, adjuvant administration of DNA methyltransferase inhibitors or NK cell infusion.

As indicated above, a better understanding of the underlying pathophysiology might, indeed, direct us one way or another when selecting patients for a given transplant regimen.

Acute Myeloblastic Leukemia

The treatment of AML remains unsatisfactory. Despite significant progress over the past two decades, the majority of patients still die from their disease. While major progress has been made in identifying genetic and molecular targets for AML, this has not yet translated into significant clinical benefit.

The session will address several important issues in the management of AML. First, current standard induction therapy for AML has not changed significantly over the past three decades. This session will explore very recent studies regarding the benefit of intensifying induction therapy. Furthermore, the non-transplant chemotherapeutic approach for post-remission therapy has also not changed significantly in recent decades. Enormous uncertainty exists regarding the amount of such therapy that needs to be given. Many of the standard regimens are not based on strict evidence-based criteria. All of this will be reviewed in detail.

Second, allogeneic transplantation clearly offers the most potent anti-leukemic therapy in AML. Harnessing the graft-versus-leukemia effect (GVL) has become recognized as the dominant therapeutic mechanism in AML. The session will address who should receive an allogeneic transplant. Should all patients with a normal karyotype be transplanted? Including NPM1+/Flt3- ? Should any patient with favourable cytogenetics be transplanted? Furthermore, the role of transplants from alternative donors in AML will be reviewed as well as the increasing use of reduced-intensity transplants AML. When and for whom?

Third, autologous transplantion has a more potent anti-leukemic activity than standard chemotherapy, as demonstrated by the reduced relapse rate. Its role has been controversial, in part due to a high mortality rate in the past when bone marrow was used as the source of stem cells. Its relevance to current practice with the use of peripheral stem cells in the management of AML will be also assessed. What is its role for patients with favourable cytogenetics? Is there any role beyond first remission? How much post-remission therapy needs to be given prior to an autologous transplant?

Overall, the intent of this session is to provide a state-of-the-art review of the current therapeutic approach in the management of induction and post -remission therapy for adults with AML ..

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1993-1997	Eastern Cooperative Oncology Group, Leukemia Committee, Chairman
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
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1999-pres	Appeals Subcommittee, Hematology, Israel Ministry of Health, Member.
2001-pres	Technion Senate Evaluation and Promotion Committee

Editor of Journals

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2. Co-editor: Blood Reviews. 1993 to present.
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4. Section Editor: Leukemia. Clinical Trials. 1995 to present.
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9. Editorial Board: Clinical Leukemia. 2006 to present.
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Induction and Non-Transplant Consolidation in AML

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Induction Therapy

Standard induction therapy in AML began in the late 1960s, when both cytarabine and anthracyclines were shown to have significant activity as a single agent. It was but a short leap to studying the combination of cytarabine and anthracyclines, where more than 50% of young adults could get into complete remission (Table 1).

Table 1. Historical Development of Standard Induction Therapy in AML

1968 - 1969
- Single agent activity of cytarabine or anthracycline

CR: 30 – 40%

1970
- Combination of Ara-C and anthracycline

CR: > 50%

A series of classic experiments in the USA by the Cancer and Leukemia Group B (CALGB) some 25 years ago established what really became standard of care for at least 2 decades. Data from carefully controlled randomized studies established that continuous infusion cytarabine was most effective; 3 + 7 was more effective than 2 + 5; daunorubicin was less toxic than adriamycin; and anything less than 45 mg/m^2 was significantly less effective. Furthermore, there was no advantage in giving 200mg rather than 100mg of cytarabine and 6-thioguanine did not improve the overall results of induction. The early 1990s ushered in a new era, studying newer anthracyclines (Table 2).

Based on these studies, standard induction consisted of daunorubicin 45 mg/m^2 i.v. for 3 days and cytarabine 100 mg/m^2 by continuous infusion for 7 days. This has been a standard against which most new regimens have been tested (Table 3).

In the early 90s, a series of randomized studies compared 45 or 50 mg/m^2 of daunorubicin with a

Table 2. Historical Development of Standard Induction Therapy in AML

1981 - 1987
- Continuous infusion Ara-C most effective.
- 3 + 7 more effective than 2 + 5
- Daunorubicin less toxic than adriamycin
- Daunorubcin 30 mg/ m^2 inferior to 45 mg/m^2
- Ara C 100 mg/m^2 = 200 mg/m^2
- DA = DAT

1990 - 1992
- Newer anthracyclines

variety of newer agents, comprising idarubicin, mitoxantrone, aclarubicin or amsacrine. Of note, in every one of these studies the alternative anthracycline or anthraquinone was superior to daunorubicin 45 mg/m^2 either in complete remission rate, disease-free survival, overall survival or in the number of courses needed to get into complete remission (Table 4)[1]. Furthermore, sequential studies of induction by the same groups of investigators showed a significant disadvantage to 45 mg/m^2 of daunorubicin[2-5]. It was therefore surprising that despite all these randomized studies daunorubicin at 45 mg/m^2 remained as the standard of care for so many years and has been widely used both in major cooperative groups and in the community at large.

Several major studies have demonstrated that higher doses of daunorubicin can be administered safely, going up to doses of 80 or 90 mg/m^2.[6,7] Recently two major cooperative groups have prospectively compared 45 mg/m^2 of daunorubicin versus 90mg/m^2. The Eastern Cooperative Oncology Group (ECOG) several years ago initiated a study in younger patients up to age 60 and very recently reported a significantly higher complete remission

Table 3. Standard Against Which Most New Regimens Are Tested

- Daunorubicin 45mg/m2 IV x 3 days
- Cytarabine 100mg/m2 continuous infusion x 7 days

Table 4. Randomized Studies of Daunorubicin 45-50mg/m2 and Cytarabine Versus Other Combinations in Adults < 50-60 years

	Daunorubicin (mg/m2)	Other (mg/m2)	CR	p	DFS better*	OS better*	More in CR after 1 course*
Vogler, 199220	45	Idarubicin 12	58 vs 71	.03			
Wiernik, 199221	45	Idarubicin 13	70 vs 88	.03		+	
Berman, 199122	50	Idarubicin 12	58 vs 80	.005		+	+
Mandelli, 199123	45	Idarubicin 12	same	-			+
Arlin, 199024	45	Mitoxantrone 12	53 vs 63	.1			+
Hansen, 199125	45	Aclarubicin 75	50 vs 64	.04	+		
Berman, 198926	50	Amsacrine 190	54 vs 70	.03	+		

* $p < .05$

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(CR) rate for patients receiving 90 mg/m^2. More importantly, the overall survival (OS) was also significantly prolonged among patients receiving the higher dose of daunorubicin, especially for those patients with favorable or intermediate cytogenetics [8]. The HOVON/ SAKK has recently completed a study in older adults giving 45 mg/m^2 or 90mg/m^2. The final data from this study are anxiously awaited. Thus, based on historic trials and the most recent data, it would be probably fair to say that 45 mg/m^2 should no longer be considered as a standard of care. For induction therapy the dose should be clearly higher – somewhere between 60 and 90 mg/m^2 – and the optimal dose has not been established.

In the MRC AML15 study in younger adults, 1115 patients in induction were randomized to receive, or not, gemtuzumab ozogamicin in addition to several other induction regimens. There was also a randomization between 3 different induction regimens, but all patients underwent the gemtuzumab ozogamicin randomization. The post-remission therapy was identical in both arms of the study. The data were initially presented at the annual meeting of the American Society of Hematology in 2006, reporting a similar complete remission rate (CR) in both arms, but a significantly improved disease-free survival (DFS) among patients receiving gemtuzumab ozogamicin – 5% versus 40% at 3 years (p= .008).[9] Further follow-up is anxiously awaited.

Table 5. Post-Remission Therapy for AML< 60 yrs

- Some form of post-remission therapy critical
- Must include AT LEAST one cycle of intensive consolidation
- Such intensification is most beneficial for patients with the CBF AML.

Little enthusiasm among the groups for prospective studies of post-remission chemotherapy

Non-transplant post-remission therapy

Young adults

Non-transplant post-remission consolidation consists of intensive chemotherapy. The need for any post-remission therapy was established in the landmark study conducted by the Eastern Cooperative Oncology Group (ECOG) in 1983 which prospectively included an observation arm as part of the post-remission strategy10. Obviously, this was a study that could not be done today, but was ethically appropriate in 1983. Importantly, the study was stopped early by the National Cancer Institute (NCI) in the USA when virtually every patient who was in an observation arm relapsed by 18 months.

A classic trial by the Cancer and Leukemia Group B (CALGB) studied post-remission therapy in young adults up to age 60 with cytarabine and compared 3 different doses of cytarabine given for 4 cycles followed by maintenance therapy. The data from this prospective study demonstrated a significant improvement for patients less than 60 years of age when a high dose of cytarabine, at 3 grams/m^2, was given[11]. The problem is that these data have been misunderstood by many. These data only demon-

Table 6. Post-Remission Therapy for AML > 60 yrs

- Probably no justification for more than one cycle of chemotherapy
- Favorable cytogenetics may be an exception
- Hard to justify any post-remission therapy for unfavorable cytogenetics
- Further data needed regarding maintenance therapy

strate that 3 grams/m^2 is better than 400mg/m^2 or 100mg/m^2 when given for 4 cycles and followed by maintenance therapy; they do not tell how many cycles one should get and they also provide no information that one could not do the same thing with other agents. Of note, in the CALGB study the data have been almost confined to patients with favorable cytogenetics[12].

Many other questions remain unanswered regarding post-remission therapy in young adults. The optimal number of cycles of any form of consolidation therapy are not known, nor is the optimal drug. Regimens that have not used high-dose cytarabine report results that are comparable to the data using high-dose cytarabine. In addition, data using one cycle of cytarabine, as published by the US Intergroup in 1998[13], are very similar to the published results when 4 cycles of high-dose cytarabine were used.

An important study by the Finnish Leukemia Group attempted to determine how much consolidation needs to be given. In this study patients were given 2 courses of consolidation and were then randomized between receiving additional 4 cycles of consolidation versus observation. No difference was seen in survival from randomization[14]. Thus, for younger adults it is fair to say that the knowledge at the present time suggests that in a non-transplant setting some form of post-remission chemotherapy is critical and reasonable data show that such therapy should include at least 1 course of very intensive consolidation. Although most people administer more than 1 cycle, it is important to note that there are no prospective data that clearly establish this. (Table 5)

II. Older Adults

Regarding older adults, the issues concerning post-remission therapy are even more basic. As opposed to younger adults, the need for post-remission therapy has never been unequivocally established for older patients. It has never been shown that any form of post-remission therapy makes a difference; although in common practice, fit older adults almost always receive consolidation therapy. What is also not known is if this is offered to patients, how many cycles should be given.

The largest study of older patients with AML was the MRC AML 11, which was published 8 years ago15. Essentially this trial compared older patients who went into remission, got one course of consolidation with daunorubicin, cytarabine and 6-thioguanine (DAT) and were then randomized to 3 further cycles versus observation only. The data demonstrated clearly that with the doses given in this study there was no particular value for further intensification after a single consolidation. Studies from other groups, such as the German AML Cooperative Group or the Cancer and Leukemia Group B (CALGB) also suggested that there is no benefit to giving more than one cycle of intensive chemotherapy[16,17].

The issue of maintenance therapy is particularly pertinent for older patients. An important study from the EORTC showed improved disease-free survival after maintenance with cytarabine, although the overall survival was not significantly improved.[18] This is clearly an area that has not been adequately explored in older patients.

The role of cytogenetics, crucial for assigning post-remission therapy in young adults, is also an important one for older patients. There are data from several studies showing that post-remission therapy, as currently given, provides little benefit over older patients with unfavorable cytogenetics[5,19]. It is therefore even more difficult to make a case for giving post-remission therapy to such patients outside of a clinical study. (Table 6)

Thus, the issue of non-transplant consolidation therapy is even more confounding than the uncertainties in induction therapy. Hopefully, future studies will set more light on these issues.

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University/Medical School Education

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MA Oxon	Oxford, June 1968
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MRCP (UK)	October 1971
MRCPath (Haematology)	June 1975
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Current Post:
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November 2000 – present

Professor of Haematology
University College London Hospital and UCLH NHS Trust
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1992 – 2000 (initially Director of Clinical Haematology since September 1977, Director of All Cancer Services for the UCH NHS Trust).

Medical Director
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Date of Medical Registration:
December 1968

CLINICAL TRAINING AND EXPERIENCE

House Physician: Medicine Chase Farm Hospital, Enfield	Feb 1969 – August 1969
House Surgeon: Surgery Edgware General Hospital	Aug 1969 – Feb 1970
Resident Clinical Pathologist Guy's Hospital	Feb 1970 – Sep 1970
Senior House Officer: Medicine University of Edinburgh Gastrointestinal Unit Western General Infirmary	Sep 1970 – Feb 1971
Registrar in Haematology Western General Infirmary, Edinburgh	Feb 1971 – June 1972
Cancer Research Campaign Research Fellow in Clinical Immunology Edinburgh Royal Infirmary	June 1972 – Oct 1973
Senior Registrar in Haematology Addenbrooke's Hospital , Cambridge and Department of Haematological Medicine, University of Cambridge	Oct 1973 – Mar 1976

Other Appointments and Affiliations
1. Fellowship of the Royal College of Physicians of London since 1983 to present.
2. Fellowship of the Royal College of Pathologists 1987 to present.
3. Member of the British Society of Haematology 1975 to present.
4. Chairman Use of Medicines Committee UCLH NHS Trust 1992-2000
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6. Co-Chairman of Clinical Governance Group UCLH NHS Trust 1998 – 2000
7. Member of Regional High Awards Committee North East Thames 1996 to 1999.
8. Chairman of North East Thames Regional Haematologists 1988 to 1992.
9. President of British Society for Blood and Bone Marrow Transplantation December 1998 to December 2000.
10. President of British Society for Haematology 1999 – 2000.
11. Editor of Journal Leukaemia and Lymphoma 1993 – 2003.
12. Editorial Review Board Bone Marrow Transplantation 1988 to 2003
13. Member of Editorial Board of Acta Haematologica 1993 to 2003.
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PUBLICATIONS (n:284) (1972-2009)

Stem Cell Transplantation in Acute Myeloid Leukemia in the Younger Adult

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Despite the fact that 70-80% of patients with AML achieve complete remission (CR) most of them eventually relapse and die of the disease. Once remission has been achieved, further intensive therapy is needed to prevent relapse. Patients under the age of 60 have three main options after going into remission: intensive chemotherapy (IC), autologous stem cell transplantation (ASCT), or allogeneic stem cell transplantation (allo SCT) of some kind. Patients with standard-risk disease have traditionally been referred for a matched sibling allograft if a donor is available and the patient's performance status is adequate. In recent years, chemotherapy post remission has improved patients' outcome, with a 50% 5-year overall survival (OS) and 40% disease-free survival (DFS) similar to that achieved with allo SCT, narrowing the differences between chemotherapy and such transplants (MRC AML 12. The high mortality of allograft (20%-25%), even today, is therefore making it less attractive in comparison with chemotherapy, and selection of patients to be given allografts in first remission (CR1) should be done very carefully

Risk Group Designation

Although all patients included in these studies were diagnosed with AML, there is a considerable variation in their risk of relapse. Cytogenetics is now considered the most powerful single prognostic factor. Whilst patients with t(15;17) or chromosomal abnormalities involving the core binding factor [t(8;21) and inversion 16] are classified as having a favorable prognosis, with approximately 30% risk for relapse, patients with abnormalities in chromosome 5/7/3(q) or multiple chromosomal abnormalities have an approximately 75% chance of relapse However, most patients do not belong to these two categories and are classified as having standard-risk disease (5-year OS = 43%). Recent studies have indicated that an internal tandem duplication (ITD) in the FLT3 gene may adversely affect clinical outcome in AML patients.

Prevention of Relapse in Young Patients

A significant reduction in relapse rate (RR) has been observed since the introduction of intensified post remission therapy. The Cancer and **Leukemia** Group B (CALGB) randomly assigned 596 patients in CR1 to receive 4 courses of cytarabine at 1 of 3 doses. High-dose cytarabine (18 g/m2/course) was demonstrated to be superior to 2 g/m2/course, with a DFS of 44% versus 29% (P = 0.003) and an OS of 52% versus 40% (P = 0.02).

A different consolidation regimen, containing no more than 1 g/m2 cytarabine rather than high dose, has been successfully used by the Medical Research Council (MRC) AML 10 trial (DFS and OS were 43% and 40%, respectively).

The number of postremission chemotherapy courses required is unresolved. Recent data of the MRC AML 12 trial seem to show no advantage for 4 consolidations compared with 3

Main Problems Interpreting Results of Prospective Trials

There remain some problems with interpreting the results of major prospective AML trials. Patients who receive allo SCT are clearly selected, because a proportion of patients with a matched sibling donor do not receive a transplant. Patients may be excluded from transplant because of early relapse/death, previous complications with chemotherapy, or other medical problems. It is not possible to predict the direction of such biases and indeed they are at the core of problems with interpreting registry data.

On intent to treat basis, "crossover" between arms and/or a failure to receive intended treatment, may in some circumstances radically underestimate differences between arms, if happening to a significant degree.

Both compliance and randomization were quite poor in most prospective trials.As a result, both beneficial and harmful effects might be underestimated.

Allo SCT is usually delayed, which might lead to greater selection of patients with favorable disease who remain in CR until transplant.

A large number of patients are needed for a difference in the efficacy between postremission therapy options to be detected. For example, to detect a 10% difference in survival from 40% to 50% (P = 0.05 with 90 power), 1000 patients are needed

Allo SCT in AML

With chemotherapy producing a less than 20% chance of survival before the early 1980s, durable survivals up to 50%, with a low relapse risk of 15-25%, were reported in patients receiving allografts in CR1. Today, the DFS and OS in nontransplanted patients begin to achieve this rate of durable survival and make such treatment comparable to that achieved with allograft (MRC AML 12, unpublished data).

Allo SCT in the main prospective trials

All trials confirmed allo SCT to be the best antileukemic treatment, associated with a relapse risk of 24%-36% compared with 46%-61% observed with ASCT/IC. However, many prospective studies failed to show an improved OS in patients assigned to allo SCT.

The MRC AML 10 trial observed a survival advantage for patients treated with allograft compared with patients treated with IC who had no available donor. However, the survival of patients who had a donor but were eventually treated with only IC was inferior to the survival of not only allografted patients but also the "no donor" group. These data indicate that patients who eventually received the transplant were biologically selected to have a favorable prognosis, as patients with poorer prognosis did not get the transplant. However, the EORTC/GIMEMA AML 10 trial has recently reported a higher survival rate in poor-risk patients assigned to allograft (OS = 50.4% versus 27.7%).

Summarizing the data regarding allograft in CR1 in AML patients remains difficult:

None of the trials is truly prospective with full biological assignment based on donor availability as surrogate for intent-to-treat analysis.

Pretransplant chemotherapy varies in its number of courses in some trials This variability in the number of courses might affect transplant outcome in relation to both toxicity and time to treatment bias.

All studies had problems in delivering the assigned treatment This might underestimate both its efficacy and toxicity.

The superiority of allo SCT depends upon comparison with the best available IC, but the best available IC was not always used in every trial

Upper age limit for transplant will affect outcome, as toxicity increases with age, probably more than with chemotherapy treatment alone

Most of the major studies were initiated more than 10 years ago. The currently improved HLA-matching stem cell transplant technology and supportive care may now make many of the toxicity figures meaningless. PBSCT may also reduce relapse risk. The problem remains, however, that big studies with a large number of patients take a number of years to conduct, and during that period various aspects of treatment can change radically.

Varying RRs of different risk groups mean that therapy should be tailored according to each individual patient's risk.

It should be noted that with the increasing availability of very closely matched unrelated donors, the "donor vs no donor" approved may no longer be valid. Increasingly, for those without a sibling donor, a closely matched unrelated donor can be found and these patients would previously have been classified in the "no donor" group. This alters the "no donor" group in a statistically way and inbalances the comparison.

T-cell depletion

GVHD is a major cause of mortality and morbidity after allo SCT, and removing the T lymphocytes from the donor bone marrow can decrease the incidence of both. However, unselected T-cell depletion may theoretically increase RR (preventing the graft-versus-**leukemia** effect) and enhance treatment-related infections due to delayed immunological recovery.

Nevertheless, it seems that T-cell depletion may not necessarily increase relapse risk in AML allografted patients, though decreasing GVHD.

However, it is still unclear whether T-cell depletion can provide any benefit beyond reducing GVHD and improving the quality of life.

Low-intensity stem cell transplantion

Low-intensity stem cell transplantation (LI SCT) is being increasingly used, aiming to exploit the curative potential of allo SCT by inducing graft-versus-

tumor effect without the morbidity and mortality associated with conventional transplantation. Low-intensity SCT is less toxic and therefore may be considered for some patients who are otherwise not eligible for conventional allogeneic transplant. However, its efficacy in AML patients has still not proven to be as good as that of high-intensity allo BMT. The EBMT reported on 69 patients (median age 51) treated with LI BMT for AML or myelodysplastic syndrome (MDS). More than half of the patients had refractory/relapsed disease at transplantation. Graft failure was more frequent than observed with conventional allo SCT, though 77% achieved > 95% donor chimerism. Patients' outcome was highly dependent on disease status at transplantation: 1-year TRM, RR, and OS were 47%, 30%, and 41% for the whole group, compared with 17%, 21%, and 67% in patients transplanted in CR (CR1 or later). However, follow-up remains short.

Peggs et al have recently reported 44% progression-free survival (PFS) and 53% OS (median follow-up, 18 months) in 24 patients aged 18-60 years (median 47) treated with low-intensity matched related/unrelated SCT (total body irradiation, melphalan, fludarabine, Campath-1H) for MDS/AML (n = 17) DFS and OS were higher in AML patients transplanted in CR1 (n = 15), approaching 57% and 62%, respectively. Longer follow-up and prospective comparison with IC are needed in order to define the role of LI SCT in selected AML patients. The MRC AML 15 trial intends to allow the possibility of LI SCT in patients aged 35-45 years who have a matched related donor, while suggesting conventional transplant for the younger recipients

Outcome of Allo SCT in Different Risk Groups

Good-risk patients

All prospective studies except the Intergroup trial-failed to show a survival advantage with allo SCT in CR1 in patients with favorable cytogenetics. It appears that the Intergroup result might reflect a random result rather than a genuine tendency, because of the small number of patients included.

Acute promyelocytic **leukemia** (APL) patients, but not patients with t(8:21) or inversion 16, were reported to have a significantly lower RR with allograft in CR1 (donor vs no donor analysis: 22% vs 43%, P = 0.02) However, it seems that since the introduction of ATRA, nontransplant therapy can provide the same good result. The only study that observed a survival advantage in good-risk patients treated with autograft was the Intergroup study. However, this "superior" outcome might actually reflect the poor results achieved with chemotherapy. It now seems that there is no place for allo SCT or ASCT in CR1 in patients with favorable-risk cytogenetics.

Standard-risk patients

Both the MRC AML 10 trial and the EORTC/GIMEMA AML 10 trial reported reduced RR and improved DFS in patients with standard-risk disease assigned to allo SCT. However, it is still unclear whether allo SCT can improve patients' OS and the outcome is probably related directly to recipient.

There is still significant heterogeneity in this group of patients and RR is influenced (independent of cytogenetics) by response to first induction and the presence of the FLT3 mutation. It is possible that some of these standard-risk patients (e.g., those who express the FLT3 mutation or failed to remit with first course of induction) will do better with allo SCT, while others will gain no advantage from being transplanted.

Poor-risk patients

Researchers from the EORTC/GIMEMA AML 10 trial have recently reported their current results. When patients are divided into risk subgroups based on their cytogenetics, it seems that patients with unfavorable cytogenetics get the maximal benefit from having allo SCT compared with ASCT or IC. Of interest, the EORTC/GIMEMA AML 10 study considered all patients without a favorable/normal karyotype as having poor-risk disease. However, the MRC AML 10, which failed to show an advantage for allograft in poor-risk patients but showed one for the standard-risk group, included approximately half of these patients with unfavorable cytogenetics in the standard-risk group rather than in the unfavorable-risk one.

Other Options for Transplantation for Patients Without a Matched Related Donor

Matched unrelated donor transplantation (MUD)

MUD in CR1. Despite the controversy about the advantage of matched related donor allograft in CR1 in poor-risk patients, the very grim prognosis observed with chemotherapy (less than 30% DFS) might justify using MUD in CR1 in this group of patients. However, there is currently little evidence that any kind of allo SCT can cure large numbers of these poor-risk patients.

MUD in CR2. Patients with unfavorable cytogenetics who achieve a second CR and have no matched related donor are often referred to MUD SCT. How-

ever, MUD in CR2 in patients with favorable-/standard-risk cytogenetics remains controversial and its superiority compared with ASCT is still questionable. Lazarus et al, on behalf of the IBMTR, have retrospectively compared the outcome of AML patients (CR1/CR2) treated with MUD versus ASCT between 1989-1996. Three-year LFS was 33% in MUD patients versus 40% with an autograft. However, long-term side effects were significantly higher in MUD patients and selection bias is unknown.

On the basis of these incomplete retrospective data, it may be reasonable to consider MUD in young patients with adverse cytogenetics and short CR1s who have a matched unrelated donor (at least 10 antigen matching). Conversely, patients older than 40 with a long CR1 may do better with ASCT, if their disease is in genuine remission and enough cells can be harvested.

T-replete versus T-depleted MUD. The reduced GVHD-related mortality achieved with T-cell depletion is often balanced by increased RR and overwhelming infections.

In contrast to patients with some other malignancies, AML patients may achieve a survival advantage with T-depleted marrows compared with T-replete ones, justifying T cell depleted MUD in selected AML patients. Nevertheless, data justifying this are still scanty and further studies are needed to support this strategy

Haploidentical BMT

Haploidentical BMT is an option for patients who do not have a matched related donor (approximately 70% of patients). The historical data concerning haploidentical BMT in AML patients were disappointing. These disappointing results might be attributed to patient selection for transplant (advanced disease) as well as to a high rate of transplant-related complications, mainly GVHD, which in turn was replaced by a high incidence of graft failure as T-cell depletion has been introduced to prevent GVHD. T-cell depletion by itself was associated with delayed immune recovery, resulting in high incidence of severe infections. However, it seems that recent modifications have succeeded in making some progress. Stem cell megadose (10^6 CD34 cells/kg) is essential to overcome the HLA barrier in full haplotype-mismatched transplants. Further reduction of T-cell dose infused reduces the frequency and the severity of GVHD significantly. Posttransplant granulocyte colony-stimulating factor (G-CSF) appears to interfere with natural killer (NK) cell recovery and has therefore been excluded. Donor's NK cell alloreactivity, a unique phenomenon of mismatched transplants, appears to play an essential role in preventing relapse and supporting stem cell engraftment. A recent update from Perugia suggests that the current morbidity and mortality in AML patients having haploidentical BMT is not higher than reported with matched allogeneic BMT. Event-free survival in high-risk patients transplanted in CR1/CR2 approached 45%, with an RR of less than 15% A donor versus recipient NK cell alloreactivity is essential for achieving graft-versus-tumor effect and may therefore become a major criterion for donor selection in mismatched SCT.

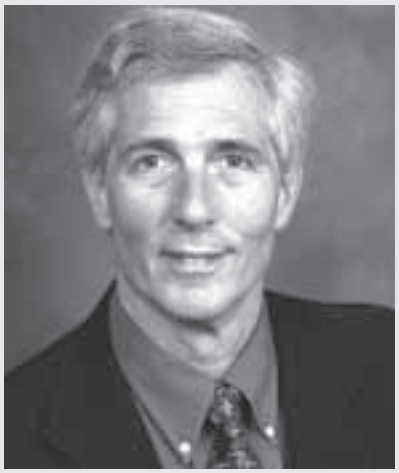
Stem Cell Transplantation

There was a modest overall survival advantage of allogeneic SCT in the MRC AML 10 Trial, but there was sufficient uncertainty to justify continuing to address the question in standard and high risk patients in the MRC AML 12 trial. In the AML 12 trial where risk was defined only on cytogenetics and morphological response to course 1, there was no overall survival benefit for transplant in either risk group. Nevertheless, the AML 15 trial, permitted standard risk patients who had a matched sibling donor to go forward to transplantation including a reduced intensity allograft, and for high risk patients a matched unrelated donor was permitted. The comparative results of transplantation in the AML 15 trial is not yet available, but both the reduced intensity allograft allograft and transplant from al unrelated donor deliver a similar survival to a matched sibling transplant.

In this large dataset the new risk score was used, in a retrospective analysis, to re-examine to role of transplantation. In patients with an intermediate score there was again no survival benefit from transplantation, however in the newly defined high risk score patients there was a significant survival difference (33% vs 18% p=0.01). This leads to the conclusion that risk score can identify a population of patients which benefits from transplantation, and comprises a larger population than defined as high risk by previous criteria. However, only 30% of such patients received a transplant.

Conclusion

The value of transplant ultimately depends upon the risks and benefits of alternatives such as new chemotherapies or antibodies. If the promise of the new Anti CD33 antibodies is maintained and outcome without transplant improves then far few patients will need to be considered for what is still a high risk treatment.



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CURRENT POSITIONS:

1993-present	Clinical Professor of Medicine, University of California, San Francisco
1999-present	Chair, Transplant Committee, CALGB
1991 – present	Cadre member, Leukemia Committee, CALGB
2004 – present	Member, Hematology subspecialty board, American Board of Internal Medicine

PAST POSITIONS:

1998-2008	Co-leader, Hematologic Malignancies Program, Comprehensive Cancer Center, University of California, San Francisco
1990-2008	Director, Hematologic Malignancies and Bone Marrow Transplant Program, University of California, San Francisco
1987-1993	Associate Clinical Professor of Medicine, University of California, San Francisco
1981-1987	Assistant Clinical Professor of Medicine, University of California, San Francisco
1981-1990	Director, Pheresis Service, University of California, San Francisco

EDUCATION:

1970	Harvard College, Cambridge, MA - B.A. (Biochemistry) Detur Prize for Academic Excellence Phi Beta Kappa
1974	Stanford Medical School, Stanford, CA - M.D.

TRAINING:

1974-1975	Intern in Medicine, Stanford University Hospital
1975-1976	Resident in Medicine, Stanford University Hospital
1977-1978	Resident in Medicine, Stanford University Hospital
1978-1981	Fellow in Hematology/Oncology, University of California, San Francisco

BOARD CERTIFICATION:

1978	American Board of Internal Medicine, Internal Medicine
1980	American Board of Internal Medicine, Hematology
1982	American Board of Internal Medicine, Oncology

MEMBERSHIPS:
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American Society of Blood and Marrow Transplantation

COMMITTEES:
Co-chair, Education Program, American Society of Hematology, 2006
Chair, Transplant Committee, CALGB (1999-present)
American Board of Internal Medicine, Hematology Board (2004-present)
Leukemia Committee, Cancer and Leukemia Group B (1991-present)
Translational Research Review Subcommittee, Leukemia Society of America (1996-2000)
Acute Leukemia Committee, Center for International Blood and Marrow Transplant Research (1998-present)
Program Committee, American Society of Hematology (1985, 1994, 2005, 2006)
Education Committee, American Society of Hematology (1986, 2005-2006)
Program Committee, American Society of Clinical Oncology (1993,2004)
Publications Committee, American Society of Clinical Oncology (1996-98)
Board of Directors, Leukemia Society of America, Northern California

PUBLICATIONS: 73
ABSTRACTS: 75
BOOK CHAPTERS & EDITORSHIPS: 7
SCIENTIFIC PRESENTATIONS AT MAJOR MEETINGS: 21

JOURNALS REVIEWED:
Annals of Internal Medicine
Archives of Internal Medicine
Biology of Blood and Marrow Transplantation
Blood
Bone Marrow Transplantation
Cancer
Cancer Treatment Reports
Gastroenterology
Journal of Clinical Investigation
Journal of Clinical Oncology
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Autologous Transplant for AML

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Autologous stem cell transplantation (ASCT) for AML is currently out of favor. There are two major explanations for this development. The first is the heightened interest in the graft-versus-leukemia (GVL) effect that is an integral part of the allogeneic transplant process. The second is the perceived lack of superiority of ASCT compared to post-remission chemotherapy.

Allogeneic transplant in enjoying increased favor as treatment for AML in first remission. Preparative regimens have become less toxic, although treatment-related-mortality (TRM) has not significantly changed during the last decade. The refinement of prognostic factors with the use of molecular markers such as NPM1 and FLT3 have has also improved decision making and clarified which patients are most likely to benefit from allografting.

The results of randomized clinical trials comparing the outcome for ASCT versus chemotherapy have not demonstrated a consistent benefit for ASCT. Two trials, EORTC-GIMEMA and MRC-10 showed an advantage in DFS for ASCT, whereas 3 other trials did not. However, in these trials, the fraction of patients receiving the assigned autograft (55 – 80%) were much lower than the fraction of patients receiving the chemotherapy comparator, and the TRM for autografting when bone marrow was used as the graft source was approximately 10%, much higher than current TRM using peripheral blood grafts. A meta-analysis of these randomized trials using bone marrow grafts concluded that DFS was better after ASCT than after chemotherapy.

A large trial comparing ASCT using peripheral blood grafts to chemotherapy showed no superiority to ASCT. The only benefit was in reduced use of resources.

Looking to the future, there are several ways in which ASCT for AML can be improved. The ability to deliver busulfan in an individualized pharmacokinetics-based targeted manner can ensure that patients receive an optimal dose. In addition, the ability to tightly control the AUC may allow further safe dose escalation of this agent. Post-transplant strategies to enhance the killing of autologous AML blasts may also be explored. The use of post-transplant IL-2 has some effect in decreasing relapse, and more effective methods of immune stimulation have the potential to build on this information.

Multiple Myeloma

This session will provide the audience with an update on state-of-the-art therapy for multiple myeloma in the context of genomics and biology. Professor John D Shaughnessy Jr from the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences will review the molecular classification of myeloma and report on a validated gene expression profiling (GEP)-derived prognostic model. He will also address how novel agents and melphalan impact the interaction of neoplastic plasma cells with components of the bone marrow micro-environment toward elucidation of signaling pathways targeted by these drugs. Professor Jean-Luc Harousseau of the University of Nantes, France, and Chair of the Intergroupe Francophone du Myelome (IFM), will address the important therapeutic advances in myeloma therapy accomplished by IFM with emphasis on the optimal use of novel agents in the context of autotransplant-supported high-dose melphalan therapy. Issues of improving pre-transplant induction therapy, high-dose regimens as well as consolidation and maintenance strategies will be covered. Special consideration will be given to the management of non-transplant candidates. Professor Bart Barlogie of the University of Arkansas, Director of the Myeloma Institute for Research and Therapy and Chair of the Myeloma Committee of the Southwest Oncology Group (SWOG) will show how the up-front application of all myeloma-active agents in the Total Therapy strategy has led to progressive improvements in disease-free and overall survival. Thus, with Total Therapy 3, incorporating bortezomib, thalidomide and lenalidomide into melphalan-based tandem autotransplants, the 5-yr estimate of sustained complete remission is 90%. These results will be presented in the context of GEP and state-of-the-art imaging methods, MRI and FDG PET-CT. As a result of this session, the audience will be expected (1) to have gained critical insight into molecular mechanisms of myelomagenesis and the key role of the bone marrow micro-environment in disease progression, clinical symptom manifestation and therapeutic response; (2) to better judge the treatment options available for both newly diagnosed and previously treated patients in the context of co-morbidities; and (3) appreciate that myeloma can be cured with a risk-adapted application of currently available agents.

Dr. Bart Barogie

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POSTGRADUATE TRAINING: University of Munich
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POSTGRADUATE TRAINING: M.D. Anderson Hospital and Tumor Institute
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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.

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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.

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Director, Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, January 1, 1997-1998.

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LOCAL, STATE, NATIONAL, INTERNATIONAL COMMITTEES:
Cell Kinetics Society - President - 1/85 to 1/86

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Research Advisory Committee 1993-1994

Multiple Myeloma Research Foundation (MMRF)
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Prospect for Cure in Multiple Myeloma Treated with Total Therapy Protocols

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The evolution of clinical outcomes of more than 1000 newly diagnosed patients enrolled in sequential Total Therapy studies will be reviewed with emphasis on the issue of curability.

231 patients were enrolled in Total Therapy 1 (TT1), applying VAD, CTX and EDAP for induction, melphalan 200mg/m2 (MEL200)-based tandem transplants, and interferon maintenance. As of 02/17/09, 51 patients are currently alive and 24 continuously event-free including 12 of initially 87 who had achieved complete remission (CR) (median follow-up, 14yr). Median durations of event-free survival (EFS) and overall survival (OS) are 2.6 and 5.7 years; the median duration of CR duration from its onset is 2.4 years. A plateau for EFS emerged at 7-10yr. Metaphase cytogenetic abnormalities (CA) represented the key adverse variable both for outcomes measured from treatment initiation and from first or successive salvage therapy interventions. Achieving CR status and proceeding with a second transplant in a timely fashion (time-dependant variables) both improved EFS and OS.

Total Therapy 2 (TT2) enrolled 668 patients and applied, after randomization to +/- thalidomide (THAL), 4 induction cycles comprising VAD, DCEP, CAD and DCEP, followed by MEL200-based tandem transplant, followed by consolidation therapy and interferon maintenance indefinitely with dexamethasone pulsing during the first year. With a median follow-up of almost 8yr, 378 patients are currently alive and 253 continuously event-free including 181 in continuous CR. As of 03/25/09, median durations of OS, EFS and CR are 9.7, 4.8, and 7.0 years for all patients; according to THAL randomization, the corresponding values were NR/7.4, 6.1/4.1 and 6.0/5.4, respectively in case of THAL/no THAL (p=0.03, 0.0003, 0.15). The projected 10-yr estimates of EFS and OS overall/THAL/no THAL are 31/38/24% and 49/57/41%, respectively; of those attaining CR status, 8-yr estimates are 44/47/40%. According to multivariate analysis of baseline prognostic variables, which included GEP risk scores in 351 patients, both OS and EFS were adversely affected by CA, elevated levels of B2M and LDH, low albumin and high-risk GEP designation applying to 13%. Timely onset of CR and of applying the 2nd transplant early both reduced the hazard of relapse and death significantly, as did THAL among patients with CA when present together with low-risk GEP. MRI-defined focal lesion (MRI-FL) number was a further adverse prognostic variable adding significantly to outcome prediction. MRI-defined CR, occurring with an 18-mo lag phase after the onset of clinical CR, was a favorable post-treatment variable. The prolonged persistence of MRI-FL harboring viable tumor cells on CT-guided fine needle aspirate examination in the face of clinical CR suggests the presence of a sizable non-secretory tumor cell compartment which may account for late relapses from a tumor dormancy state.

We next added bortezomib into the front-line therapy for 480 patients receiving Total Therapy 3 (TT3), pursued under 2 different protocols TT3A (n=303) and TT3B (n=177), which differed by the use of lenalidomide instead of THAL during the 3-yr maintenance phase in TT3B. Compared with TT2, both trials applied abbreviated induction prior to and consolidation therapy after MEL200-based transplants, employing VTD-PACE for 2 cycles each. With a median follow-up of 3.1yr in both studies combined, the projected 5-yr estimates of EFS and OS are 67% and 71%, respectively, with a 4-yr estimate of sustained CR of 85%.The predictive power of GEP-defined high-risk, developed in TT2, was validated in TT3, distinguishing 15% of patients with 5-yr OS/EFS estimates of 31/16% compared to 80/77% for the remainder with low-risk disease; the 4-yr sustained CR estimate was an unprecedented 91% in low-risk as opposed to 48% in high-risk myeloma. According to molecular subgroup analysis, the 14% with MMSET/FGFR3-type myeloma fared significantly better with TT3 than TT2 and in fact no longer represented an ad-

verse prognostic feature in multivariate analysis of pre-treatment variables in TT3. Similarly, TP53 deletion status inferred from low GEP expression no longer represented an independently significant outcome variable. As with TT2, achieving CR status early and applying 2nd transplant promptly both improved survival outcomes.

A novel investigation in TT3 was the prospective evaluation of PET-CT examination at baseline, within 7 days of starting treatment and prior to first transplant. Results revealed that, for the 239 patients with baseline studies in TT3A, FDG-defined focal lesion (FDG-FL) exceeding 3 was a highly significant parameter that affected both OS and EFS adversely; whereas complete FDG suppression pre-transplant conferred improved outcomes.

A further first in myeloma investigation was dedicated to studying the pharmacogenomic effects of bortezomib in TT3A which were validated in TT3B. Thus, 48hr following a test-dose application of 1.0mg/m2, prognostically highly relevant GEP alterations were discovered both at the level of CD138-purified plasma cells and when examining whole bone marrow biopsy material.

Owing to the concern of treatment-induced myelodysplasia (MDS), identified by MDS-typical CA (MDS-CA), cytogenetic analyses were performed as part of every bone marrow examination for myeloma re-staging. The 5/10/15yr MDS-CA estimates were 5/8/9% when all TT patients were considered together. Clinical MDS and AML were uncommon and were diagnosed in altogether only <1% and 2%, respectively.

Collectively, our TT experience has propelled major progress in the treatment of newly diagnosed myeloma. Extrapolating from TT1 and TT2 survival observations, we predict 10-yr estimates of sustained CR with TT3 in excess of 65%, most of which should be durable beyond this landmark and thus boding well for cure.

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Using High-Resolution Genomics to Define the Pathogenesis and Prognosis of Multiple Myeloma

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Cancer-causing mutations disrupt coordinated, precise programs of gene expression that govern cell growth and differentiation. Microarray-based gene-expression profiling (GEP) is a powerful tool to globally analyze these changes to study cancer biology and clinical behavior. Despite overwhelming genomic chaos in multiple myeloma (MM), expression patterns within tumor samples are remarkably stable and reproducible. Unique expression patterns associated with recurrent chromosomal translocations and ploidy changes defined molecular classes with differing clinical features and outcomes. Combined molecular techniques also dissected two distinct, reproducible forms of hyperdiploid disease and have molecularly defined MM with high risk for poor clinical outcome. GEP is now used to risk-stratify patients with newly diagnosed MM. Groups with high-risk features are evident in all GEP-defined MM classes, and GEP studies of serial samples showed that risk increases over time, with relapsed disease showing dramatic GEP shifts toward a signature of poor outcomes. This suggests a common mechanism of disease evolution and potentially reflects preferential expansion of therapy-resistant cells. Correlating GEP-defined disease class and risk with outcomes of therapeutic regimens reveals class-specific benefits for individual agents, as well as mechanistic insights into drug sensitivity and resistance. Here, we review modern genomics contributions to understanding MM pathogenesis, prognosis, and therapy.

Multiple myeloma: the disease

Multiple myeloma (MM) is a plasma cell dyscrasia that homes to and expands in the bone marrow, where it causes a constellation of disease manifestations that include osteolytic lesions due to osteoblast inactivation and osteoclast activation, anemia and immunosuppression due to loss of normal hematopoietic stem cell function, and end-organ damage due to excessive monoclonal immunoglobulin secretion (1); increased bone marrow angiogenesis is also frequently observed (2). MM presents with a common histological diagnosis, but it displays enormous genomic complexity as well as marked variations in clinical characteristics and patient survival. To advance treatments, clinical outcome data must be interpreted within the framework of genetic entities, which has proved useful in leukemia and lymphoma (3-11) and over the past 10 years has contributed to advances in treatment and survival of patients with MM.

For many years, investigations into the molecular lesions driving initiation and progression of MM languished, in part because of the enormously complex karyotypes typically seen in this malignancy. In fact, MM has cytogenetic features more similar to tumors of epithelial origin than to hematological malignancies. Whereas most leukemias and lymphomas present with single chromosomal translocations, karyotypes of myeloma cells from newly diagnosed disease have an average of seven different structural and/or numeric chromosomal abnormalities. This genomic chaos, along with the rarity of the disease, made it difficult to perform the comprehensive correlative studies necessary to identify and better understand the abnormalities involved in initiation and/or progression of the disease and to distinguish nonspecific bystander effects of chromosome instability. Indeed, the first link between a recurrent chromosome abnormality and prognosis was observed only 10 years ago, when deletions of chromosome 13 were associated with aggressive clinical course (12).

The advent of new technologies, such as interphase fluorescence in-situ hybridization (FISH), spectral karyotyping, comparative genomic hybridization, single nucleotide polymorphism (SNP) genotyping, and gene-expression profiling (GEP), has provided the necessary tools to study MM in unprecedented detail. Combining these approaches with maturing technologies, such as high-throughput proteomics, microRNA profiling, and whole-genome sequencing, broadens the spectrum of molecular variables that can be tested but also poses immense bioinformatics challenges to integrate the massive complexity of these high-dimensional datasets to improve

management of MM. This review focuses on the use of GEP of primary disease to classify the disease, define risk, and elucidate underlying mechanisms that are beginning to change clinical decision-making and inform drug design.

Studying the complexities of the transcriptome

It is likely that each of the six hallmarks of cancer, outlined in the Hanahan-Weinberg model (13), ultimately causes or is related to reproducible changes in the expression of subsets of genes within clonal tumor cells and that these patterns are unique and specific to each malignancy. This hypothesis was difficult to test, however, until the completion of the human genome project (14, 15) and the development of high-throughput tools capable of analyzing the activities of all genes simultaneously (16). It is now believed that the human genome consists of approximately 25,000 mRNA-encoding genes, and this complexity is increased by post-transcriptional modifications, such as alternative splicing.

In the mid-1990s, Brown and colleagues developed a system that used DNA microarrays to monitor the expression levels of thousands of genes in parallel (16-18), which paved the way for tools that revolutionized molecular biology. The system worked similar to reverse northern blots: cloned DNA fragments immobilized on a solid matrix were used simultaneously to probe mRNA pools from a control source and from the tumor or other tissue of interest, each labeled with a different fluorescent dye (e.g., Cy5 and Cy3). Building on this concept, more advanced high-density oligonucleotide microarrays capable of unprecedented levels of sensitivity and throughput was developed using photolithography and solid-phase chemistry. Now the industry standard, these whole-genome high-density oligonucleotide microarrays contain hundreds of thousands of oligonucleotide probes, packed at extremely high densities (19). The probes are designed to maximize sensitivity, specificity, and reproducibility, which allows consistent discrimination between specific and background signals and between closely related target sequences (20). Using microarrays for GEP generates large amounts of complex data, demanding equally complex analyses. Indeed, GEP analysis has evolved into a field of its own and in many ways represents a central node in translational research; a comprehensive review of the principles and tools used to analyze microarray data was recently published (21). Here, we focus on the specific use of microarray profiling in MM, research that has exploded over the past 10 years.

Microarray technology was first used to study cancer in 1996 (22), and De Vos and colleagues were the first use gene-expression profiling to study MM in 2001 (23). In these early experiments, human myeloma cell lines and plasma cell leukemia samples were analyzed on small-scale, filter-based cDNA arrays to identify genes involved in intercellular signalling. In spite of its small scale, this study revealed that key signalling molecules within the Wnt pathway were altered in MM. Subsequently, Stewart et al. used a combination of high-throughput DNA sequencing and microarrays on cells pooled from several cases of plasma cell leukemia to establish a comprehensive list of genes expressed in MM (24).

Microarray profiling of MM

Because of the heterogeneous nature of MM growth within the bone marrow, with variable percentages of tumor in a given site as low as 5%, molecular profiling of unfractionated bone marrow aspirates complicates interpretation of results. To overcome this limitation, researchers have employed various means of cell enrichment of plasma cells from bone-marrow aspirates. Plasma cells typically make up less than 1% of the cells in healthy human bone marrow, so isolation of sufficient numbers of plasma cells from healthy human marrow made large-scale GEP experiments an impractical endeavor for most laboratories. To isolate sufficient numbers of cells for GEP, two different but complementary specialized methodologies were developed. Zhan et al. employed automated immunomagnetic bead sorting of plasma cells from large-volume bone-marrow aspirates using a monoclonal antibody, BB4, raised against syndecan-1/CD138 (25); this technique routinely has isolated highly homogeneous populations of healthy plasma cells from both bone marrow and tonsil (26). To create a source of polyclonal plasma cells from healthy donors, Tarte and colleagues developed a method for in vitro differentiation of peripheral blood B cells (27). Global GEP of polyclonal plasma cells and healthy bone marrow plasma cells derived from immunomagnetic sorting has revealed strong similarities but also distinct and reproducible differences between the two populations and myeloma cells (27, 28), suggesting that polyclonal plasma cells may not fully recapitulate the molecular biology of a bone marrow plasma cell.

Early studies made several contributions to understanding the molecular basis of MM by comparing gene-expression profiles of CD138-enriched plasma cells from the bone marrow of healthy donors and patients with MGUS, newly diagnosed MM,

and end-stage MM (25). These studies uncovered potential clues to the molecular pathogenesis of MM—disease-specific changes in gene expression. Myeloma plasma cells can be clearly distinguished from those of healthy donors based on expression of approximately 120 of 6,800 genes analyzed. Unsupervised clustering of these early global gene-expression data showed that MM could be divided into four distinct molecular subgroups, MM1–MM4, with MM1 being more like MGUS and MM4 being related to myeloma cell lines. The MM4 group also had a higher incidence of cytogenetic abnormalities (CAs) and high serum levels of beta-2-microglobulin, clinical features historically linked to poor prognosis. Consistent with these data, genes distinguishing MM4 from the other groups were related to cell proliferation. More advanced microarray technologies and larger sample sizes have now further divided MM into seven disease classes (discussed below).

These results provided the first evidence that MM is likely numerous molecular entities that presumably employ different molecular mechanisms to get to a tumor with a common histology, which has enormous clinical implications. First, the high resolution of molecular classifications allows retrospective evaluation of class-specific efficacy of current therapeutic regimens, which is exceedingly important when designing clinical trials. For example, a new drug might not show a significant effect on a given endpoint when considering MM as a whole, but the results might be dramatically different if the endpoint is examined in the context of a particular molecular classification of MM, which might include only 5% of the overall population. Second, identifying the genes whose expression is driving these classes can inform the use of existing agents that might not have been considered and can direct development of new class-specific drugs.

To provide insights into the molecular characterization of plasma cell dyscrasias and to investigate the contributions of specific genetic lesions to the biological and clinical heterogeneity of MM, Mattioli et al. compared the GEP of plasma cells isolated from 7 cases of MGUS, 39 of MM, and 6 of plasma cell leukemia. MM was heterogeneous at the transcriptional level, whereas MGUS was distinguished from plasma cell leukemias and the majority of MM cases by differential expression of genes involved in DNA metabolism and proliferation. The clustering of MM cases was mainly driven by the presence of one of five recurrent translocations involving the immunoglobulin heavy-chain (IGH) locus (29). For example, overexpression of CCND2 and genes involved in cell-adhesion pathways was observed in cases with t(14;16) and t(14;20), whereas upregulated genes showed apoptosis-related functions in cases with t(4;14). The peculiar finding in cases with t(11;14) was downregulation of the alpha-subunit of the interleukin-6 receptor (IL6R). Finally, cancer-testis antigens were specifically expressed in a subgroup of patients characterized by aggressive clinical evolution of MM (30).

GEP reveals universal event in MM is cyclin D dysregulation

Genomic profiling in a large cohort of primary disease revealed that dysregulated expression of cyclin D might be a universal event in myelomagenesis. Relative to plasma cells from the bone marrow of healthy donors, myeloma plasma cells exhibit increased and/or dysregulated expression of either CCND1, CCND2, or CCND3 (31). IGH-mediated translocations can directly activate CCND1 (11q13) (32) or CCND3 (6p21) (33); MAF- (16q23) or MAFB- (20q11) activating translocations lead to their transactivation of adhesion molecules and CCND2, which is elevated in t(4;14)-positive tumors (34). Biallelic dysregulation of CCND1 occurs in nearly 40% of tumors, most of which are hyperdiploid (31). Elevated levels of CCND2 and the absence of IGH translocation spikes characterize a novel form of MM discovered through GEP of primary disease (termed "Low Bone," discussed below) (35); interestingly, elevated expression of CCND2 is not an adverse prognostic factor in this setting (36).

Validated molecular classification of MM

Using a supervised classification approach that utilizes prior knowledge of the disease, Bergsagel et al. developed a classification schema based on GEP spikes of the five recurrent translocations, specific trisomies, and expression of cyclin D genes (29). Reducing the complexity of the microarray from over 50,000 probes to less than 30 genes, eight translocation/cyclin D (TC) groups were identified. These were termed the 11q13/TC1, 6p21/TC2, 4p16/TC3, maf/TC4, D1/TC5, D1+D2/TC6, D2/TC7, and none/TC8 classes (31). The authors proposed that these genetic entities are defined by early, perhaps initiating, oncogenic events. The classes exhibited significant, uniform differences in global gene-expression profiles and clinical features, such as prevalence of bone disease, frequency distribution at relapse, and progression to extramedullary tumor growth (31).

Agnelli and colleagues used this GEP class-prediction model on purified plasma cells from 50 MM

Table 1. Characteristics of validated molecular classes as defined by unsupervised hierarchical clustering

Molecular subtype	% of newly diagnosed patients*	Genetic characteristics	Characteristic genes elevated in class	Risk	Features
MS (MMSET)	17	t(4;14)	FGFR3, MMSET, CCND2, IL6R	High	Overexpression MMSET and FGFR3' FGFR3 not evident in ~30%; bone disease is rare
MF (MAF/MAFB)	6	t(14;16) or t(14;20)	MAF or MAFB, CCND2, IL6R	High/ Moderate	Elevated expression of CCND2; bone disease rare; low DKK1; High NF-kB signature; low TNF-α induced gene TNFAIP8.
CD-1 (CCND1 or CCND3)	6	t(11;14) or t(6;14)	CCND1 or CCND3	Low	Few cases express CCND2 in absence of CCND1 or CCND3; can have high DKK1
CD-2 (CCND1 or CCND3) + CD20	12	t(11;14) or t(6;14)	CCND1 or CCND3, CD20, VPREB3	Low	Few cases express CCND2 in absence o CCND1 or CCND3
HY (HYperdiploid)	31	typical trisomies +3, +5, +7, +9, +11, +15, +19;	GNG11, DKK1, FRZB	Moderate	Ectopic expression of CCND1; del13 and gain of 1q are rare; high expression of interferon-induced genes
LB (Low Bone disease)	12	typical HY trisomies; exception is frequent del13, gain of 1q, rare gain of 11	CCND2, CST6, ARHE, IL6R	Low	Expression of CCND2; low level DKK1, FRZB,CCR2, HIF1A, SMAD1; low expression of interferon-induced genes
PR (PRoliferation)	10	Made up of all subgroups	CCNB1, CCNB2, PCNA, MKI67, TOP2A, TYMS	High	Overexpression of 1q genes; evolves from other groups

*Approximately 13% of newly diagnosed cases were not classified. Unclassified samples typically derived from bone marrow aspirates containing low bone marrow plasmacytosis. This so called MY subgroup exhibits superior survival relative to other groups. CD138 purified cells from these cases have GEP of signatures consistent with contamination of preparations with of the myeloid, T-cell, B-cell, and plasma cell lineages. Group consists of all molecular classes described above as spikes and class-specific GEP features are evident in most.

cases. The TC1, TC2, TC4, and TC5 groups were characterized by 112 probe sets, but TC3 samples showed heterogeneous phenotypes and no gene biomarkers. The TC2 group, with extra copies of the CCND1 locus and no IGH translocations or 13q deletion, was characterized by overexpression of genes involved in regulation of protein translation (37). The failure to validate all TC classes likely is related to the small sample size. Another possibility is that the TC classification is not robust because several of the classes are difficult to classify using this approach; new, different methods of classification are required when dealing with large datasets.

Complementing the supervised approach, unsupervised hierarchical clustering allows samples to self-organize based on underlying correlations in gene-expression patterns (Figure 1). Using a training set of 351 MM cases and a test set of nearly 200 newly diagnosed MM cases, Zhan and colleagues divided MM into seven different reproducible classes (Table 1) (35). These molecular classes, largely consistent with the TC classification, are strongly influenced by distinct gene-expression profiles associated with known genetic lesions, including hyperdiploidy, translocations, cell proliferation, and tumor cell interactions with the bone marrow microenvironment (35).

Four (MF, MS, CD-1, and CD-2) of the seven subclasses are characterized by hyper elevated expression that results from recurrent chromosomal translocations present in approximately 40% of MM, which occur as a result of errors in switch re-

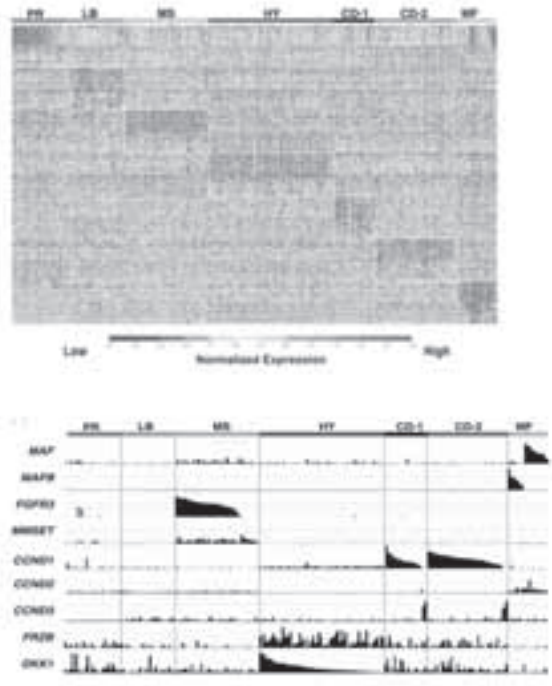

Figure 1. Classes are characterized by unique GEP patterns. (Upper panel) A supervised clustergram of the expression of 700 genes (50 SAM-defined overexpressed and 50 underexpressed genes from each of the 7 classes) across 256 newly diagnosed cases. Genes are indicated along the vertical axis and samples on the horizontal axis. The normalized expression value for each gene is indicated by a color, with red representing high expression and blue representing low expression. (Lower panel) The Affymetrix gene expression signal (expression level: vertical axis) for the mRNA of MAF, MAFB, FGFR3, MMSET, CCND1, CCND2, CCND3, FRZB, and DKK1, within classes presented in the upper panel, are indicated. The normalized expression level for each gene across the samples is given by the height of each bar. Note that spiked expression of CCND1, MAF and MAFB, and FGFR3 and MMSET is strongly correlated with specific subgroup designations. Also note that cases retaining the MMSET spike but lacking FGFR3 spikes maintain similar cluster designation, and MAF and MAFB spikes cluster in the same subgroups. Several MMSET and CCND1 spikes cases are evident in the PR class. CCND3 expression is mutually exclusive of CCND1 expression. While overexpressed in the HY subgroup, FRZB and DKK1 are significantly underexpressed in LB and MF. Figures reproduced with permission from Blood.

combination and/or somatic hypermutation (38). These translocations cause normally silent genes to become juxtaposed with powerful immunoglobulin enhancer elements, resulting in expression "spikes" readily detectable in microarray studies. HY is characterized by low ectopic expression of CCND1 and overexpression of genes mapping to the odd-numbered chromosomes that typically exhibit trisomy in MM. The LB class, characterized by a low incidence of magnetic resonance imaging (MRI)-defined bone lesions, expresses high levels of CCND2 and a unique constellation of genes, including endothelin-1/EDN1. Unique, reproducible gene-expression programs can define at least six molecular entities; the seventh class of MM, PR, is not related to a primary genetic lesion but to high expression levels of proliferation-associated genes. This class likely consists of the other classes, but underlying features are masked by expression of proliferation genes. The 700 most differentially expressed genes across seven molecular classes can be found supplemental Table 2 and 3 in reference 35. In the following section we highlight subsets of these 700 genes thought to significant in class specific disease pathogenesis.

MS class

The t(4;14)(p16;q32) translocation characterizes the MS class of MM, which is a high-risk entity that predicts poor prognosis (39). The t(4;14)(p16;q32) reciprocal translocation results in hyperactivation of both FGFR3 and MMSET/WHSC1 genes (40). All t(4;14)-positive disease expresses elevated levels of MMSET, but in about 30% of these cases expression of FGFR3 is lost (39, 41). Because loss of FGFR3 expression is the only obvious GEP difference between these two types of t(4;14)-positive MM, it appears that MMSET plays a central role in driving downstream transcriptional events in the MS class. Furthermore, 25% of MM cases in other classes also exhibit upregulation of MMSET, supporting its importance in MM pathogenesis (42). In a comparison of cases with and without t(4;14), GEP studies identified 127 genes as differentially expressed (42), including MMSET and CCND2. Notable genes overexpressed in the MS class, relative to other classes, encode N-cadherin/CDH2, cadherin family member desmoglein2/DSG2, Wnt receptors FZ2 and FZD8, and B-cell oncogene PBX1. Underexpressed genes with potential relevance encode adhesion molecules ICAM4, cadherin 7/CDH7, and transcription factor PAX5.

Functional studies suggest that MMSET plays a role in cell proliferation by decreasing cell viability and cell-cycle progression, possibly acting through desmoglein 2 (DSG2), a cell-surface cadherin molecule involved in cell adhesion and perhaps drug resistance. Thus, desmoglein 2 may be a therapeutic target for MS class MM (43).

MF class

Accounting for approximately 6% of cases, the MF class of MM is characterized by the t(14;16)(q32;q23) and t(14;20)(q32;q11) translocations, which result in activation of c-MAF and MAFB proto-oncogenes, respectively. Cases lacking characteristic c-MAF or MAFB spikes can be classified as MF, suggesting that other genes of the MAF family may be activated in these cases or that low ectopic expression of either gene is sufficient to drive this classification. Although translocations involving c-MAF are seen in less than 5% of MM cases, c-MAF expression is elevated in myeloma cell lines lacking the translo-

cations and in up to 50% of primary samples (34). These data strongly suggest that c-MAF expression may be activated by other mechanisms and attest to the importance of this family of transcription factors in MM pathogenesis. The NF-kB gene-expression signature in the MF class is significantly higher than in the other classes, with the exception of the LB class (see below) (44). It is perhaps noteworthy that TNF-induced TNFAIP8 is the gene most significantly underexpressed in the MF class, relative to the other disease classes. Clinically, the MF class has relatively low incidence of bone lesions and, consistent with this, has low expression of DKK1, a Wnt antagonist produced by myeloma cells and associated with bone disease (45).

Although mutually exclusive, MAF- and MAFB-activating translocations induce a common gene-expression signature, suggesting that ectopic expression of the MAF family of transcription factors results in dysregulation of common downstream targets. In GEP studies aimed at identifying MAFB targets in MM, 284 transcripts were modulated—14 were common to c-MAF and some had functional relationships with MAFB (46). Additional genes uniquely overexpressed in the MF class that represent known and putative targets of these transcription factors include NUAK1/ARK5 (47), NTRK2, ARID5A, SMARCA1, TLR4, SPP1, and G6MB6.

CX3CR1 and ITGB7 are overexpressed in the MF class (48), consistent with the report that CCND2, CX3CR1, and ITGB7 are targets of the c-MAF transcription factor (34). c-MAF-driven expression of ITGB7 enhanced adhesion of myeloma cells to bone marrow stroma and increased production of VEGF in these cells, suggesting that MAF can drive myeloma cell adhesion to the extracellular matrix and cellular stroma, resulting in drug resistance and angiogenesis. Because expression of ITGB7 also is elevated in other MM classes, it could be a critical adhesion molecule in MM that can be activated via multiple mechanisms. Expression of CCND2 is elevated in other disease classes but is highest in the MF class. Hurt and colleagues showed that c-MAF transactivated the CCND2 promoter and enhanced MM proliferation, whereas dominant inhibition of c-MAF blocked tumor formation in immunodeficient mice, which highlights the potential significance of this transcription factor in myelomagenesis and the recognized association between MM and activation of one the three CCND genes.

CD-1 and CD-2 classes

The t(11;14)(q13;q32) and t(6;14)(p21;q32) translocations, characteristics of the CD-1 and CD-2 classes, directly activate expression of CCND1 and CCND3, respectively. Tumors with CCND1 and CCND3 spikes have gene-expression profiles that cluster membership, suggesting that activation of the two cyclin D orthologs results in dysregulation of common downstream transcriptional programs.

Nevertheless, CCND1 and CCND3 spikes are associated with two distinct, non-overlapping gene-expression signatures that were used to distinguish the CD-1 and CD-2 classes. CD-2 is characterized by elevated expression of CD20/MS4A1, VPREB3, and PAX5—genes expressed in B cells but normally extinguished in terminally differentiated plasma cells. Of note, CD20 mRNA and protein levels are correlated (35), but cells expressing elevated PAX5 mRNA do not express the protein (49). Unlike CD-2, CD-1 lacks expression of CD59 (potent inhibitor of complement membrane-attack complex), Notch-like protein NOTCH2NL, and Notch target gene HES1. CD-1 is characterized by overexpression of KLHL4 (a transcription factor), INHBE, FYN proto-oncogene, CEBPB/NF-IL6, and EVER1 and EVER2, two cytoplasmic proteins that colocalize with calnexin, an integral membrane protein of the endoplasmic reticulum (35).

HY class

Hyperdiploid MM is characterized by trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. The trisomies are one of two central genetic pathways in development of MM, and this type of disease was previously shown to have a distinct gene-expression signature (29). The HY signature is present in nearly 50% of cases and is associated with hyperdiploid karyotypes in more than 90% of these; however, the signature is also observed in cases that are not identified as hyperdiploid by flow cytometry analyses. Such cases may arise through a similar initiating genetic mechanism (trisomies of odd chromosomes) with clonal evolution that results in DNA loss from other chromosomes, resulting in a DNA complement that is essentially diploid. Indeed, recent array-based comparative genomic hybridization (aCGH) data revealed that all molecular classes have at least a partial complement of the common trisomies (our unpublished data).

Genes uniquely overexpressed in the HY class encode guanine nucleotide binding protein, gamma 11/GNG11, Trail/TNFSF10, Wnt signaling antagonists FRZB/SFRP3 and DKK1, and MIP1-alpha chemokine receptor CCR5. Overexpression of several interferon-induced genes, including OAS2, IFI27, and IFI35, is also characteristic of this class. Genes significantly underexpressed in the HY class, rela-

tive to the other classes, included CD52 and genes mapping to chromosome 1q—TAGLN2, CKS1B, and OPN3—whose overexpression has been linked to poor survival (50). Consistent with these results, integration of aCGH and GEP studies has shown that HY disease rarely exhibits gain of 1q (manuscript submitted). These data are also consistent with aCGH studies that defined disease clusters based on copy number variation (51). These studies revealed that the classical hyperdiploid trisomies defined a specific subset of MM that lacks gains of 1q and deletion of chromosome 13.

LB class

A novel class of MM, LB (low bone disease) is characterized by low incidence of MRI-defined focal bone lesions and lacks evidence of translocation spikes or HY gene-expression features. Consistent with the absence of MRI-defined focal lesions in the LB class, recent studies integrating positron emission tomography (PET) imaging with GEP also revealed that the LB class is uniquely inversely correlated with F18-fluorodeoxyglucose PET-defined focal lesion number and intensity [F18-Fluorodeoxyglucose Positron Emission Tomography In The Context Of Other Imaging Techniques And Prognostic Factors In Multiple Myeloma Twyla B Bartel, Jeff Haessler, Tracy LY Brown, John D Shaughnessy Jr, Frits van Rhee, Elias Anaissie, Terry Alpe, Edgardo Angtuaco, Ronald Walker , Joshua Epstein, John Crowley and Bart Barlogie ,submitted].

LB disease is distinguished by overexpression of endothelin 1/EDN1, a soluble factor that is secreted by prostate cancers and that causes osteoblastic metastases of prostate cancer. Interestingly, purified EDN1 induces osteoblast differentiation via suppression of Wnt/β-catenin signaling antagonist DKK1 (52, 53), and the LB class is characterized by significantly lower expression of DKK1, suggesting that EDN1 may downregulate DKK1 in myeloma cells. LB is also associated with high expression levels of IL6R; the MS and MF classes that also have low DKK1 and lower incidence of MRI-defined focal bone lesions, relative to HY, CD-1, and CD-2 classes, share this feature. In contrast to LB, the HY class rarely expresses IL6R and expresses high levels of DKK1 and EDN1 decoy receptor EDNRB. These data suggest a potential connection between EDN1 signaling and DKK1 production and bone disease in MM. It is also noteworthy that relative to the other classes the LB class expresses higher levels of the apoptosis inducing gene BIK and the Notch target gene and transcriptional repressor HES5, and lower levels of the chemokine receptor CCR2, hypoxia-induced Factor 1- alpha (HIF1A), and SMAD1, a transcription factor that mediates BMP signaling.

PR class

The PR (proliferation) class is characterized by overexpression of numerous genes related to cell-cycle progression and cell proliferation, including CCNB2, CCNB1, MCM2, CDCA2, BUB1, CDC2, and TYMS, and also cancer-testis antigen genes, including MAGEA6, MAGEA3, GAGE1, and GAGE4. Plasma cells from all MM classes have a higher gene-expression–defined proliferation index than plasma cells from healthy donors, but that of the PR class is similar to myeloma cell lines and is significantly higher than non-PR classes. Metaphase CAs, a surrogate for cell proliferation, are present in an extraordinarily high percentage of cases in the PR class. The PR class is associated with poorer survival than other classes, and both hyperdiploid and nonhyperdiploid cases are equally common, with and without concomitant translocation spikes, suggesting that hyperdiploid versus nonhyperdiploid status likely is not sufficient as a sole parameter for risk assessment. Indeed, those cases with both PR signature and hyperdiploidy are at higher risk than those with the HY signature. Several factors—overexpression of proliferation-associated genes in all non-PR classes, the presence of expression spikes in the PR class, and a shift to the PR class upon disease progression—suggest that the PR class is driven by a transformation event secondary to underlying primary genetic lesions.

Classification outliers

In the study by Zhan et al., about 25% of newly diagnosed cases could not be classified because gene-expression signatures of myeloid/lymphoid-lineage cells and/or polyclonal plasma cells predominated and, like the PR signature, prevented unsupervised classification. The presence of translocation spikes in these cases supports the idea that this is not a unique class of MM. This contamination signature appears to hold important clinical implications because patients with this signature have lower levels of bone marrow plasmacytosis, lower incidence of CAs, low beta-2-microglobulin and creatinine, and better event-free survival (EFS) and overall survival (OS) than those without the signature (35).

Using GEP to dissect specific genetic features of MM

GEP and hyperdiploid disease

GEP has been used to further dissect hyperdip-

loid and nonhyperdiploid disease. A combination of FISH and GEP showed that differential expression of genes involved in protein biosynthesis, transcriptional machinery, and oxidative phosphorylation distinguished the two types of disease (54). Of 204 genes upregulated in hyperdiploid disease, the majority mapped to the hyperdiploid chromosomes, and 29% of genes upregulated in nonhyperdiploid disease mapped to chromosome 16q (54); these findings were validated in independent datasets (54). Consistent with previous studies (51), hyperdiploid MM was further divided into two distinct molecular and transcriptional entities, one characterized by trisomy 11 and another lacking this feature but harboring chromosome 1q gains and chromosome 13 deletion (54).

Chng et al. used GEP to show that hyperdiploid MM is primarily defined by a protein biosynthesis signature driven by a gene-dosage mechanism and to identify four independently validated patient clusters within hyperdiploid MM. One prominent cluster was characterized by cancer-testis antigen, proliferation-associated genes, and higher median plasma-cell labeling index; these patients experienced much shorter survival times than those in the other three clusters (55). Genes involved in tumor necrosis factor alpha/TNF-a and NF-kB signaling and anti-apoptosis characterized another cluster, and these patients had better responses to bortezomib than those in other clusters. This hyperdiploid disease cluster is probably the same disease entity as the hyperdiploid disease characterized by gain of 1q, lack of trisomy 11, and deletion of chromosome 13, as well as the LB class of MM. Studies integrating aCGH and GEP revealed that the LB class is primarily composed of this novel type of hyperdiploid disease (56), and the LB class is significantly associated with increased NF-κB activation (44).

GEP and chromosome 13 deletion

A cohort of MM cases followed for 9 years was used to evaluate the prognostic implications of all individual CAs. Among all CAs and standard prognostic factors examined prior to therapy, only nonhyperdiploid and deletion of chromosome 13 (del13), alone or in combination, were associated with shortest EFS and OS (57). A combination of metaphase cytogenetics (to identify CAs), GEP, and interphase FISH (to identify del13) on 146 patient samples demonstrated that overexpression of cell-cycle genes distinguished disease with CA from that without CA; this was especially evident in cases lacking FISH-defined del13 (57). Interphase FISH evidence of del13 was significantly associated with reduced expression of a subset of genes mapping to chromosome 13, including RB1. The authors proposed that haploinsufficiency of genes mapping to chromosome 13, as well as significant upregulation of IGF-1R (insulin-like growth factor receptor), may have an amplifying effect on expression of cell-cycle genes, providing a molecular explanation for the dire outcome of patients with del13 compared with those with CA but lacking del13.

Historically, del13 has been associated with an unfavorable prognosis, but increasing data indicate that its prognostic relevance must be related to the presence of other molecular features. Studies using FISH to detect del13, combined with GEP, on highly purified plasma cells from 80 patients newly diagnosed with MM identified 67 differentially expressed genes, all of which were downregulated in disease with del13. Of these, 44 mapped to chromosome 13, 7 to chromosome 11, and 3 to chromosome 19. del13-positive and -negative cases were differentiated by modulations in global gene expression; in particular, FISH-defined del13 was associated with upregulation of genes mapping to 1q21–1q42 and downregulation of genes mapping to 19p and most of chromosome 11 (58).

GEP and gains of chromosome 1q

Found in up to 45% of patients, abnormalities of chromosome 1 are among the most frequent chromosomal alterations in MM (59); the short arm is most often associated with deletions and the long arm with amplifications (51). Gains/amplification of 1q21 increases the risk of MM progression, and incidence of the amplification is higher in relapsed than in newly diagnosed MM (59, 60). GEP studies comparing MM with and without 1q gains (61) identified 61 genes that distinguished the two groups. In cases with 1q gains, 41 of the 43 upregulated genes mapped to 1q12–q44, whereas most of the 18 downregulated genes were localized to chromosomes 13q (7/18) and 11 (6/18). These data suggest that cases with 1q gains typically also harbor del13 and lack trisomy of chromosome 11, features consistent with the LB class.

Gains of 1q are associated with upregulation of genes involved in intracellular protein transport; prominent in the list were COPA and ARF1, which play roles in vesicle-mediated transport from the endoplasmic reticulum (ER) to the Golgi, and RABIF and RAB3GAP2, which are related to the Rab GTPases that regulate membrane-vesicle transport. These findings may also partially account for increased expression of genes encoding proteins involved in energy-production pathways. Genes downregu-

lated in cases with 1q gains include three genes involved in protein translation (RPLP2, RPL21, and FAU), which is potentially significant because recent studies suggest that survival of B-cell malignancies (including MM) may be highly dependent on ER–Golgi protein transport, thus targeting this process may be a novel therapeutic strategy (62).

Cases with 1q gains also showed significantly modulated expression of genes involved in ER stress-induced responses, including upregulation of CLN3 (chaperone gene), UBAP2L and UBE2Q1 (ubiquitin cycle), PSMD4 (proteasome degradation), and CASP4 (initiates apoptosis in response to ER stress) (61). Because ER stress-induced apoptosis can play an important role in malignant cells' sensitivity to certain drugs, including bortezomib, these studies suggest that a better understanding of ER stress-induced responses may contribute to important new treatment strategies (61).

GEP and deletion of 17p13/TP53

A high-risk feature in MM, deletion of 17p13 presumably leads to loss of heterozygosity of TP53 (63), a tumor suppressor gene that transcriptionally regulates cell-cycle progression and apoptosis to modulate cellular responses to DNA damage. Xiong et al. (64) found that low expression of TP53, seen in approximately 10% of newly diagnosed patients, is highly correlated with FISH-defined TP53 deletion and inferior clinical outcome and is an independent risk factor. Only a few of the 122 known p53 target genes were highly correlated with TP53 expression in primary myeloma cells. GEP following ectopic expression of TP53 in four TP53-null cell lines identified 85 significantly differentially expressed genes—50 upregulated, 35 downregulated. Using these 85 putative target genes, unsupervised hierarchical clustering of myeloma-cell samples from 351 newly diagnosed and 90 relapsed patients revealed two major subgroups that strongly correlated with TP53 expression and survival. These data suggest that loss of TP53 expression in MM confers high risk and probably results in deregulation of a novel set of p53 target genes specific to MM and perhaps unique to different cell lineages (64).

Integrating GEP and high-resolution DNA analyses

Cigudosa et al. (65), Gutiérrez et al. (66) and Avet-Loiseau et al. (67) first applied traditional comparative genomic hybridization approaches (68) to expand our knowledge about chromosome instability and copy-number changes in MM. Recently developed, aCGH, like GEP, allows simultaneous, high-resolution investigation of copy-number alterations across the entire genome (69-71). GEP and high-resolution analysis of recurrent copy-number alterations defined 87 discrete minimal common regions within recurrent, highly focal copy-number alterations (51); unsupervised classification using nonnegative matrix factorization uncovered four subtypes of disease and two subtypes of hyperdiploid disease. One hyperdiploid subtype had classic features—trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21—while the other, associated with inferior survival (51), lacked trisomies of chromosomes 7 and 11 and also harbored deletion of chromosome 13 and gains of 1q. Another subtype was characterized by amplification of 1q21 and deletion of 1p, suggesting a relationship between this group and GEP-defined high-risk. Indeed, a recent analysis of 92 additional cases revealed that copy-number alterations in chromosome 1q and 1p are highly correlated with gene-expression changes that are strongly correlated with risk of death from disease progression, gene-expression–based proliferation index, and 70/17-gene model of high risk (discussed below, GEP and risk stratification) (56).

High-density SNP microarrays of genomic DNA in the KMS-26 myeloma cell line showed that an amplicon within an unstable chromosomal region (17p11.2-p12) was characterized by a large number of low-copy repeats that mediate deletion and duplication in several genomic disorders and amplifications in solid tumors. Combining this data with GEP and FISH mapping narrowed the region of interest to the TNFRSF13B/TACI gene, an important receptor in B-cell development (72).

In a FISH study of over 800 MM cases, deletion of 16q was identified in 19.5% of cases, was associated with poor outcome, was an independent prognostic marker, and conferred additional adverse survival in cases with t(4;14) and/or del(17p) (73). GEP and SNP-mapping arrays revealed loss of heterozygosity at 16q12, mapping near CYLD, and at 16q23, near WWOX. Cases with low expression of CYLD, a negative regulator of the NF-κB pathway, defined a "low-CYLD signature." Cases with 16q loss of heterozygosity or t(14;16) had significantly reduced expression of WWOX, a tumor suppressor gene involved in apoptosis that lies at the t(14;16) breakpoint (73).

GEP and risk stratification

While most cases of MM initially respond to treatment, a subset exhibits resistance to therapy from the outset, and most will develop resistance over time. Therefore, long-term survival in patients

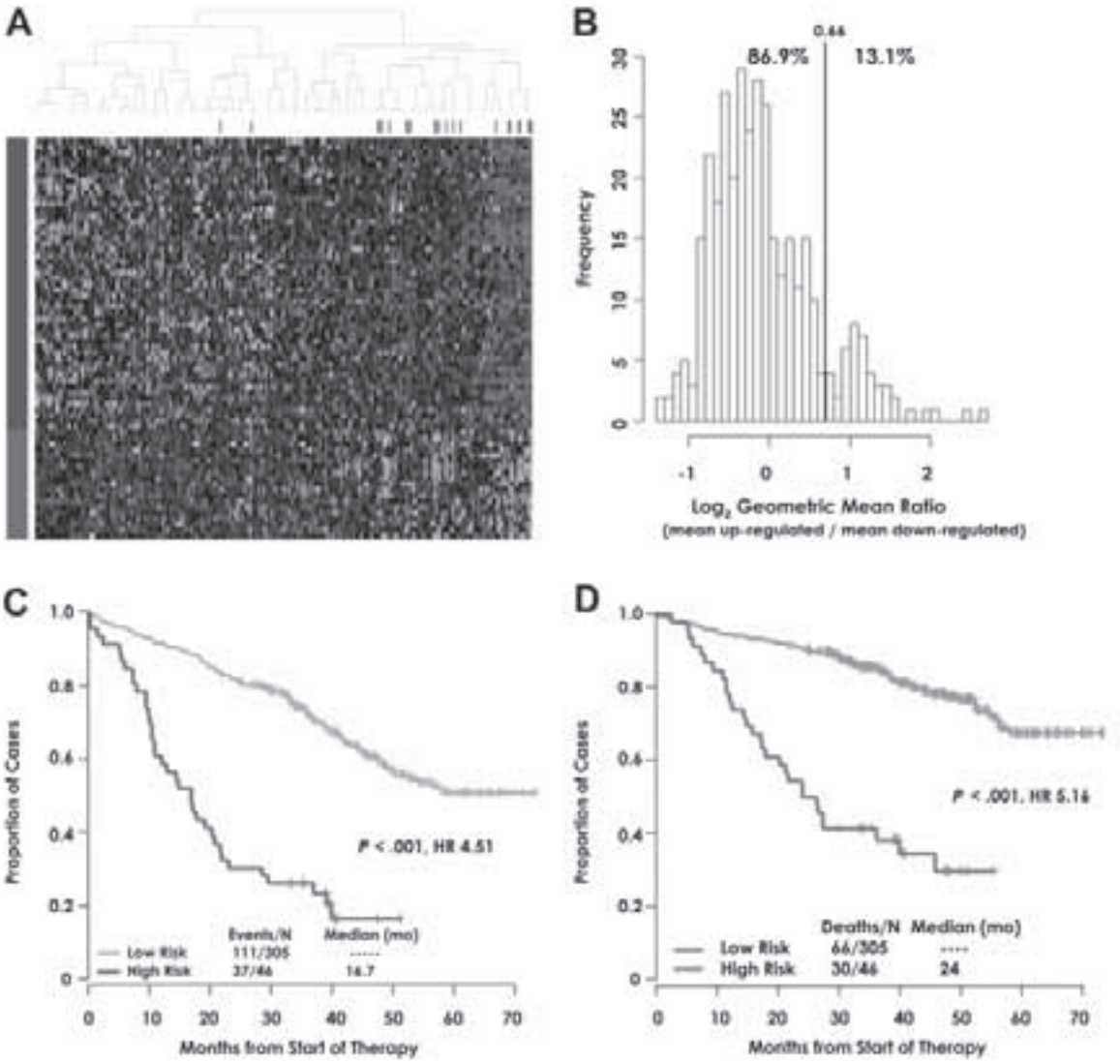

Figure 2. A GEP based 70-gene score can define high risk myeloma **(A)** Heat map of the 70 genes illustrate remarkably similar expression patterns in CD138+ selected tumor cells among 351 newly diagnosed patients. Red bars above the patient columns denote patients with disease-related deaths at the time of analysis. The 51 genes in rows designated by the red bar on the left (top rows; up-regulated) identified patients in the upper quartile of expression at high risk for early disease related death. The 19 gene rows designated by the green bar (down-regulated), identified patients in the lower quartile of expression at high risk of early disease-related death. **(B)** frequencies of the risk score defined as the log2 geometric mean ratio of the 51 quartile 4 genes and 19 quartile 1 genes. This self-normalizing expression ratio has a marked bimodal distribution, consistent with the upper/lower quartile log-rank differential expression analysis, which was designed to detect genes that define a single high-risk group (13.1%) with an extreme expression distribution. Interpreted as an up/downregulation ratio on the log2 scale, higher values are associated with poor outcome. The vertical line shows the high-risk versus low-risk cutoff for the log2-scale ratio determined by K-means clustering: the percentage of samples below and above the cutoff is also shown. Kaplan-Meier estimates of EFS **(C)** and OS **(D)** in low-risk myeloma (green) and high-risk myeloma (red) showed inferior 5-year actuarial probabilities of EFS (18% vs 60%, P < .001; HR = 4.51) and OS (28% vs 78%, P < .001; HR = 5.16) in the 13.1% patients with a high-risk signature. Reproduced with Permission from Blood.

with MM can vary considerably, and it is difficult to predict outcome based on current laboratory tests. High-risk MM is routinely defined by laboratory parameters alone or in combinations as in the Durie-Salmon staging system (74) and International Staging System (ISS) (75). A staging system based on cell morphology, the Bartl grade, has also been developed (76), and the presence of abnormal metaphase or interphase genetics (77), high plasma-cell labeling index (78), and a recently defined flow cytometry-based test on minimal residual disease are also used (79). Importantly, the molecular mechanisms by which cells develop resistance are not yet known, but understanding the mechanisms underlying disease escape from initial drug responsiveness will contribute to more robust prognostic strategies.

To determine whether GEP might provide a better measure of risk stratification, microarray data was correlated with outcome in two independent cohorts, permitting identification and validation of a high-risk gene-expression signature present in approximately 15% of newly diagnosed disease (50) (Figure 2). The high-risk signature is evident in a subset of all molecular classes and negatively influences regardless of class—e.g., low-risk MS disease fares much better than high-risk MS disease. The "70/17-gene model" of high risk is based on expression patterns of 70 genes, reducible to 17 genes—predominately increased expression of genes from the q arm and reduced expression of genes from the p arm of chromosome 1 (50)—which was confirmed by whole-genome microarrays and high-resolution comparative genomic hybridization (our unpublished data).

When subjected to multivariate analysis including the ISS and a gene-expression–based proliferation index, the 70/17-gene model remained a significant predictor of outcome. Improving on risk stratification provided by the ISS, Mulligan and colleagues used U133A microarray data to develop response and survival classifiers for relapsed disease treated with single-agent bortezomib or high-dose dexamethasone that were significantly associated with outcome (80); a modified version of the 70/17-gene model also predicted poor outcome in relapsed disease (81). U133A data from newly diagnosed disease validated the 70/17-gene model but also showed that the t(4;14) translocation remained a significant variable for poor outcome (82).

Decaux and colleagues recently used a custom cDNA microarray to define a 15-gene model of high risk related to cell proliferation, with a hyperdiploid signature being related to a better survival (83). Multivariate analysis comparing the 70/17-gene model with the 15-gene model revealed that the 70/17-gene model was significant in all datasets tested, but the 15-gene model was significant in bortezomib trials only. These data, together with unpublished studies, suggest that the 70/17-gene model captures more outcome variability than models or indexes of cell proliferation, considerably improving standard measures; however, it must be noted that the R2 is only ~30%.

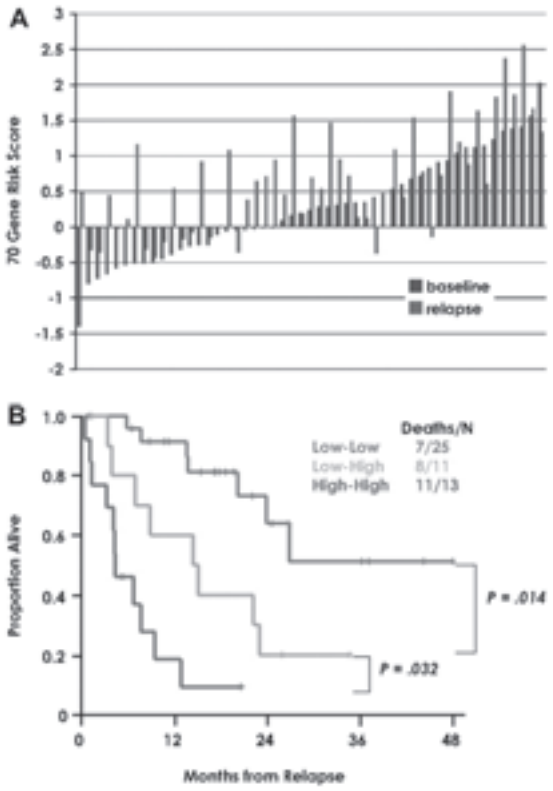

Figure 3. 70-gene risk score can increase in relapsed relative to newly diagnosed disease and an increase predicts poor post-relapse survival. (A) The 70-gene risk score in paired diagnostic (blue) and relapse (red) samples of 51 patients. The gene expression risk score is indicated to the left. Sample pairs are order from left to right based on lowest baseline score. (B) Kaplan-Meier plots of post-relapse survival of the 3 groups defined by low risk both at diagnosis and relapse (Low-Low), low risk at diagnosis and high risk at relapse (Low-High), and high risk at both time points (High-High). Reproduced with Permission from Blood

Conversion of GEP low- to high-risk at relapse

GEP on 71 paired diagnostic and relapse samples indicated increased 70/17-gene model scores in 80% of cases, and this conversion from low- to high risk severely impacted post-relapse survival in 14 of 24 cases (58%) (Figure 3). This quantifiable increase in the high-risk score over time, combined with the report that percentages of cells with gains of chromosome 1q increased over time (50), suggests expansion of a dominant clone with survival and/or proliferation advantages. The almost universal increase in this risk score during disease evolution suggests that evaluating minimal residual disease may benefit from monitoring this traceable molecular signature, in combination with flow-cytometry–based surrogate. An urgent task is to determine whether a specific baseline GEP signature can prospectively identify which low-risk cases will convert to high risk at relapse.

GEP and the centrosome index

The mechanisms underlying aneuploidy in MM are unclear, but centrosome amplification has been implicated as the cause of chromosomal instability in a variety of tumors and may be involved in MM. Immunofluorescence staining detected centrosome

amplification in 67% of monoclonal gammopathies (84). A GEP-based centrosome index (CI) was created from gene expression of centrosome proteins, which correlated well with Immunofluorescence-detected centrosome amplification. High CI (>4) was associated with poor prognostic genetic features and was an independent prognostic factor in a small cohort of heterogeneously treated cases of MM (84). Prognostic significance of the CI was subsequently validated in two large cohorts of patients entered into clinical trials, showing that a high CI is a powerful independent prognostic factor in both newly diagnosed and relapsed patients, whether treated by intensive therapy or novel agents (85). Human myeloma cell lines with higher CIs are more responsive to treatment with a novel aurora kinase inhibitor, suggesting the potential for aurora kinases as novel therapeutic targets for patients with poor prognoses (85).

GEP and CD200

Elevated expression of CD200 is an additional prognostic marker that emerged from GEP studies as a high-risk feature in MM (86). CD200 is a membrane glycoprotein that imparts an immunoregulatory signal through CD200R, leading to suppression of T-cell–mediated immune responses (87). CD200 expression was predictive for EFS independent of ISS stage or beta-2-microglobin serum levels (86), but it has not yet been validated in independent datasets or evaluated in the context of OS and all molecular subtypes and models. Because failure of immune surveillance may account for MM progression, CD200 modulation might be an important adjunct to cellular immunotherapy. As a cell-surface protein, CD200 is a potential target for monoclonal antibody therapy, but such strategies will have to consider off-target effects and the critical role of this molecule in immune regulation.

Using GEP to understand signaling in disease and its response to therapy

GEP and cancer-testis antigen expression in MM

Cancer-testis antigens are expressed in testis and malignant tumors but rarely in non-gametogenic tissues, which makes them attractive targets for cancer vaccination approaches. GEP studies determined that patients newly diagnosed with MM expressed variable numbers of cancer-testis genes (98% expressed at least one, 86% at least two, and 70% at least three) and that expression of six or more cancer-testis genes was associated with shorter EFS (88). Ten cancer-testis genes are desirable for circumventing tumor escape mechanisms, and GEP could be useful in identifying which antigens should be used to vaccinate a given patient (88). Global GEP studies showed that cancer-testis antigen NY-ESO-1 could be an ideal tumor target antigen for immunotherapy of patients with MM. NY-ESO-1 expression was higher in tumor cells from patients with CAs than in those with no CAs (89), and NY-ESO-1 expression was significantly higher in cases of relapsing MM, especially in patients with CA.

GEP and IGF signaling

Insulin-like growth factors and their receptor (IGF-1R) have been implicated in cancer pathophysiology, and IGF-1R is universally expressed in various cells of hematologic malignancies (i.e., MM, lymphoma, leukemia) and solid tumors. Specific in vitro inhibition of IGF-1R with neutralizing antibody, antagonistic peptide, or selective kinase inhibitor (NVP-ADW742) has activity against diverse tumor-cell types (particularly MM), even those resistant to conventional therapies. Global transcriptional profiles also delineated pleiotropic antiproliferative/proapoptotic molecular sequelae — specifically, modulated intracellular concentrations of key components of these pathways, including Akt, Raf, and IKK. Therapy with NVP-ADW742, alone or in combination with cytotoxic chemotherapy, had significant antitumor activity in an orthotopic xenograft MM model, providing in vivo proof-of-principle for therapeutic use of selective IGF-1R inhibitors (90). Sprynski and colleagues showed that an IGF-1 autocrine loop promoted survival in CD45-negative MM cell lines, while CD45-positive cells required addition of either IL-6 or IGF-1 (91). GEP analysis in primary disease revealed that elevated expression of IGF-1R and IL6R conferred an adverse prognosis. High expression of both IGF-1R and IL6R is seen in the MS class, but elevated IGF-1R expression is also seen in non-MS classes and is associated with a poor prognosis. Combining IGF-1-targeted therapy with anti-IL-6 therapy could be promising in the subset of patients with myeloma cells that express IGF-1R.

Pharmacogenomics of short-term in vivo exposure can reveal drug efficacies and mechanisms of action

Mechanisms of cancer cell resistance to chemotherapy are poorly understood, and efficacy measures typically rely on clinical outcome data; however, GEP studies potentially can delineate mechanisms and identify novel strategies for avoiding or overcoming drug resistance, which is a major hurdle for MM therapy and cure. Marton et al. (92) and Gray et

al. (93) were the first to use microarrays to discover targets and effects of therapeutic agents in yeast, and Cheok et al. first revealed gene-expression patterns in drug responses of human cancer (94).

By comparing GEP of myeloma cells before and 48 hours after single-agent therapy with dexamethasone, thalidomide, or lenalidomide, Burrington et al. found that genes differentially expressed after therapy were prognostic for EFS and OS and were enriched for genes involved in oxidative stress reactions and actin cytoskeleton rearrangements (95). Remarkably, gene expression altered by thalidomide in newly diagnosed disease and associated with subsequent survival was also altered by lenalidomide, a thalidomide analogue, and the changes were associated with EFS in a salvage trial of patients with relapsed disease (95). This finding strongly suggests that these genes are powerful biomarkers, and the similar acute gene-expression responses to two related chemotherapeutic agents may provide important insights into the drugs' potential mechanism(s) of action. These results also highlight the similar acute molecular responses to chemotherapies in both primary and refractory disease.

GEP studies following therapy with proteasome inhibitor bortezomib in 142 newly diagnosed symptomatic MM cases identified 113 genes with significantly altered expression—predominately downregulated proteasome genes—seen in tumor cells from 76% of patients (96). The post-bortezomib gene-expression signature was associated with a 3-year survival estimate of greater than 80%, which dramatically contrasts a median survival of less than 24 months in those with activated proteasome genes (96). Multivariate analysis demonstrated that the post-bortezomib score was an independent predictor of outcome that alone accounted for greater than 50% of outcome variability (96). These data implied that the activation status of proteasome genes in tumor cells after short-term proteasome inhibition is associated with significant outcome differences in patients with MM receiving polychemotherapy that includes bortezomib (96).

Conclusions

Utilizing high-throughput genomic analyses and data-mining techniques, a complete landscape of MM molecular pathogenesis is emerging, and powerful validated prognostic models have been developed. Unsupervised clustering of GEP data of large patient cohorts also have revealed that MM heterogeneity can be accurately cataloged and disease classes defined. Importantly, the improved survival observed in specific classes through the use of new treatments, such as thalidomide and bortezomib, buttress the concept of personalized treatment approaches.

Large-scale gene-expression data and large cohorts of uniformly treated patients with long follow-up times have provided more precise and independent prognostic models for stratifying patients with MM. Investigating GEP changes between baseline and relapse has shed light on the mechanisms underlying MM progression and the nearly universal development of multidrug-resistant MM. Pharmacogenomics studies comparing gene-expression profiles at diagnosis and following short-term single-agent therapy have identified genes associated with drug responses, contributing to mechanistic understanding. This is critical for improving existing therapies with personalized treatments and for informing research and discovery of new therapeutics.

It is well known that MM growth and survival are highly dependent on interactions with the bone-marrow microenvironment, and GEP has uncovered many molecular details of these interactions, which might prove to be the Achilles heels of MM. A prominent example was the use of GEP and MRI imaging of bone to learn that myeloma cells aberrantly synthesize DKK1, a potent inhibitor of Wnt/β-catenin signaling, which is required for osteoblast differentiation and function. These data provided a potential underlying mechanism for the unique MM osteolytic bone disease characterized by complete loss of osteoblast function. An inhibitor of DKK1 is in early Phase I/II clinical trials, attesting to the translational potential of GEP studies. GEP of whole-bone biopsies that contain tumor cells and all the accessory cells are also beginning to reveal details of MM pathogenesis and potential therapeutic targets.

After 10 years of applying GEP to thousands of patient samples in numerous institutions, GEP is emerging from the research laboratory as a clinical tool with the potential for transforming routine management of MM. While the majority of MM patients can anticipate long-term disease control via a variety of treatment approaches, patients with molecularly defined high-risk disease do not benefit from current approaches. To address this, clinical trials designed to reduce toxicities in low-risk disease and to test new treatment strategies in high-risk disease are underway. When routinely available, molecular-based classification and risk stratification will meet their potential to shift strategies for MM treatment and cure.

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Combining Genotoxic and Novel Agents toward Optimizing Myeloma Outcomes

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In patients with multiple myeloma less than 60 years of age, autologous stem cell transplantation (ASCT) remains the standard of care. During the last decade, novel agents have been incorporated into this procedure in order to improve the response rate and the outcome. Induction therapy prior to ASCT has been modified. The VAD regimen is no longer used. Ongoing studies will define the best treatment option prior to ASCT: bortezomib-dexamethasone-ImiD combinations are promising. The role of novel agents as part of consolidation treatement after ASCT is also under evaluation. Maintenance treatment using either thalidomide or lenalidomide has also been explored. Overall, the incorporation of novel agents in the design of ASCT trial has increased the CR + VGPR rate up to 80% with impressive survival results.

In patients older than 65 years of age, the combinations of MP + novel agents are now routinely used. MP + thalidomide has been approved and the progression free survival rate is up to 27 months with an expected over median overall survival of more than 4 years. MP + bortezomib has also been approved with similar results. MP + lenalidomide is under evaluation and results of phase I-II studies are promising. The British group is evaluating in elderly patients the efficacy of cyclophosphamide, thalidomide and dexamethasone with impressive preliminary results. Another promising combination without alkylating agents is under evaluation: lenalidomide + low dose dexamethasone. Overall, novel agents in combination with alkylating agents or dexamethasone have changed the outcome of elderly patients with improved progression free and overall survival.

The most recent available data will be presented during this meeting.

Acute Lymphoblastic Leukemia

This session is aimed at discussing the changes that have occurred in recent years in the management of acute lymphoblastic leukemia (ALL). This has largely stemmed from a better knowledge of the biology of ALL and from the progressive development of always more refined technologies. Robin Foà ("Sapienza" University of Rome) will discuss the possibility today of utilizing targeted and tailored treatment strategies in ALL, the illuminating examples being the management of BCR/ABL+ cases and the impact of monitoring of minimal residual disease. Cristina Mecucci (University of Perugia) will cover the major advances in our understanding of the genetic features that underlie the different subgroups of ALL. Particular attention will be given to T-ALL, for which only recently the genetic characterization has being unraveled. Finally, Jean Pierre Marie (Hospital Hotel Dieu, Paris) will cover the important issue of the management of adolescents and young adults with ALL. Based on the results obtained in childhood ALL, pediatric-like protocols are always more frequently utilized also in adult age.

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His main interests have been the biological characterization of acute and chronic lymphoproliferative disorders, the role of molecular biology in the diagnosis and monitoring of hematological malignancies, the role of cytokines in lymphoid malignancies, microarray analyses in acute and chronic leukemias, design of innovative therapeutic strategies for hematological neoplasms. Over the years has received support from many national and international sources. Is part of the European Leukemia Network and referee for national and international funding agencies. Author or co-author of over 350 papers and reviews.

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With D. Catovsky has written the book "The Lymphoid Leukaemias", Butterworths, 1990 and UTET, 1991. With G. Forni, A. Santoni and L. Frati, has edited the book "Cytokine-Induced Tumor Immunogenicity. From Exogenous Molecules to Gene Therapy", Academic Press,1994. With S. McCann, O. Smith and E. Conneally has written the book "Case-Based Haematology", Blackwell Publishing Ltd, 2005.

Chairman of the Scientific Committee of the 4th EHA Congress, Barcelona (1999). Councilor of EHA up to December 2002. Member of the Education Committee of EHA up to December 2005. Member of the National Committee for Health Research for the Ministry of Health (Italy). Chairman of the GIMEMA Working Party for chronic lymphoproliferative disorders and member of the board of the Working Party for acute leukemias. President-Elect of EHA for 2007-2009. Will become President of EHA as of June 2009.

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- November 1999 → Professor of Hematology, University 'La Sapienza' of Rome.
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- Founder and co-Editor of Leukemia and Lymphoma and of Reviews in Clinical and Experimental Hematology. Associate Editor of the British Journal of Haematology and of The Hematology Journal, journal of the European Hematology Association (EHA) up to December 2002. As of January 2003, Editor-in-Chief of The Hematology Journal. Is or has been member of the Editorial Board of the following journals: British Journal of Haematology. European Journal of Haematology, Leukemia, Cytokines and Molecular Therapy, Journal of Experimental and Clinical Cancer Research, Forum, Clinical Leukemia. From January 2005 to February 2008, Editor-in-Chief of Haematologica-The Hematology Journal, the official organ of EHA, together with M. Cazzola.
- Has been Scientific Director of Accademia Nazionale di Medicina, Genoa.
- Author or co-author of over 400 papers and reviews (over 350 on peer-reviewed journals).
- Together with D. Catovsky (London) has written the book "The Lymphoid Leukaemias" published in 1990 in English by Butterworths and in 1991 in Italian by UTET, Torino.
- In 1994, in collaboration with G. Forni, A. Santoni and L. Frati, has edited the book "Cytokine-Induced Tumor Immunogenicity. From Exogenous Molecules to Gene Therapy" published by Academic Press.
- Together with S. McCann, O. Smith and E. Conneally has written the book "Case-Based Haematology", published in 2005 by Blackwell Publishing Ltd (second edition in publication).
- The book has been published in 2008 in Italian by Piccin as "Ematologia. Casi clinici di base".
- Together with Paolo Corradini has edited the book "Testo di Ematologia" for undergraduate students, which has been published by Minerva Medica, Turino, Italy in September 2008.
- Chairman of the Scientific Committee of the 4th Congress of the European Haematology Association, Barcelona, 9-12 June 1999.
- Councilor of the European Hematology Association (EHA) up to December 2002.
- Member of the Education Committee of EHA up to December 2005.
- Has been member of the Scientific Committee of the 3rd Italy-USA project on 'Therapy of Tumors'.
- Has been member of the Italian Committee on 'Hematopoietic Stem Cells'.
- Member of the British Journal of Haematology Research Trust.
- Member of the National Committee for Health Research for the Ministry of Health.
- Member of the Board of Directors of GIMEMA.
- Chairman of the GIMEMA Working Party on chronic lymphoproliferative disorders and member of the Working Party on acute leukemias.
- Councillor of EHA from June 2007.
- President-Elect of EHA 2007-2009.
- President EHA 2009-2011.

As project leader, has obtained over the last 20 years research grants from the following sources:

1. CNR, within the projects 'Controllo della Crescita Neoplastica', 'Oncologia' and 'Applicazioni Cliniche della Ricerca Oncologica' .
2. MURST 40% and 60% projects.
3. CNR, strategic project on 'Farmaci per Malattie Orfane'.
4. Istituto Superiore di Sanità, within the 1st and 2nd Italy-USA project on 'Therapy of Tumors'.
5. AIRC, coordinator, together with Dr. G. Parmiani, of the Special Project 'Gene Therapy'.
6. Istituto Superiore di Sanità, within the strategic project on 'Gene Therapy'.
7. AIRC, from 1998 onwards.
8. Istituto Superiore di Sanità, 1% projects.
9. European Commission, "Leonardo da Vinci" project, 2002-2003.
10. Ministry of the University, FIRB, "Post-Genoma" Strategic Project, 2002-2004.
11. Istituto Superiore di Sanità, "Stem Cells" project.
12. European Commission, "European Leukemia Network" project.
13. "Microarray Innovations in LEukemia" (MILE) International Project.

- Has coordinated over the years many phase II and III GCP trials for patients with different acute and chronic hematologic malignancies.

AREAS OF INTEREST:
1) Biological characterization of acute and chronic lymphoproliferative disorders. 2) Role of molecular biology in the diagnosis of hematological malignancies. 3) Lymphocyte function in chronic lymphoproliferative disorders.
4) Role of cytokines in hematological malignancies.
5) Pre-clinical and clinical studies of IL2 based immunotherapy in acute leukemia.
6) Transduction of human tumor cells with cytokine genes and design of cytokine gene therapy protocols in oncology.
7) Immunogenicity and immunotherapy of hematological malignancies.
8) Characterization of the stem cell compartment in hematological malignancies.
9) Microarray analyses in acute and chronic leukemias.
10) Design of innovative therapeutic strategies for acute and chronic lymphoproliferative disorders.

Targeted Therapies in ALL

Dr. Robin Foà

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Important advances in the diagnostic and prognostic work-up, as well as in the clinical management of adult and childhood acute lymphoblastic leukemia (ALL) have occurred over the last years. These have progressively impacted in our understanding of the disease and have relevant implications in the treatment and overall outcome of patients.

ALL can be identified on the basis of morphologic, cytochemical and immunophenotypic criteria, and a modern management of ALL is also based on cytogenetic and genetic evaluations at presentation. More recent technologies, such as gene expression profile analysis, allow to further unravel the intrinsic biology of the disease and to improve the diagnostic and prognostic stratification, as well as to identify targets of innovative therapeutic strategies.

A precise biologic characterization at diagnosis of the pathological cells enables also to define the "profile/signature" of the neoplastic clone of each individual case. This can then be utilized to monitor precisely the disease over time and, in turn, to define prognostic subgroups of patients. As a consequence, monitoring of minimal residual disease (MRD) by immunophenotypic and/or molecular analyses is nowadays always more frequently utilized to decide the algorithm of treatment (or non-treatment) in many hematologic conditions, including ALL, thus allowing a more tailored therapeutic intervention.

Primary treatment may change considerably if certain markers are present and rapidly identified. Ph+/Bcr-Abl+ ALL is an illuminating example of how our advancements in knowledge can guide today the therapeutic decision and highlights how the understanding of a specific genetic abnormality linked to a given condition has led over time to the use of targeted (intelligent) therapies aimed at correcting/targeting the given abnormality. This, in turn, has enabled significant improvements in the management of such patients. This scenario was opened years ago for patients with acute promyelocytic leukemia (APL) and a similar reality is occurring toady for Ph+/Bcr-Abl+ ALL, the worse possible leukemic condition. The results obtained with the tyrosine kinase (TK) inhibitors – Imatinib first and, more recently, Dasatinib – as first line treatment for adult Ph+ ALL are in fact changing our overall approach for this condition. The use of TK inhibitors alone has indeed allowed to improve the rate and degree of responses for this most unfavorable subgroup of ALL. Even elderly patients, over the age of 60, respond well to Imatinib/Dasatinib and steroids alone given upfront. Hematologic responses in the order of 100% have been reported in adult ALL in all age ranges. The relevance of this observation is underlined by the fact that Ph+/Bcr-Abl+ ALL accounts for about 25% of adult ALL and that the prevalence of such cases increases with age. This further highlights the importance of a rapid and accurate diagnostic work-up of ALL patients at all ages.

A broader use of genetic-based technologies is progressively opening the way to the identification of new genes against which innovative strategies of targeted therapy can be hypothesized.

In conclusion, through the advancements in our understanding of the biology of ALL witnessed over recent years and through the development of always more sophisticated technologies, the possibility of designing in adult ALL targeted and individualized therapeutic strategies according to an always more refined characterization of the leukemic cells and on the presence or absence of minimal residual disease is progressively becoming a reality.

Dr. Cristina Mecucci

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Curriculum Vitae
October1967-July 1972 ,Greek-Latin, Lyceum A.Mariotti of Perugia (60/60).
November 1978, Graduated in Medicine at the University of Perugia (110/110 cum laude).
November 1984, Specialist in Internal Medicine at the University of Perugia (50/50).
June 1987, PhD at the University of Leuven (Belgium), thesis : "Human hematologic malignancies: A cytogenetic approach".
July 1987, "Geaggregeerde" Professor at the University of Leuven (Belgium).
October 1994, Specialist in Hematology at the University of Perugia (50/50).
Present Position: Associate Professor in Hematology. Head of the Laboratory of Cytogenetics and Molecular Genetics, University of Perugia

Active member of :
- International Workshops for Chromosome Aberrations in malignant hemopathies
- International Cooperative Groups for MIC (Morphology,Immunology, Cytogenetics)Classifications of leukemias.
- Italian GIMEMA group for therapy of acute leukemias in adults.
- European Community financed studies on malignant hemopathies (BIOMED; Concerted Actions).

Funding Member of :
European Haematology Association.
Member of the following Societies:
Italian Society of Hematology
Italian Society of Experimental Hematology
Italian Society of Genetics
European Haematology Association
European Society of Human Genetics
American Society of Hematology

Board Councilor of:
European Haematology Association
Italian Society of Experimental Hematology

Consultant of:
Istituto Superiore di Sanità
Accademia Nazionale di Medicina

Associate Editor of:
Haematologica

Member of the **Editorial Board** of the following Journals:
British Journal of Haematology
Cancer Genetics & Cytogenetics
Leukemia Research
Les Annales de Genetique
Am J Hematol

Activity of **Reviewer** for the following journals :
Leukemia
European Journal of Haematology
Blood
Oncogene
Genes Chromosomes and Cancer

Prizes :
Heraeus Prize at the "7th International Congress of Human Genetics", Genova, Italy, 18-20 September,1986.
AULL, "Associazione Umbra per lo Studio e la Terapia delle Leucemie e Linfomi", Perugia, Italy, April 1987.
ARFACID, "Associazione per la Ricerca Fondamentale ed Applicata sul Cancro, Invecchiamento e Malattie Degenerative", Napoli, Italy, October 1988.

274 Articles in Indexed Journals (Pubmed).
250 Posters or Oral Presentations at International Congresses.
16 Chapters in Books of Hematology or Genetics.

New Advancements in the Genetic Characterization of ALL

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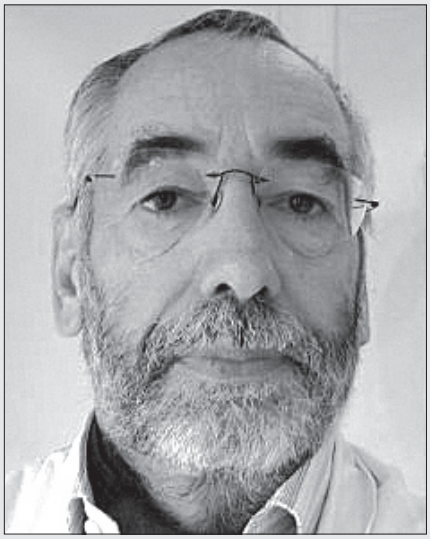
Genetic classifications of ALL in children and adults.have been significantly enriched by new technologies.

B-ALL

80-90% of cases show genetic aberrations. Several correlations between chromosome rearrangements and immunophenotype have been established. Besides the well standardized cytogenetic classification which has been inspiring therapeutic protocols over years, new genes and mechanisms are emerging in distinct entities. Among them, involvement of the CEBP family; deletions and, less frequently, translocations involving PAX5 gene; c-MYC deregulation by genes other than immunoglobulin genes.

T-ALL

Conventional cytogenetics has been largely unsuccesful. Instead a huge amount of information is available by integration of advanced genomic studies, such as FISH, expression profile, microarray-CGH. The number of abnormal cases deeply increased from 20% to 80%. Although clinical correlations remain to be understood, new recurrent rearrangements have been discovered. Among them NF1 deletion; NUP214/ABL1; MYB duplication; NUP214/TAF1. Moreover mutations affecting NOTCH1, FBW7, JAK1 have been characterized. It becomes also clear that multiple hits are necessary for development of T-ALL in each individual case.



Dr. Jean-Pierre Marie

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1/ Research Responsibilities

- Head of an INSERM/ University lab (Team 18/UMRs872) « Resistance and Survival of Tumoural Cells) : 2005-
- Secretary of the Leukemia Group of the EORTC : 1999-2005
- Chairman of the Leukemia Group of the EORTC : 2009-

2/University and Medical Training:

- Professor of Hematology, Paris since 1982 (1st class since 1998), University Pierre & Marie Curie (Paris 6)

3/ Post Graduate Training

- Ontario Cancer Institute, Princess Margaret Hospital,
  In Dr EA McCulloch's laboratory
  University of Toronto, Canada: 6-12/1980
- Stanford University School of Medicine, Oncology Division,
  In Dr BI Sikic's laboratory
  Stanford, USA: 7-1988/8-1989

4/ Hospital Responsabilities

- Head of the Department of Hematology and Medical Oncology(53 beds), Hôtel-Dieu of Paris, 1998-

5/ Memhership and Awards

- Member of American Association for Cancer Research
- Member of the American Society of Hematology
- Member of the European Association of Hematology
- Member of the European Society of Medical Oncology
- Member of the French Society of Hematology
- Fellowship of the EORTC/NCI Research Training Program, 1989

6/ Scientific review responsibilities

- Section Editor for the LEUKEMIA journal (topic : drug résistance) 1995-
- Reviewer for BLOOD, British Journal of Cancer, Cancer research
- Reviewer and chairman for the American Society of Hematology Meetings in 1997, 1999, 2004, 2007 section "Drug resistance and pharmacology"
- Member of the Scientific Committee of the European Hematology Association Meetings, 2001 and 2002

7/ Publications

- 261 publications, including:
- 198 in journals with peer review (76%):
- 63 didactic articles

8/ Fields of interest

Onco-hematology : Acute and chronic leukemia, Myeloma, Lymphoma, Chemotherapy, Drug resistance, Phases I-II trials, Treatment of febrile neutropenia

Management of ALL in Adolescent and Young Adults

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Survival for adult with ALL is lower than in children, mainly due to the relapse rate. A pressing question is whether the age-related differences in outcome are predicated by the disease per see or whether they result from a different approach to, or tolerance of, therapy. Boissel et al. (1) compared the outcome of adolescents (15-20 years) with ALL treated in France in either the pediatric FRALLE 93 or the adult LALA-94 clinical trials. With a median follow up of about 3.5 years, the CR rate (94% vs. 83%), event free survival (EFS) at 5 years (67% vs.41%), and the DFS for the CR patients (72% vs. 49%) were far superior in the pediatric group and multivariate analysis confirmed the independent effect of the treatment trial on outcome. The major differences between the pediatric or adult approach were the actually given dosages of asparaginase, corticosteroids and vinca-alkaloids. Another difference was the strict discipline with which the treatment courses were administered by the pediatricians compared to the flexibility of the internists. Analyses with similar outcome have been reported by comparing ALL patients aged 15 till 21 years treated in Dutch and British children and adult protocols (2,3). We recently tested the feasibility of a pediatric regimen (4) in 28 adult ALL patients (age 16-57 years), of whom 83% reached a CR. Ten patients had undetectable minimal residual disease (MRD) and none of them experienced relapse. Grade 3 - 4 toxicities included a considerable number of severe infections, liver function abnormalities, unexpected peripheral neuropathies and denutrition. These toxicities increased with age. The adherence discipline with respect to time-lines of the treatment schedules was successful in approximately 50% of the limited number of patients studied so far. Similar experience was observed in the HOVON-70 study, which included 54 patients aged 18 to 39 years. Overall, it was concluded that results appeared very encouraging, but that side effects necessitated prolongation of the induction/ consolidation/ intensification phase in a considerable number of patients and that the protocol seemed too intensive for older patients. In conclusion, adolescents but also "young" adults (<40yo) with ALL treated with a pediatric-based schedule have a better chance of EFS/survival than those treated with an "adult" schedule.

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2. de Bont JM, van der Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia 2004;18:2032-5.
3. Chessells JM, Hall E, Prentice HG, Durrant J, Bailey CC, Richards. The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. Leukemia. 1998; 12: 463-473.
4. Haiat S, Vekhoff A, Marzac C, et al. Improved outcome of adult acute lymphoblastic leukemia treated with a pediatric protocol: results of a pilot study. Blood 2007;110:2822.

Hodgkin Lymphoma

Today four out of five patients with Hodgkin`s disease (HD) will be cured with modern treatment strategies depending on stage and risk factor profile.

In early stages favorable HD cure rates of > 90% are achieved with extended field (EF) irradiation, the traditional standard treatment. However, the concept of EF irradiation therapy is now being abandoned by most study groups due to the recognition of fatal long-term effects, especially the high rates of second solid tumors. Newer approaches include mild chemotherapy for control of occult disease in combination with involved field (IF) irradiation. Combined modality treatment is already the treatment of choice in early stages unfavorable (intermediate) HD, where EF irradiation is substituted by IF irradiation for the same reasons.

Due to the high relapse rates of 30% to 50% after first-line polychemotherapy these standard regimens like MOPP or ABVD were often modified in the last three decades. However, these efforts could not change the relatively poor outcome of advanced-stage patients until recently. The introduction of a new dose-intensified regimen (BEACOPP) has now significantly improved the prognosis of patients with advanced HD.

Patients who relapse following radiation therapy alone for early stage HD have satisfactory results with combination chemotherapy and are not considered as candidates for high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT). For patients with relapsed HD after combination chemotherapy the current data support the use of HDCT with ASCT.

More recently, several small studies have suggested that the results of a PET scan performed early during treatment can strongly predict the response of Hodgkin lymphoma.

Effective therapies, however, have several drawbacks that might limit their use. Chemotherapy as well as radiation therapy induced severe acute and late toxicities which may diminish the long-term benefit of curative treatment. Several studies including a quality of life approach have highlighted the difficulties that survivors may experience even long after the treatment such as secondary neoplasia, general fatigue, poor health and social problems.

Dr. Andreas Josting

Dr. Andreas Josting

Date of birth:	04.07.1962
Place of birth:	Enger, Germany
Nationality.	German
Marital status.	Married since 2000, 2 sons
1986-1993:	Medical studies at the Heinrich Heine University in Düsseldorf, Germany
1989-1990:	Student Assistant at the Institut of Clinical Chemistry and Laboratory Diagnostics, Prof. Dr. Wirnt Rick
1990-1991:	Student Assistant in the Laboratory for Experimental Haematology and Bone Marrow Transplantation (Professor Dr. Stefan Burdach)
May 1993:	Graduation from Medical School; MD
Dissertation 1993:	Title: „The Influence of Cytomegalovirus Infection on the Production of IL-6 in T-lymphocytes and Bone Marrow Stromal Cells.“
Clinical activity since 1993:	Clinical physician at the First Department of Internal Medicine of the University Hospital Cologne (Director. Prof. Dr. Volker Diehl), Clinic for Internal Medicine, Hematology and Oncology
February 2000:	Doctor of Internal Medicine
June 2001:	Consultant of the First Department of Internal Medicine, University Hospital Cologne
January 2002:	Habilitation: Title: „Value of High-dose Chemotherapy in Patients with Relapsed and Refractory Lymphoma“
May 2002:	Doctor of Hematology and Oncology
Since March 2002	Member of the German Hodgkin Study Group
April 2005 – September 2006:	Consultant in the Department of Gastroenterology at the St. Elisabeth Krankenhaus Köln Hohenlind
May 2006	Specialty in Palliative Care Medicine
March 2007	Doctor of Gastroenterology
September 2007	Head of the Department of Internal Medicine EVK Lippstadt
Main scientific interest:	Studies and several publications on salvage therapy, high-dose chemotherapy followed by stem cell transplantation in lyphomas, studies, on stem cell mobilization procedures, studies on new drugs in the treatment of lymphomas, studies on prognostic factors in relapsed lymphomas, studies on late effects and quality of life in Hodgkin`s disease. Member of the American Society of Hematology (ASH), Member of the American Society of Clinical Oncology (ASCO), Member of the European Society for Medical Oncology (ESMO), Member of the Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO), Member of the Deutsche Gesellschaft für Innere Medizin (DGIM), Member of the German Hodgkin`s Lymphoma Study Group (GHSG), Member of the Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen (DGVS)

Lippstadt, 8. März 2009

Treatment of Advanced and Relapsed Hodgkin`s Disease

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Up to the middle of the last century, patients with advanced stages of HD were incurable. With the advent of more effective drugs used early in childhood leukemia, de Vita and colleagues at the NCI were the pioneers who paved the road for an incredible success of modern chemotherapy in oncology with a 50% cure rate for advanced stage HD patients, purely with the drug combination MOPP (mechlorethamine, vincristin (Oncovin), procarbazine, and prednisone). [1]

Inspite of the great accomplishments with MOPP and MOPP-like regimens, there were major obstacles: a) 15-30% of the patients did not reach a CR and only about 50% patients could be cured and b) MOPP had a significant acute toxicity and an increased risk of sterility and acute leukemia, due to the alkylating agents.

In 1975 Bonadonna and colleagues introduced the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen in an attempt to develop a regimen for patients who had failed after MOPP.[2] Vinblastine had demonstrated high activity as a single agent and lacked cross-resistance with vincristine in human tumors. Both doxorubicin and bleomycin were very active drugs and showed objective responses in about 50% of patients. Dacarbazine was added since it was active as a single agent and also showed synergism with doxorubicin.

Results of prospective multicenter trials using the traditional standard regimes MOPP, ABVD or alternating, sequential or hybrid combinations of these two very effective, non-cross resistant drug regimens, mostly assisted by additive radiotherapy, have shown satisfactory complete remission rates up till 80-90%. However, the failure-free survival (FFS) and overall survival (OS) rates at 5 years were only 65-70% and 75-85%, respectively. The pivotal CALGB trial in advanced HD, which compared MOPP, ABVD and alternating MOPP/ABVD without additive radiotherapy showed equal therapeutic results for ABVD and MOPP/ABVD as far as PFS and OS were concerned. Both regimens were superior to MOPP. ABVD had less germ cell and hematopoietic stem cell toxicity. A long-term follow up of this study over 15 years has recently been published demonstrating a 45-50% PFS and a 65% overall survival for ABVD and MOPP/ABVD.[3]

There are single center reports with more favorable results using ABVD, MOPP/ABV or similar regimen, but the numbers of patients are small and seem to carry a bias of selection.

These rather disappointing results raised a number of questions:

1. is ABVD good enough with 30-35% failures within 5-10 years?
2. how to improve initial tumor control without compromising long term cure?
3. do we need consolidating radiotherapy after effective chemotherapy?
4. are the fourth generation regimen Stanford V, BEACOPP, ChlVPP/EVA, MEC better than ABVD short and long term?
5. what is the role of PET scanning in advanced disease
6. how to improve Quality and Quantity of life by reducing acute and long term toxicity?

These questions led the GHSG in 1992 to investigate a new principle on the basis of the COPP/ABVD regime by using the same drugs, except dacarbazin and vinblastine, adding etoposide and introducing a time- and dose-escalated schedule in lymphoma treatment for the first time, formulating the BEACOPP principle. This regimen allows to give the most tumoricidal drugs on day 1-3 and to recycle on day 21 instead on day 28 -or in the BEACOPP-14 regimen on day 15- and, by the help of G-CSF, to escalate the dosage of etoposide, cyclophosphomide and adriamycin by 100%, ~90% and ~40%.

In a randomized three armed phase III study COPP/ABVD was tested against baseline BEACOPP and

escalated BEACOPP. Radiotherapy in this study was given to initial bulk and residual tumors with 30 Gy in about 65%-70% of patients.[4]

At the last analysis in June 2003, after a median follow up of 7 years, the escalated BEACOPP arm showed highly significant superiority over the COPP/ABVD arm for FFTF: 85% versus 67% (p< 0.0001), and OS: 90% versus 79% (p< 0.0001), in spite of the higher number of 11 AML/MDS in the BEACOPP escalated arm versus 1 in the COPP/ABVD arm. However, the death rate due to progression of HD was 9,6% in the COPP/BVD arm and only 2,4% in the BEACOPP escalated group of patients. Furthermore, there was no survival difference after salvage treatment between the three treatment arms.

However, the superiority of 8 cycles of escalated BEACOPP over the former standard arm COPP/ABVD, had the prize of a considerably higher acute and late toxicity. Therefore the GHSG started to undertake two successive studies, HD12 and HD15, to

- de-escalate BEACOPP
- reduce radiotherapy

hence reduce the toxic burden of this very effective principle.

In the HD12 study, 8 cycles of escalated BEACOPP were compared with 4 cycles of escalated and 4 cycles of baseline BEACOPP, and following a factorial design there was a further randomization for radiotherapy yes or no.

65% of patients in the radiotherapy arms got 30Gy IF-RT, whereas in the non-radiotherapy arms 10% were radiated due to a decision of a panel which independently of the randomization judged every CT after end of chemotherapy.

In this study, 1396 patients were evaluable. After a median follow-up of five years in this sequential analysis there is neither a difference between the 8 BEACOPP escalated and 4 BEACOPP escalated + 4 BEACOPP baseline arms nor is there a difference for the radiotherapy yes and no arms, neither for FFTF, nor for OS. At a median follow up of 30 months, the FFTF for the total cohort was 86.9% and the OS 93.8%. At this time of observation the rate for AML/MDS was only half of that observed in the HD9 trial at the same time point. These results favor the continuation of the global study, chaired by Dr. Patrice Cadre from the EORTC, comparing ABVD with BEACOPP (4+4) +/- RT.

In conclusion, ABVD is not generally accepted worldwide as the gold standard chemotherapy regimen for advanced stages of HL patients, whilst it is the most favored regimen for early and intermediate stages of HL. The new generation of dose intensified or dose dense chemotherapy regimen, like BEACOPP have to be tested in different cultural and health structure settings to prove their expected superiority over conventional schemes, like ABVD, MOPP/ABV or others, to improve long term quantity and quality of lives of HL patients. The role of consolidating radiotherapy after reaching clinically, CT/MR- or PET- confirmed complete or partial remission (CR/PR) has been assessed in ongoing studies.

Prognostic factors in relapsed and refractory Hodgkin`s disease

It was first noted in 1979 that the length of remission to first-line chemotherapy had a marked effect on the ability of patients to respond to subsequent salvage treatment.[5] In 1992 the National Cancer Institute (NCI) updated their experience with the long-term follow up of patients who relapsed after polychemotherapy.[6] Derived primarily from investigations involving failures after MOPP and MOPP variants, the conclusions are thought to be relevant to other chemotherapy programs as well. On this basis, chemotherapy failures can be divided into three subgroups:

- Primary progressive Hodgkin`s disease, i.e. patients who never achieve a complete remission
- Early relapses within 12 months of CR
- Late relapses after CR lasting > 12 months

Using conventional chemotherapy for patients with primary progressive disease, virtually no patient survives more than eight years. In contrast, the projected 20-year survival for patients with early relapse or late relapse was 11% and 22%, respectively.[6]

Primary progressive Hodgkin`s disease

The German Hodgkin`s disease Study Group (GHSG) retrospectively analysed 206 patients with progressive disease (PD) defined as progression during induction treatment or within 90 days after the end of treatment to determine outcome after salvage therapy and identify prognostic factors.75 The five year freedom from second failure (FF2F) and OS for all patients was 17% and 26%. As reported from transplant centers, the five year FF2F and OS for patients treated with HDCT is 42% and 48%, respectively, but only 33% of all patients re-

ceived HDCT. The low percentage of patients who received HDCT was due to rapidly fatal disease or life-threatening severe toxicity after salvage therapy. Other reasons not to proceed to HDCT were insufficient stem cell harvest, poor performance status and older age. In a multivariate analysis, Karnofsky performance score at progress ($p < 0.0001$), age ($p = 0.019$), and attainment of a temporary remission to first-line chemotherapy ($p = 0.0003$) were significant prognostic factors for survival. Patients with none of these risk factors had a 5-year OS of 55% compared with 0% for patients with all three of these unfavorable prognostic factors.

Early and late relapsed Hodgkin`s disease

Although the results reported with HDCT in patients with late relapse have been superior to those reported in most series of conventional chemotherapy, the use of HDCT in late relapses had been an area of controversy because patients with late relapse have satisfactory second CR rates when treated with conventional chemotherapy with OS ranging from 40% to 55%. However, the HDR-1 trial of the GHSG showed improved FFTF after HDCT compared with conventional chemotherapy also in patients with late relapse.

The GHSG has recently performed a retrospective analysis including a much larger number of relapsed patients (n=422) than previous reported. The analysis of prognostic factors suggests that the prognosis of a patient with relapsed HD can be estimated according to several factors. The most relevant factors were combined into a prognostic score. This score was calculated on the basis of duration of first remission, stage at relapse and the presence or absence of anemia at relapse. Early recurrence within 3 to 12 months after the end of primary treatment, relapse stage III or IV and haemoglobin <10.5g/dl in female or < 12g/dl in male patients comtribute to a score with possible values 0, 1, 2 and 3 in order of worsening prognosis.8 This prognostic score allows distinguishing patients with different FF2F and OS. The actuarial 4-year FF2F and OS for patients relapsing after chemotherapy with three unfavorable factors were 17% and 27%, respectively. In contrast, patients with none of the unfavorable factors had FF2F and OS at 4-year of 48% and 83%, respectively. In addition, the prognostic score was also predictive for patients relapsing after radiotherapy, for patients relapsing after chemotherapy who were treated with conventional therapies or with HDCT followed by ASCT, and for patients under 60 years and a Karnofsky performance status ≥ 90% being the major candidate groups for dose intensification. The prognostic factor score uses clinical characteristics which can be easily collected at the time of relapse. It separates groups of patients with substantially different outcomes.

Treatment strategies

Patients who relapse following radiation therapy alone for localized Hodgkin's disease have satisfactory results with combination chemotherapy and are not considered candidates for HDCT and ASCT.

HDCT followed by ASCT has been shown to produce 30%-65% long-term disease-free survival in selected patients with refractory and relapsed HD. In addition, the reduction of early transplant-related mortality from 10% - 25% reported in earlier studies to less than 5% in more recent studies has led to the widespread acceptance of HDCT and ASCT.

Although results of HDCT have generally been better than those observed after conventional-dose salvage therapy, the validity of these results has been questioned due to the lack of randomized trials. The most compelling evidence for the superiority of HDCT and ASCT in relapsed HD comes from two reports from the British National Lymphoma Investigation (BNLI) and the German Hodgkin's Lymphoma Study Group (GHSG) together with the European Group for Blood and Marrow Transplantation (EBMT).

In the BNLI trial, patients with relapsed or refractory HD were treated with a combination of carmustine (BCNU), etoposide, cytarabine and melphalan at a conventional-dose level (mini-BEAM) or a high-dose level (BEAM) with autologous bone-marrow transplantation.[9] The actuarial 3-year event-free survival (EFS) was significantly better in patients who received high-dose chemotherapy (53% vs 10%).

The largest randomized, multicenter trial was performed by the GHSG/EBMT to determine the benefit of HDCT in relapsed HD. Patients with relapse after polychemotherapy were randomly assigned between four cycles of Dexa-BEAM (dexamethasone, BCNU, etoposide, Ara-C and melphalan) and two cycles of Dexa-BEAM followed by HDCT (BEAM) and ABMT/PBSCT. The final analysis of 144 evaluable patients revealed that from 117 patients with PR or CR after two cycles of chemotherapy, FFTF in the HDCT group was 55% versus 34% for the patients receiving an additional two cycles of chemotherapy. OS was not significantly different.[10]

Sequential high-dose chemotherapy

In recent years, sequential high-dose chemotherapy has increasingly been employed in the treatment of solid tumors, hematologic and lymphoproliferative disorders. Initial results from phase-I/II studies indicate that this kind of therapy offers safe and effective treatment. In accordance with the Norton-Simon hypothesis, following initial cytoreduction, few non-cross-resistant agents are given at short intervals. In general, the transplantation of PBSC and the use of growth factors allow the application of the most effective drugs at the highest possible doses at intervals of one to three weeks. Sequential high-dose chemotherapy thereby enables the highest possible dosing over a minimum period of time (dose intensification).

In 1997 a multicenter phase-II trial with a high-dose sequential chemotherapy program and a final myeloablative course was started to evaluate the feasibility and efficacy of this novel regimen in patients with relapsed HD.[11] Eligibility criteria included age 18-60 yrs., histologically proven relapsed or primary progressive HD, second relapse with no prior HDCT and ECOG performance status 0-1. The treatment program consists of two cycles of DHAP (dexamethasone, ara-C, cisplatin) in the first phase in order to reduce tumor burden before HDCT. Patients with partial remission (PR) or complete remission (CR) after two cycles of DHAP, receive sequential high-dose chemotherapy consisting of cyclophosphamide 4 g/m^2 iv, methotrexate 8 g/m^2 iv plus vincristine 1.4 mg/m^2 iv; and etoposide 2 g/m^2 iv. The final myeloblative course was BEAM followed by PBSCT with at least 2 x 106 CD34+ cells/kg.

At the last interim analysis 102 patients were available for the final evaluation. State of remission was multiple relapse in 10 patient, progressive disease in 16 patients, early relapse in 29 patients and late relapse in 44 patients. At 30 months of median follow-up (range 3-61 months) results are as follows: Response rate (RR) after DHAP 87% (23% CR, 64% PR) and RR at final evaluation 77% (68% CR, 9% PR). Toxicity was tolerable with no treatment related deaths. FFTF and OS for patients with early relapse were 64%/87% for early relapse; 68%/81% for late relapse; 30%/58% for patients with progressive disease and 55%/88% for patients with multiple relapse.

In conclusion, sequential administration of high doses of cyclophosphamide, methotrexate and etoposide is feasible and did not affect the tolerability of final myeloablative BEAM. This new, three-phase treatment regimen is well tolerated and feasible in patients with relapsed and primary progressive HD. The preliminary data suggests a high efficacy in relapsed HD patients, warranting further randomized studies.

HDR-2 Protocol

In January 2001, the GHSG together with the EORTC, the GEL/TAMO and the EBMT started a prospective randomized study to compare the effectiveness of a standard HDCT (BEAM) with a sequential HDCT after initial cytoreduction with 2 cycles DHAP (HD-R2 protocol, Figure 3).

Patients with histologically confirmed early or late relapsed HD, and patients in second relapse with no prior HDCT fulfilling the entry criteria receive two cycles of dexamethasone, high-dose cytarabine and cisplatin (DHAP) followed by G-CSF.

Patients achieving NC, PR or CR after DHAP are centrally randomized to receive either BEAM followed by PBSCT (arm A of the study) or HD cyclophosphamide + G-CSF, followed by HD-MTX + vincristine, followed by HD etoposide + G-CSF and a final myeloablative course with BEAM (arm B of the study).

Allogeneic transplantation after reduced conditioning in HD

Allogeneic transplantation (alloBMT) has clear advantages compared with autologous transplantation: Donor marrow cells uninvolved by malignancy are used avoiding the risk of infusing occult lymphoma cells, which may contribute to relapse in patients who undergo autologous transplantation. In addition, donor lymphoid cells can potentially mediate a graft-versus-lymphoma effect.

Generally, donor availability and age constraints have limited a broader application of alloBMT in HD. Moreover, alloBMT is associated with a high treatment related mortality rate of up to 75% observed in patients with induction failure which casts doubt upon the feasibility of this approach in HD patients. In most cases, allogeneic transplantation from HLA-identical siblings is not recommended for patients with HD. The reduced relapse-rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity.

Nevertheless, patients with induction failure and relapsed patients with additional risk factors have

a poor prognosis also after HDCT and ASCT. Therefore, the role of alloBMT should be further evaluated in these patients taken advantage of new developments like non-meloablative conditioning regimens and alloPBSCT.

To circumvemt the problems inherent to the toxicity and treatment related mortality associated to allografting, the posibility to achieve engraftment of allogeneic stem cells after immunosuppressive therapy combined with myelosuppressive but non-myeloablative therapy has been assessed. Several groups have recently updated their experience with non-myeloablative conditioning regimens.12

The EBMT together with the GEL/TAMO, the EORTC and the GHSG activated a multicenter phase II study to evaluate the treatment-related mortality (TRM) of patients with primary progressive or relapsed HD (early relapse, multiple relapse and relapse after autologous SCT). Patients with an HLA compatible sibling donor or an HLA matched unrelated donor will be initially treated with 1-2 cycles of DHAP or other salvage protocols to reduce tumor burden before alloPBSCT. PBSC will be collected after G-CSF priming of the donor and reinfused after conditioning with fludarabine and melphalan.

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Treatment Strategies in Early and Intermediate Stages Hodgkin's Disease

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Summary- Limited stages of Hodgkin's lymphoma (HL) include the majority of patients suffering from this disease; they have a large spectrum of prognosis. The term of early stage, by opposition to advanced stages makes one think that there is a progression from stage I to stage IV. This view is not adequate and should be amended for other definitions as there is some heterogeneity in treatment outcome. However when speaking about limited stages everybody understands that the disease is accessible to radiotherapy which was once the only curative treatment and remains still the major part of the current treatments. The sustained improvement of the treatment results for decades did not follow a more favourable overall survival for these rather young patients and the hazard of the treatment became the major issue in the management of HL. This issue led to tailor the treatment according to prognostic groups, assuming that the treatment burden could be halved for favourable (F) patients and intensified for unfavourable (U) cases. The delineation of these prognostic groups depends on prognostic factors, the strongest being age, B symptoms, tumour bulk (mainly mediastinum), number of involved lymph node areas and ESR, F group has none of them and U group at least one of them. In F group combined modality treatments with limited radiotherapy fields is the standard of treatment. In this group the comparison of the standard dose of 36 Gy to the experimental dose of 20 Gy gave equivalent results in controlled trials. In the U group the need still remains to improve treatment results, especially with more effective chemotherapy. However the comparison of a more aggressive chemotherapy such as BEACOPP did not result in a better outcome when compared with ABVD in the EORTC-GELA H8 trial similar to GHSG-HD11 trial. Moreover, in these trials it was shown that 4 AVBD yield the same results as 6 and finally, more is not better. According to these controlled trials the standard for U group is a combined modality treatment with 4 ABVD and IF radiotherapy of 30 Gy. The question to be answered now is whether we could modulate the amount of the treatment according to the response in F as well as in U group and especially whether we can omit radiotherapy in F group in remission after chemotherapy. In order to answer this question there is currently large tri-

als such as EORTC-GELA H10 trial to see whether we can limit the treatment burden and avoid radiotherapy in F group and on the opposite side whether we can rescue PET positive patients by another and more intensive chemotherapy. The results are awaited in a couple of years.

Limited stages of Hodgkin's lymphoma (HL) defined according to the Ann Arbor classification and Cotswolds criteria have the common denomination of being accessible to a curative radiotherapy whatever the extension, they usually gather stages I & II. It appeared soon that these stages have not a homogenous outcome and do not share the same prognosis, so the concept of stage has to be amended. The introduction of chemotherapy before radiotherapy addressed new questions as some cured patients died of late treatment complications widely described 1-3 and it is established that the overall survival of the cured patients does not follow that of the general population of the same age4 because of cardiovascular complications and secondary cancers. Hence, the global approach to the treatment evolved from an aggressive trend to a prognosis adapted management with definition of risk factors and prognostic groups. However initial prognostic factors defined for radiotherapy alone lost most of their significance and new factors appear and are under evaluation with new standards of chemotherapy and radiotherapy.

Favourable and Intermediate stages of Hodgkin's lymphoma (HL) are prognostic subgroups of patients for limited stages that account for about 80% of all cases. The terminology of intermediate as opposed to favourable or advanced, is issued from the German Hodgkin's Study Group (GHSG) and is corresponding to unfavourable limited stages and we should keep in mind these different definitions while discussing about patients. Whatever the treatment in two subgroups is, the purpose for both is reducing toxicity and improving efficacy for the best survival.

Prognostic factors- The prognosis adapted treatment is based on two approaches. First after the definition of (initial) ab initio prognostic factors and then response adapted treatment amount. The former is rather static and defined before any treatment, the latter appears more individual adapted treatment and perhaps more realistic.

1- Pretherapeutic factors - Almost all prognostic factors have been defined after retrospective analysis of patients included in clinical trials or at least treated according to the standard of time meaning radiotherapy and it is likely that some of them lose their significance in combined modality schemes or with more efficient treatments5. The French group Pierre-et-Marie-Curie (GPMC) had defined two groups alpha as favourable and beta as unfavourable with at least one of the following adverse prognostic factors: B symptoms, E extension, age over 40, pathologic type 3 or 4, and stage II without mediastinum involvement6. The purpose of this trial was to give an adapted treatment according to disease aggressiveness. It was also the opportunity to confirm the impact of the prognostic factors on treatment decision in a controlled trial. All of these factors mainly clinical and radiological were analysed later and allowed the emergence of two main prognostic groups according to the following criteria: number of the involved lymph node areas, presence of B symptoms, the width of mediastinum or tumour bulk, erythrocyte sedimentation rate (ESR) and finally patient's age. They were introduced in the further trials but there are some little differences from one to other study groups such as EORTC, GHSG and Canadian NCI7-15. Some of these factors are powerful enough to consider the patient as unfavourable straightaway (table 1), some others have to be gathered to push the patient into the unfavourable group. This is the case of age as a continuous factor as well as the ESR and the number of involved lymph node areas (NIA). The limits for these factors are sometimes unsettled. In the GHSG there is another additional factor which is E extension. The weight of these factors has been

Table 1- Prognostic factors defining Prognostic Groups

Adverse prognostic factors*	GPMC	EORTC	GHSG	NCIC/ECOG
Age (years)	≥40	≥50	≥40	≥40
Mediastinum/thorax ratio	-	≥35%	≥35%	≥1/3
Number of involved areas	-	≥4	≥3	≥4
B symptoms	+	+	+	+
ESR	-	≥50	≥40	≥50
Pathologic type	3-4			3-4
E extension	+	-	+	-

GPMC: Group Pierre-et-Marie-Curie, EORTC : European Organisation for Research and Treatment of Cancer, GHSG: German Hodgkin Study Group, NCIC: National Cancer Institute Canada.
Favourable Group (F): none of these factors*
Unfavourable Group (U): at least one of these factors*
Others: not included in these two groups

evaluated in a large meta-analysis16. In summary, wide mediastinum over 35% of thorax, more than 3 involved areas, high ESR over 50, B symptoms and age over 50 are each an adverse prognostic factor to put the patient in an unfavourable prognostic group whereas sex, moderate ESR, and medium age have to be put together to constitute an adverse prognostic group. According to these factors there are two prognostic groups, favourable and unfavourable requiring different approaches. Favourable group (F) has any of these factors and unfavourable group (U) at least one of them. There is however some patients who do not belong to one or to another and they are treated occasionally in F or in U group. Other biological factors have been described17 but so far none of them has been specified as significant in a controlled trial.

2- Early response as a prognostic factor – a) Early response evaluated by standard evaluation includes routine clinical and radiological examination such as CT scan. Previous reports mainly on advanced stages indicate that an early response to chemotherapy is surrogate of a better outcome. These reports concerning patients under chemotherapy alone are however heterogeneous and combination with radiotherapy in limited stages yield difficult any clear conclusions18-20. Considering the only limited stages the early response (complete remission, CR) showed a better outcome compared to non CR discriminating low and high risk patients staged just in the Ann Arbor system. For instance evaluation of response after 3 courses of MOPP showed 100% CR in stage I and 76% in stage II and relapses occurred mainly in patients without CR in spite of planned extended-field radiotherapy. Among patients with unfavourable features (B, large mediastinum, E extension) the early response after 3 MOPP, complete remitters showed a better outcome (90% versus 55% at 8 years) and moreover the multivariate analysis showed the early response as only prognostic factor18. This “dynamic” approach was applied to advanced stages and was confirmed20. However published results may have been influenced by the treatment design, treatment intensity and heterogeneity of the evaluation21. Considering that such early response weighting is not standard and in someway too late for treatment adaptation new techniques (such as PET-scan) have been introduced and are under evaluation.

b) Early response evaluated by 18F-fluoro-deoxyglucose positron emission tomography (PET-scan)

Although PET-scan has become standard in the initial staging of HL its impact for the management of the treatment has to be settled. There are few studies dedicated to this and most are retrospective and concern very few patients22-27. Most if not all consider that PET is superior to CT-scan. In a prospective study on 108 unfavourable cases28, 17 out of 20 patients with PET positive after 2 ABVD progressed, were treated by high dose therapy and PSCT. Whether this evaluation would be superior to the standard re-staging or would it change ultimately the treatment decision it has to be demonstrated. Considering the role of PET scan in the initial staging the sensitivity and specificity of this test is about 85 and 90% and it has been suggested that early evaluation would be also relevant to identify early failures28. The predictive value of PET-scan for treatment outcome is surely real but is it going to change our practice and more, the prognosis of HL? Such a provocative question has already been asked and is the basis of the current EORTC-GELA H-10 trial30. In this trial patients are randomised to have either a standard treatment or a PET-adapted treatment. PET scan has to be performed at the staging and after 2 courses of ABVD with a strict schedule. The standard arm will have the same evaluation as the experimental one but any decision will be taken according to the interim PET results. In the experimental arm patients with early PET-negative will have chemotherapy alone versus combined modality treatment in F group and modulate chemotherapy in U group. PET-positive patients (about 20%) will have a more intensified chemotherapy by BEACOPP31.

Treatment choices

1- Favourable group- The discussion around the best choice for limited favourable group has not yet finished. For a long time radiotherapy alone was the standard of care whatever the field extension. Limited radiotherapy has still some supporters considering that most relapses after radiotherapy are easy to salvage with combined modality and even bone morrow transplantation and finally the overall survival is identical in both methods. However different phase III trials have demonstrated the superiority of combined modality treatment in terms of progression-free survival9-12,14-15,34 and radiotherapy alone is almost totally abandoned. In the EORTC-H7-F trial9 extended-field radiotherapy (subtotal nodal irradiation: STNI) was randomly compared to combined modality treatment with brief (and “slight”) chemotherapy (EBVP: epirubicin, bleomycin, vinblastine, dacarbazine) and involved-field radiotherapy. The 10-year event-free survival was 78% vs 88% and although the survival was better in combined modality treatment the difference was not significant. The same comparison was carried out in the following trial

EORTC-H8-F using MOPP/ABV in the combined modality arm10. Once again the combined modality showed a better PFS than STNI (95 vs 75%, p: <.001). Moreover the overall survival was better in the combined modality treatment (97 vs 92%, p: 0.001). Converging results were demonstrated by the GHSG and SWOG33,35. In the GHSG-HD7 trial 2 courses of ABVD before Extended field did better than the extended field radiotherapy in terms of PFS (67 vs 88% p: .0001)33 and the same in the SWOG trial35 (81 vs 94%, p: .001) with no impact for OS. In spite of some heterogeneity in the status of patients all these trials confirm the superiority of the combined modality over radiotherapy alone and most suggest that limited-field radiotherapy is sufficient. According to GPMC-H76 trial comparing involved-field to extended-field radiotherapy after 3 courses of MOPP there was no difference in terms of relapse-free and overall survival between two arms (DFS 82 vs 84%, OS 90 vs 93%)6 similar to the Milan trial (PFS 93 vs 94, OS 94 vs 96%)36. Briefly in all these trials the extension of radiotherapy beyond involved areas has no positive impact on treatment outcome and the cure of HL in these favourable cases could be obtained by chemotherapy followed by a limited radiotherapy providing that patients have been treated by an effective chemotherapy such as ABVD. So the scheme of combined modality treatment is considered as the standard assuring the cure in about 95% of cases. As in favourable cases the main concern is to avoid long term complications, the discussion is shifted to reduce the amount of chemotherapy and the dose of radiotherapy: How many courses should be given and what is the necessary dose of radiotherapy?

2-Unfavourable group- Some of these unfavourable cases (stages II bulky or II-B) have been considered as advanced stages and treated so by intensive chemotherapy alone. However such a view is not widely admitted and most physicians consider them as limited stages with aggressive behaviour. There are few discussions about the treatment of these cases and combined modality treatment is the standard. The extended-field radiotherapy did not show better results in several trials such as GPMC-H76, EORTC-H8-U, GHSG-HD8 using MOPP, MOPP/ABV or ABVD before IF or EF radiotherapy6,10,35 at the standard dose of 30 Gy. However to improve a less favourable outcome more aggressive chemotherapy such as BEACOPP has been used. In the GHSG-HD11 the comparison of 4 BEACOPP to 4 ABVD in a randomised fashion did not show significant difference for EFS and OS but more acute toxicity38,39 and currently ABVD remains the standard chemotherapy for this group. At this point we have to consider the optimum amount of chemotherapy and the number of cycles. In the EORTC-H9U trial comparison between 4 ABVD to 6 ABVD and to 4 BEACOPP followed by IF radiotherapy yielded the same results in terms of PFS and OS (EFS 92 vs 89 vs 91, p: 0.43 and OS 91 vs 92 vs 91, p: 0.97)39. So obviously, more is not better and the same comment may apply to the radiotherapy dose. In the GHSG-HD1138 with 4 arms ABVD vs BEACOPP and 20 Gy versus 30 Gy interim analysis give so far the same results but a longer follow-up is surely necessary. In conclusion for unfavourable Hodgkin's lymphoma the standard treatment remains 4 ABVD and IF radiotherapy until the oncoming results of the EORTC-H10 trial and similar trials.

C- Treatment hazards and future challenges

The whole current discussion about prognostic factors and tailored treatment has raised and fuelled by long term complications of chemo and/or radiotherapy. If secondary tumours and cardiovascular complications are the most dramatic, other side-effects, unfortunately more frequent and more routine have to be kept in mind, they poison the daily life of cured patients for a considerable length of time. Fatigue, ill-being, paresthesia feelings, depression and social failure are the daily grind of these patients. The relationship with treatment is obvious and it led to trials comparing combined modality to chemotherapy alone at least for favourable group. Theirs conclusions are not yet admitted world wild because of some discrepancies in the results. In the EORTC-H9F40 all patients in CR (with standard evaluation) after EBVP were randomised to have 36 Gy or 20 Gy or even no radiotherapy. There was no difference in EFS nor in OS between 36 and 20 Gy. The no radiotherapy arm had to be closed because of unaccepted number of events according to the stopping rules (89 vs 86 vs 70% p <.001). Recently Nebraska team reported a similar report with Stanford V regimen but it was not a randomised trial41. However other trials showed the same outcome for chemotherapy and combined modality treatment16,37 and so far chemotherapy alone could not be considered as standard in favourable group. In both groups F and U with standard treatment there are a significant percentage of patients who progress or relapse soon after the treatment. The challenge is perhaps to detect them as soon as possible, to conceive different treatment for rescue and avoid unnecessary treatment for others. This issue is the basis of the EORTC-H10 trial30. In this trial patients are monitored with PET-scan during and after chemotherapy and the treatment is adapted to the early response. Favourable and unfavourable patients according to the EORTC criteria are randomized to have the standard ABVD and IF or

ABVD alone in case of confirmed CR after PET. If they are not in CR they will have a more intensified chemotherapy and radiotherapy. The purpose is to investigate the role of confirmed CR according to PET and to see whether radiotherapy could be omitted in patients with early confirmed remission and on the other hand to improve the outcome of PET positive patients by more intensified chemotherapy. The results will be available in two years with the necessary follow-up after the last inclusions.

In conclusion, in all limited stages of Hodgkin's lymphoma, combined modality treatment with ABVD and involved-field radiotherapy yields excellent results and all efforts should be done to reduce long term toxicity among cured patients and improve the overall survival of progressions or relapses by an anticipated treatment change.

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Medical Education

1981 – 1983	Medical Studies at RWTH Aachen
1984 – 1989	Medical Studies at the University of Cologne
1989 – 1991	Clinical physician at the Clinic for Hygiene & Microbiology (Director: Prof. Dr. Dr. G. Pulverer)
1991 – 1993	Clinical physician at the First Department of Internal Medicine of the University Hospital Cologne, Chairman: Prof. Dr. Volker Diehl, responsibel for the German Hodgkin Study Group
1993 – 2001	Clinical physician at the First Department of Internal Medicine of the University Hospital Cologne (Director: Prof. Dr. Volker Diehl), Clinic for Internal Medicine, Hematology and Oncology
1999	Senior for Internal Medicine
2002	Habilitation „Untersuchungen zur Langzeittoxizität nach kurativer Therapie des Hodgkin-Lymphoms „
Since 2002	Assistant Professor in Private Practice Production of medical films

Membership:

- DGIM	German Society of Internal Medicine
- DGHO	German Society of Hematology and Oncology
- DKG	German Cancer Society
- PSO (Beirat)	Working Group of Psychooncology in the DKG
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Long Term Sequelae of Hodgkin's Disease and It's Treatment

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Depending on stage and risk factor profile, more than 80% of patients with Hodgkin`s disease (HD) can be cured with front-line treatment. However, long-term survivors of HD are at risk for late complications.

A first attempt to summarize long term sequelae was done by Saul Rosenberg in 1985. In this decade pioneer oncologists realized that treatment of patients had always to be waged out to possible side effects. The focus was widened from just treating a tumour to more attention for the whole patient. The description of side effects by Rosenberg differs between potentially lethal, severe, mild acute and long term side effects. This classification is still helpful since already at this time Rosenberg and co-worker considered psycho-social problems as severe late effects.

Potentially lethal	Severe	Mild
• 2nd neoplasia • Sepsis after splenectomy	• radiation induced - carditis - pneumonitis • infertility • infections • Psycho-social problems	• hypothyreosis • decrease in lymphocyte function due to extensive radiation

Potentially lethal

Secondary Malignancies

Among long term sequelaes, secondary malignancies are the most serious since they often are fatal. The most reported secondary malignancies are solid tumours, acute leukaemia, and non-Hodgkin`s Lymphoma (NHL). The mechanism underlying the pathogenesis of secondary malignancies in HD patients remains to be clarified. Mutagenic effects of cytotoxic therapy, histologic conversion of HD in case of NHL, and defective immune surveillance have been considered.

Several analysis found an increased rate of acute leukaemia in patients treated with chemotherapy alone whereas patients treated with radiotherapy alone show an increased risk for the occurrence of solid tumours.

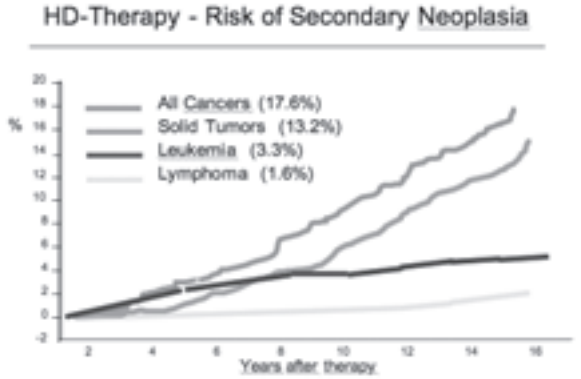
Acute leukaemia and myelodysplastic syndrome (MDS)

Secondary leukaemia and MDS are mostly diagnosed two to ten years after therapy, with an increasing incidence up to five years followed by a plateau. Overall the rate for secondary leukaemia after 15 years is estimated to be 3.3%. Several factors are contributing to the risk of secondary leukaemia. Thus, patients being older than 40 years at the time of diagnosis and those having been treated with regimens containing alkylating agents show a higher risk. After six cycles of MOPP-chemotherapy there is a 14-fold increased risk to suffer from secondary leukaemia. Also Topoisomerase-II-Inhibitors (e.g. Etoposide) are associated with the occurrence of leukaemia showing very often a typical chromosomal translocation. Especially patients undergoing salvage therapy are at risk. Radiotherapy is of minor importance, patients treated with radiotherapy alone show only a slightly increased risk to develop secondary leukaemia. Ten to 15 years after therapy HD patients are comparable to the normal population.

Therapeutical strategies in second malignancies after HD are not standardized. The prognosis for patients suffering from secondary leukaemia is extremely poor. Although modern therapeutic approaches basing on bone marrow transplantation might improve the prognosis for some of these patients the majority will stay with a fatal diagnosis. Thus, future effort must focus on avoiding the use of leukaemiogene drugs while maintaining the good treatment results.

Non-Hodgkin-Lymphoma (NHL)

In several series the incidence of NHL ranges from 1.0% to 5.9%. This variation might be explained by differences in observation time, infrequent use of rebiopsy at the time of disease progression or relapse, and the lack of a pathologists review panel. The majority of secondary NHL are intermediate or aggressive lymphomas of B-cell immunophenotype. Factors possibly contributing to the occurrence of secondary NHL are radiochemotherapy, older age, lymphocyte predominant histologic subtype, sple-



nectomy, and spleen irradiation. Most authors reported that secondary NHL generally develops five to 15 years post treatment but might occur even later.

For about 20% of patients with secondary NHL, long-term disease-free survival could be achieved. The treatment outcome of secondary NHL is influenced by the time of occurrence after first diagnosis of HD and variables included in the Age-Adjusted IPFI.

In conclusion, whereas secondary NHL patients with favourable prognostic features can be cured with multi-agent chemotherapy regimens, a palliative treatment approach should be provided for those with unfavourable subtypes.

Solid tumours

All studies with a median follow-up of at least 15 years show an incidence of solid tumours in 15 up to 20% of long term survivors. (Table 1) While the risk of dying from HD is declining by time it is increasing for dying from secondary solid tumours. Beside treatment related factors also habits and environment are contributing to the chance of getting secondary solid tumours. (Table 2) In a series of 818 patients within the German Hodgkin Study Group only a small number of patients being asked five years after treatment had changed their smoking habits. In respect of the high incidence of secondary tumours a high priority should be given in informing the patients about these complex conditions.

The prognosis of secondary solid tumours does not seem to be different to primary manifestations. Although there are no studies available comparing the prognosis one can assume, that with standard diagnostic and treatment procedures the results in secondary tumours are comparable to those in first treatment. However, this assumption is only valid if the condition of the patient and the choice of treatment are not compromised by the treatment of HD.

HD-Therapy - Risk Factors for Secondary Neoplasia

NHL	AML/MDS	Solid Tumors
combined modality treatment gender (male > female) age	alkylating agents age topoisomerase II targeting agents (?) splenectomy (?)	age smoking radiation

Sepsis

The OPSI (overwhelming post splenectomy infection) is an extremely seldom complication in HD and is related to splenectomy or intensive spleen irradiation. Since these therapy concepts are not longer part of a modern treatment approach one can expect that this fatal complication might become history in the treatment of HD. However, if for any reason a splenectomy or an irradiation of the spleen is planned patients have to undergo vaccinations against Streptococcus Pneumoniae, Haemophilus Influenzae, and Neisseria Meningitides.

Severe late effects

Treatment induced cardial and pulmonal alterations

Mediastinal radiotherapy significantly increased the risks of myocardial infarction, angina pectoris, congestive heart failure, and valvular disorders (2- to 7-fold). Anthracyclines significantly added to the elevated risks of congestive heart failure and valvular disorders from mediastinal radiotherapy. The 25-year cumulative incidence of congestive heart failure after mediastinal radiotherapy and anthracyclines in competing risk analyses was 7.9%. In conclusion, risks of several cardio-vascular diseases are 3- to 5-fold increased in survivors of HD compared with the general population, even after prolonged follow-up, leading to increasing absolute excess risks over time.

A reversible decrease in lung capacity after mediastinal radiation is observed in up to 10% of the irradiated patients. Pneumonitis and pulmonary fibrosis occur in 5% of these patients depending on irradiated volume and total dose. Chemotherapy in normal dosage does not significantly increase pulmonary late effects. The rate may be increased with higher age (>70), COPD and additive radiation.

Infertility

Post treatment infertility presents a high psycho-social burden for young patients limiting their perspectives to build up a family. In general, the gonadal damage is attributed to toxic effects on the germinal epithelium caused by chemotherapy containing alkylating agents, especially cyclophosphamide and procarbazine. In about 90% of male patients treated with MOPP or MOPP-like regimens a reduced gonadal capacity has been reported.8 Recovery rates one year to 15 years after the end of treatment with alkylating agents have been reported to be 2% to 25%.

However, in small series some authors found a reduced fertility of patients with HD prior to therapy indicating that HD associated factors contribute to infertility.

With modern treatment approaches male and female patients in early and intermediate prognostic groups can be treated without loss of fertility. Only patients in advanced or relapsed treatment stages have a much higher risk to become infertile.

With sperm donations male patients have a very effective possibility to compensate treatment related sterility. One should talk about family planning with the patient as soon as possible not to prolong treatment onset without need.

For female groups investigators have found a beneficial effect of applying gonadotropin-releasing hormone (GnRH)-agonists (GnRH-a) on minimizing the chemotherapy-associated gonadotoxic effect. Moreover, GnRH-a coadministration proved to prevent the menometrorrhagia of young women during chemotherapy-induced thrombocytopenia more effectively than gestagens. GnRH-a cotreatment appears to minimize ovarian damage. If these preliminary results are consistent in a larger group of patients and proven in a prospective randomized study, the GnRH-a cotreatment should be considered as a clinical routine for every woman in the reproductive age exposed to gonadotoxic chemotherapy. A final evaluation of assisted reproductive technology, and ova, follicles, or ovarian cryo preservation for future in-vitro maturation of primordial follicles, and ovarian autotransplantation or xenotransplantation has to be performed.

Infections

The well known defective immune surveillance in patients with HD may lead years after treatment to even life threatening infections. The following infections are oberved more often in patients with HD: Herpes Zoster, mycotic infections, Toxoplasmosis, Listeriosis und Pneumocystis carinii Pneumonia (PCP). Risk factors for developing these infections are higher age with diagnosis, high dose chemotherapy or high dose radiotherapy.

Psycho-social problems

For the most part, retrospective analyses of long-term survivors of HD have tried to assess the burden of psycho-social problems. These analyses have shown that a substantial subgroup of patients still carry a great burden from disease and its treatment even years after therapy. A number of factors have been outlined contributing to a high risk of maladaption even years after cure, e.g. low income, unemployment, low education level and others. In one investigation 22% of the 273 studied patients met the criteria suggested for a psychiatric diagnosis. Currently, it remains unclear at which point in the course of the disease patients with a good coping capacity are able to be distinguished from those without. Many questions have been raised about how the quality of life of patients is affected by the disease and treatment and which measures could help overcome negative effects of treatment and disease. In order to further enhance the effectiveness of treatments and to lower acute and late side effects as much as possible, more information is needed about how patients cope with the illness and late effects of treatment after returning to normal life. Prospective longitudinal approaches are necessary where QoL assessment is carried out continuously during treatment and follow-up at least for five to ten years after completion of treatment. To obtain information from the patient's point of view, instruments should be provided to address the relevant issues from the start of therapy until at least ten to 15 years later. To more precisely characterise phases of readaption and maladaption during return to normal life and to clarify the contributing factors in regard to QoL outcome, the assessment of the subjectively reported domains of QoL has to be implemented in prospective randomised clinical trials.

Recently a special aspect in the field of QoL in HD has become a focus of interest: the cancer related fatigue. Several reports state that up to 40% of long term survivors suffer from severe fatigue. This leads to enormous limitations in terms of post treatment reintegration into normal life. Patients are unable to return to normal work or normal social life. Fatigue hereby is the most important negative factor on the QoL of long term survivors.

In summary, in the treatment of HD we have achieved treatment results better than in nearly all other entities. The treatment of HD was always a leading paradigma for the whole cancer treatment. Now it is time to open a new chapter dealing with late effects, mainly the late maladaptive effects induced by the treatment. With the growing number of long term survivors, not only in HD, we have to make a new effort to identify strategies to support these patients on the their way back to normal life. Therefore we have to find out which treatment regimen causes which late effects. Thus, we are able to counsel the patient regarding the limitations he will expect after treatment and decide the treatment regarding his special daily life challenges.

Chronic Myeloproliferative Disorders

The myeloproliferative neoplasms (MPN) session will provide both an information update and practical translation of recent scientific advances in the field. JAK2, MPL and TET2 mutations will be discussed in the context of MPN and related myeloid neoplasms. New information on host susceptibility to MPN-associated JAK2V617F will be reviewed. An in depth discussion of clonal origination and evolution in MPN will constitute part of the session. The 2008 WHO classification system for hematologic malignancies will be summarized. New genetics-based diagnostic algorithms will be provided. Current results of JAK2 inhibitor and other drug trials in myelofibrosis and related disorders will be discussed."

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1983 - 1986, Internal Medicine residency, St. Joseph Hospital, Chicago, IL.
1986 - 1989, Hematology fellowship, Mayo Graduate School, Rochester, MN.

SPECIALTY CERTIFICATION:
American Board of Internal Medicine, 1987
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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
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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)
Scientific Advisory Board Member for Bio-reference Laboratories, New Jersey (2003-)
Scientific Advisory Board Member for Apotex Inc. Toronto, Canada (2003-2005)
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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-)

Associate Editor:
1. Mayo Clinic Proceedings
2. European Journal of Hematology

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1. Current Hematology Reports

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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
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Postgraduate Training
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Board Certification
Internal Medicine Board Certification, 1998
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Associate Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 9/2007–present

Administrative Appointments/Responsibilities
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Medical Advisory Board Member, The Chronic Myeloproliferative Disorders Education Foundation, N/A, 2005–present
Executive Committee Member, International Working Group for Myelofibrosis Treatment and Research (IWG-MTR), N/A, 2005–present

Endowed Positions
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Consultantships
Ziopharm, Inc, Boston, 4/2005–present
Military or Other Governmental Service
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Institutional Committee Activities
Clinical Research Committee I, UT MD Anderson Cancer Center, Member, 9/2003–9/2006
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Institutional Animal Care and Use Committee, UT MD Anderson Cancer Center, Member, 8/2006–12/2006

HONORS AND AWARDS
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Achievement in Cancer Research Award, UT MD Anderson Cancer Center, Division of Medicine, Fellowship Program, 2001
Ronald Cates Memorial Fund for Leukemia, 2002
Cancer Treatment and Research Award, 2006
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PUBLICATIONS
Articles in Peer-Reviewed Journals: 160
Editorials: 3
Other Articles: 14
Abstracts: 144

EDITORIAL AND REVIEW ACTIVITIES
Editor/Service on Editorial Board(s)
Board Member, American Journal Hematology, 2008
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Journal Reviewer
Reviewer, Cancer Immunology Immunotherapy, 1993–1995
Reviewer, Cancer, 2002–present
Reviewer, Hematologica, 2004–present
Reviewer, American Journal of Hematology, 2005–present
Reviewer, Blood, 2006–present
Reviewer, Journal of Clinical Oncology, 2006–present
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Reviewer, Leukemia Research, 2006–present
Reviewer, Annals of Oncology, 2007–present
Reviewer, Clinical Leukemia, 2007–present

Presentations at National or International Conferences Invited
Development of an organic arsenic derivative as a therapy for leukemia, Third Croatian Congress of Hematologists and Transfusiologists, Opatija, Croatia, 11/1/2003
New drugs for treatment of acute myeloid leukemia., Third Croatian Congress of Hematologists and Transfusiologists, Opatija, Croatia, 12/1/2003
Arsenic based therapy for hematological malignancies, 7th Seminar, New Trends in the Treatment of Acute Leukemia, Dubrovnik, Croatia, 9/1/2004
Novel Therapies for Myeloproliferative Diseases, The Mayo Clinic -- CMPD Education Foundation, Myeloproliferative Conference, Copperwynd Resort, Scottsdale, AZ, 2/1/2005
Novel therapies for myeloproliferative disorders, UTMDACC and LiveMed, Educacion Medica de Calidad Mundial, Update Session on Leukemia, Queretaro, Qro, 5/1/2005
Update on acute promyelocytic leukemia, UTMDACC and LiveMed, Educacion Medica de Calidad Mundial, Update Session on Leukemia, Queretaro, Qro, 5/1/2005
Current Therapy for Acute Promyelocytic Leukemia, Annual Meeting of National Group for Hematology, Klinički Bolnički Centar Zagreb, Zegreb, Croatia, 6/1/2005
New Approaches in the Treatment of Acute Leukemia, ASH 2005, Pittsburg, PA, 1/1/2006
Recent and Ongoing Studies for Systemic Mastocytosis, Portland, ME, 10/2006
New drugs for the MPD's, 4th International CMPD Patient Conference at the Mayo Clinic, Scottsdale, AZ, 2/2007
Diagnostics and Treatment of Myeloproliferative diseases: an update, Klinicka Bolvica, Zagreb, Croatia, 7/2007
New Therapeutic agents for myeloproliferative disorders, Leukemia and Lymphoma; East and West Together, Croatia, 9/15/2007
A Phase I/II Trial in Patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF), 13th Annual European Hematology Association Conference, Copenhagen, Denmark, 6/2008
JAK2 Inhibitors and Myeloprolifertive Disorders, The 2008 Amgen Australia clinical Haematology Symposium, Sydney, Australia, 7/2008
JAK2 Inhibitors - A Reality? A Hope?, Fourth International Conference Leukemia 2008, The University of Texas MD Anderson Cancer Center, Houston, TX, 9/27/2008
An Update on New Therapies for Systemic Mastocytosis, TMS Annual Concerence, Bloomington, MN, 10/17/2008
Clinical studies for patients with systemic mastocytosis at MD Anderson Cancer Center: dasatinib, denileukin diftitox, daclizumab, and RAD001, Novartis Investigator Meeting, Budapest, Hungary, 11/2008

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JAK2 Inhibitor Therapy in Myelofibrosis: Clinical Update

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Abstract

The discovery of the JAK2 V617F mutation in patients with myeloproliferative neoplasms (MPN) was a major milestone in understanding their biology. Several groups simultaneously reported on the high incidence of this mutation in patients with MPN: almost all patients with polycythemia vera (PV) harbor the mutation, and about 50% of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) have the mutation, making the development of JAK2 tyrosine kinase inhibitors an attractive therapeutic goal. In addition, inhibition of JAK2 kinase may have a therapeutic role in other hematologic malignancies, such as chronic myeloid leukemia or lymphoma. A number of molecules that inhibit JAK2 kinase have been developed, and several are being evaluated in a clinical setting in patients with MF. Here we summarize current clinical experience with JAK2 inhibitors.

Introduction

A link between the activated intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and the pathogenesis of several hematological diseases has been previously described [1-3]. However, it was not until recently that an activating JAK2 kinase mutation was identified in patients with myeloproliferative neoplasms (MPN)[4-8]. Several groups described almost simultaneously a novel activating somatic point mutation in the gene encoding the cytoplasmic JAK2, characterized by the substitution of valine for phenylalanine at codon 617 (JAK2 V617F). In these reports, this mutation was identified in about 50% of patients with ET and PMF, but in PV it is present in more than 90% of patients. Since identical JAK2 mutations can be found in patients with all 3 diseases, it is unclear how the same molecular abnormality evolves into different phenotypes. Additional rare molecular events recently identified are mutations in c-MPL (c-MPLW515L/K), and additional mutations in exon 12 of JAK2, among patients not expressing the JAK2 V617F mutation. These discoveries are now opening a new exciting era in the development of targeted therapy for MPN. The most difficult MPN is primary myelofibrosis (PMF), for which no standard therapy exists, and no medication has been approved to treat this disease, and all attempts to help patients with medications are palliative in nature. Stem cell transplantation remains the only therapy with curative potential for this disease[9]. Median survival for patients with PMF is about 5-7 years, but varies widely according to prognostic factors [10]. Identifying the JAK2 V617F mutation in patients with MPN has led to a number of Phase I/II clinical studies focused on patients with advanced PMF or post ET or PV MF as they have the worst prognosis.

Clinical experience with JAK2 inhibitors

TG101348 is a selective and potent inhibitor of JAK2. The IC50 for JAK2 tyrosine kinase was 3 nM and when profiled in 223 kinases, only FLT3 and RET had an IC50 <50nM. It has a 35 and 334-fold selectivity for JAK2 as compared to JAK3 and JAK1 respectively. It selectively induced apoptosis in HEL and Ba/F3 cells harboring the JAK2V617F. In a murine model of JAK2 V617F-Induced PV, mice treated with TG101348 showed a decrease in hematocrit, in spleen size, and longer overall survival[11]. TG101348 is currently being evaluated in a multicenter dose escalation phase I study for patients with MF. TG101348 is administered orally in 28 day cycles with a planned dose escalation from 30mg 800mg. Intrapatient dose escalation is permitted after completion of at least three cycles of therapy. Patients with PMF or post PV/ET MF having high-risk or intermediate-risk disease that is unresponsive to available therapy are eligible. The preliminary results were presented at the American Society of hematology (ASH) meeting in December of 2008. Of the 22 patients enrolled, 19 (86%) patients had V617F mutation and 9 (41%) were transfusion dependent. The doses of medication ranged from 30mg to 680 mg daily. Pharmacokinetic studies confirmed a half life of 10-35 hours with little intrapatient variability. After a median follow up of 14 weeks the most common non-hematologic grade

3 or 4 toxicity was nausea and vomiting (5%), and abdominal pain (5%). Grade 3 or 4 anemia, neutropenia and thrombocytopenia occurred in 32%, 9%, and 23% of patients, respectively. The maximum tolerated dose (MTD) has not been reached. Rapid reduction of spleen size was seen in all patients receiving >360 mg, and leukocytosis was corrected in several patients[12]. TG101348 effect on anemia, constitutional symptoms and bone marrow fibrosis remain to be determined.

INCB018424 is potent and selective JAK1 and JAK2 inhibitor. It inhibits JAK2 at <1 nM . In cells harvested from patients with JAK2V617F mutation, the IC50 was 67nM in clonogenic assay, while colony formation from healthy donor cells was inhibited at >400nM. These encouraging preclinical data led to it's evaluation in a phase I/II trial for patients with MF. Following the initial dose escalation, 25 mg PO bid was identified as the MTD with thrombocytopenia as the dose limiting toxicity. In the expansion study, more than 100 patients with PMF or post PV/ET MF were enrolled. Several doses were explored including 10mg and15mg bid, and 25, 50, 100 and 200 daily. Patients were evaluated for reduction in spleen size, improvement of constitutional symptoms, and improvement in overall level of daily activity. Results were updated at ASH 2008. Of the 134 patients enrolled, 108 remain on the study with a median duration of therapy of 6.8 months. Median spleen size on physical exam ranged from 17cm to 20cm below left costal margin, and about a third of patients were transfusion dependent. The therapy did not produce significant non-hematologic toxicity. Detailed hematologic toxicity analysis was presented for the 114 patients who received 50mg daily, 25mg bid, 15mg bid and 10mg bid: 19 patients developed grade 3/4 thrombocytopenia and of the 75 transfusion independent patients 13 patients developed grade 3/4 anemia. The hematological toxicity was dose dependent. Great majority of patients experienced a rapid reduction in spleen size within the first month of therapy, irrespective of the JAK2 mutational status[13]. Clinically those patients had a marked improvement in quality of life, with a mean percentage improvement of 40-60% in night sweats, fatigue and pruritis. In addition, a marked improvement in daily activity was also reported in those patients. Patients receiving INCB018242 had progressive weight gain. Interestingly the level of inflammatory cytokines decreased after therapy with INCB, which correlated clinically with the improvement of symptoms seen in those patients[14]. However, all the above mentioned clinical improvements were not associated with marked reduction of the mutational (V617F: WT JAK2 ratio) tumor burden[15].

Another potent and selective JAK2 inhibitor, XL109 is currently being evaluated in phase I/II trial for patients with MF. It inhibits JAK2 kinase at concentrations of <2nM, while other JAK kinases are inhibited at concentrations ranging from 134-344 nM. Patients with PMF or post PV/ET MF were enrolled and 3 regimens were explored: daily x 21 days (100-300mg), continuously daily 25-50mg, and 25 mg on Monday, Wednesday and Friday. Of the 30 patients enrolled, 57% had PMF, 80% had harbored the V617F or MPL W515 mutation, and 37% were transfusion dependant. The results were updated at ASH 2008. XL109 was relatively well tolerated at doses ranging from 25-50 mg. No hematologic toxicity was observed. The most common grade 1/2 non-hematologic toxicity was formication, confusion and peripheral neuropathy. At the lowest dose of 25 mg daily, 1 of 16 patients developed grade 1 peripheral neuropathy and 3 had abnormal nerve conduction study result but no symptoms. XL109 has a half life of 20 hours with a 5 fold accumulation in the daily regimen and 2 fold with the M-W-F regimen. Of the 12 patients harboring the JAK2 mutation or MPLW515F mutation, all experienced a reduction in spleen size, while none of the patients with wild type JAK2 had it. All patients harboring the JAK2 V617F mutation reported an improvement in generalized constitutional symptoms including pruritis and fatigue. Interestingly, of the 4 patients with 10-19% blasts in the peripheral blood, 3 had a reduction in circulating blasts. Further studies are planned in the patients with advanced JAK2 mutation positive myeloid malignancies[16].

CEP-701 is an oral small molecule tyrosine kinase inhibitor of FLT3, that is being evaluated in patients with AML harboring the FLT3 mutation[17]. However, it was found to inhibit the growth of cell lines carrying both the wild type and mutated JAK2, and to inhibit the growth of cells obtained from patients with MPN[18]. CEP-701 is currently being evaluated in patients with different MPN. In a multicenter trial, CEP-701 was given in escalated doses from 80 mg twice daily to 120 mg twice daily to patients with PV and ET. Of the 8 patients with splenomegaly, 5 have experienced reduction in spleen size[19]. No other significant benefit has been observed and mild toxicity has been recorded, limited to GI disturbance (nausea, vomiting and diarrhea). Phase II study of CEP701 in MF has recently been concluded and preliminary results will be presented.

Conclusion

Identification of the role of mutated JAK2 tyrosine kinase in pathophysiology of MPN has led to the development of a new class of drugs, the JAK2 in-

hibitors. Currently several JAK2 inhibitors are in phase I/II clinical trials for patients with most aggressive of MPN, the MF or post PV/ET MF. Marked clinical improvement has been seen in patients on therapy, with significant decrease in spleen size and improved quality of life. On the other hand, no significant improvement in anemia in these patients has been reported so far. It seems that the JAK2 inhibitors have a potential to control the disease well (particularly the INCB018424). It remains to be seen if they will affect the natural history of the disease and improve survival. As for the utility of JAK2 inhibitors in ET and PV, one must carefully balance the possible benefit versus possible toxicity. In patients with ET and PV thrombotic complications remain a main cause for morbidity and mortality, and there is questionable association between the JAK2 mutated allele burden, or even the presence of the JAK2 mutation and thrombosis[20]. Despite many unanswered questions, these are exciting times as we witness for the first time the evaluation of new medications targeting specific abnormality present only in the malignant cells in MPN patients.

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BIOGRAPHICAL SKETCH
Provide the following information for the key personnel in the order listed for Form Page 2. Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME: **Skoda, Radek C.**	POSITION TITLE: Professor of Molecular Medicine		
EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Zürich Medical School, Zürich, Switzerland	Medical Diploma	1981	
University of Zürich Medical School, Zürich, Switzerland	M.D.	1983	Cell biology
Swiss Board for Internal Medicine	FMH Internal Medicine	1999	

A. Positions and Honors.

1981-83 MD thesis, Dept. of Biochemistry, University of Zürich, Switzerland
1983-86 Postdoctoral Fellow, Biozentrum, University of Basel, Switzerland
1986-89 Resident in Internal Medicine, University Hospital Basel, Basel, Switzerland
1989-93 Postdoctoral Fellow, Dept. of Genetics, Harvard Medical School, Boston, MA
1993-2000 Group leader, Biozentrum, University of Basel, Basel, Switzerland
2000-2002 Head, Molecular Hematology-Oncology, German Cancer Research Center (DKFZ)
2002-present Professor of Molecular Medicine and Chair, Department of Research, University Hospital Basel, Basel, Switzerland
2006-present Chair, Department of Biomedicine, University of Basel

Other Experience and Professional Memberships

1994-present: Member, American Society of Hematology; 1995-present: Member, Swiss Society of Hematology; 2001-2004: member of the editorial board of the Journal of Molecular Medicine; 2003: Co-chair of the Educational and Scientific Committee, 9th Meeting of the European Hematology Association; 2004 and 2006: Co-chair ESH-Conference on Myeloproliferative Disorders, Cascais, Portugal (2004), Madeira, Portugal (2006), and Athens, Greece (2008); since 2004: Member of the Scientific Committee of the European School of Hematology since 2006: Councilor to the Board of the European Hematology Association

Awards

1997: Prize of the Swiss Society of Hematology; 1999: Ellermann-Prize for Hematology; 2004: Research Prize of the Cloetta-Foundation; 2007: Ham-Wasserman Lecture Award, American Society of Hematology, Atlanta; 2008: Hematological Malignacies Award, Bristol-Myers Squibb and Swiss Society of Hematology

B. Selected peer-reviewed publications (in reversed chronological order): 25
Review articles: 8

C. Research Support

Ongoing Reserch Support

2008-2011 "Genetic analysis of myeloproliferative disorders". Grant from the Swiss National Science Foundation

"The pathogenesis of myeloproliferative disorders". Grant from the Swiss Cancer League/ OncoSuisse

Completed Research Support

1982-1983 Postgraduate Course in Experimental Medicine and Biology, Stipend by the Swiss National Science Foundation

1989-1991 Postdoctoral fellowship from Schweizerische Stiftung für medizinisch-biologische Stipendien

1993-1998 „SCORE-A" career development award from the Swiss National Science Foundation (5 year fellowship for independent group leaders at the junior faculty level)

1993-1996 „The role of mpl in hematopoiesis". Grant from the Swiss National Science Foundation (Role: PI)

1996-1998 "The pathogenesis of essential thrombocythemia". Grant from the Swiss Cancer League (Role: PI)

1996-1998 „Extracellular signals in the regulation of hematopoiesis": Grant from the Swiss National Science Foundation (Role: PI)

1997 "The pathogenesis of essential thrombocythemia". Grant supplement from the Swiss Life Foundation (Role: PI)

1998-2000 "The pathogenesis of essential thrombocythemia". Grant from the Swiss Cancer League (Role: PI)

1998-2000 „Extracellular signals in the regulation of hematopoiesis": Grant from the Swiss National Science Foundation (Role: PI)

2002-2004 "The pathogenesis of myeloproliferative disorders". Grant from the Swiss Cancer League/ OncoSuisse (Role: PI)

2002-2005 The role of extracellular signals in the control of normal and aberrant hematopoiesis". Grant from the Swiss National Science Foundation (Role: PI)

2004-2006 "The pathogenesis of myeloproliferative disorders". Grant from the Swiss Cancer League/ OncoSuisse (Role: PI)

2005-2008 "Genetic analysis of hematopoietic stem cell disorders". Grant from the Swiss National Science Foundation (Role: PI)

2005-2007 "The Role of Smad4-Dependent Signaling in Anemia". Grant from the RoFAR Foundation (Role: PI)

The Genetics of Clonal Evolution in Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis

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An acquired somatic mutation in the JAK2 gene resulting in a valine to phenylalanine substitution at position 617 (JAK2-V617F) is present in the majority of patients with myeloproliferative disorders (MPD). The JAK2-V617F mutation is located in the "pseudo-kinase" domain of JAK2, which physiologically exerts an inhibitory effect on the kinase domain. The mutation is thought to de-repress the kinase activity by an allosteric mechanism. Expression of the mutated JAK2 cDNA in mouse models resulted in increased white blood cell numbers and red cell mass, recapitulating the MPD polycythemia vera phenotype. Therefore, JAK2-V617F represents an attractive drug target for the treatment of patients with MPD. Recently, mutations in exon 12 of the JAK2 gene have been identified in a subset of MPD patients negative for JAK2-V617F and mutations in exon 16 were found in 18% of patients with B cell ALL and Down syndrome. A number of observations suggest that JAK2-V617F in patients with MPD may be acting in concert with mutations in as yet unknown gene(s). The presentation will focus on the following questions:

1. Why does JAK2-V617F cause 3 different clinical phenotypes?

2. Is JAK2-V617F the primary cause of MPD?

3. What is the role of JAK2 mutations in leukemic transformation?

The currently available data suggest that JAK2 mutations may be sufficient to cause an MPD phenotype. However, evidence has accumulated indicating that a considerable proportion of MPD patients carry additional mutations. Predisposition to acquiring JAK2 mutations can be increased in cases of familial MPD and the hereditary component is more frequent than is generally assumed. Transformation of JAK2 positive MPD to secondary leukemia negative for the JAK2 mutation has been observed in more than 50% of cases examined. Taken together these data suggest that a pre-JAK2 stage exists that increases the likelihood of leukemic transformation and or acquisition of a JAK2 mutation. The discovery of JAK2 mutations in MPD has initiated an exciting new phase and has already substantially improved diagnostics and advanced our knowledge of the MPD pathogenesis. Within 4 years since the discovery there is now the exciting prospect that patients with MPD may soon benefit from targeted treatment for their disease.

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 Goldstone 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 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.

Dr. Peter Dreger

Dr. Emili Montserrat

Emili Montserrat is Full Professor of Medicine at the University of Barcelona and Director of the Institute of Hematology and Oncology at the Hospital Clinic of Barcelona, one of the leading institutions in hemato-oncological research in Europe. His main areas of interest are chronic lymphoproliferative disorders and lymphoma, in which he and his group have made seminal descriptions. He is one of the founding members of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) and the European Research Initiative for CLL (ERIC). He also coordinates the CLL Spanish Group CLL and has been the Chairman for CLL in the International Bone Marrow Transplantation Registry. He is also a WHO expert for lymphomas and chronic lymphocytic leukemia. He has contributed more than 500 articles and 50 book chapters on hemato-oncology. Emili Montserrat and his group have produced seminal contributions to the study of leukemias and lymphomas. He has been President of the European Hematology Association and has received many national and international awards, among them the ESMO life time achievement award 2008. Emili Montserrat has been recently elected Chairman of ERIC.

Chronic Lymphocytic Leukemia: State of the Art of Treatment and Its Indications

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In the last few years, important progress has been made in the management of patients with chronic lymphocytic leukemia (CLL). Regarding indications for therapy, treatment is only justified in the presence of signs or symptoms of disease activity such as B-symptoms, lymphadenopathy or splenomegaly increasing in size or causing compressive problems, decreasing Hb levels or platelet counts due to bone marrow infiltration, autoimmune hemolytic anemia not responsive to corticosteroids, rapid lymphocyte doubling time (i.e., less than 6 months) and hypogammaglobulinemia with infections. Of note, an increased WBC count or hypogammaglobulinemia with no infections are not indications for therapy by themselves. Likewise, treatment is not justified on the sole basis of poor biologic markers such as unmutated IGVH genes, high expression of ZAP-70 in neoplasic lymphocytes or poor cytogenetics (e.g., 17p-). Once a given patient requires therapy it is highly recommended to perform a FISH chromosome analysis because patients with 17p- abnormalities do not respond to conventional therapy. Alemtuzumab is useful in 17p- cases without a high tumor burden. Flavoporidol and lenalidomide might also be useful in such cases. In patients without this aberration, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is the best therapy. However, FCR can be only safely applied to patients with good performance status and a normal renal function. Moreover, patients older than 70 poorly tolerate FCR, this leaving the vast majority of patients with CLL (>30%) without a satisfactory treatment. The CR rate with FCR is 40%-70%. Importantly, in a proportion of CRs no residual leukemic cells (MRD) can be detected by flow cytometry, which conveys longer survival. It is recommended, however, not to pursue MRD negativity as a goal of therapy except in clinical trials. An extremely challenging situation is the treatment of patients who are refractory to- or have a short response duration (e.g., less than 1 year) with FCR since their prognosis is very poor (median survival inferior to 2-3 years). Due to this fact, the possibility of performing an allogeneic stem cell transplant should be considered in good candidates for the procedure. Besides cases refractory to therapy, the management of elderly patients or those with comorbidities require new and more effective forms of therapy. For patients not participating in trials, chlorambucil continues being a reasonable approach. An already approved "new" agent for CLL is bendamustine, wich along with other agents (e.g. rituximab) is being investigated in different trials. The monoclonal antibodies GA-101, ofatumumab and lumiluximab as well as a number of other biologic agents add to the list of treatments that offer promise in CLL.

Dr. Eva Kimby

Dr Eva Kimby is Associate Professor of Haematology at the Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.

Dr Kimby studied medicine at Karolinska Institutet in Stockholm, where she obtained her M.D. and Ph.D. degrees. Dr Kimby is a member of several national and international scientific societies and a working member of the EBMT CLL subcommittees and the International Workshop on Waldenströms macroglobulinemia. She was elected chairman of the group for indolent lymphomas within the Swedish and Nordic Lymphoma Group in 1997 and since 2004 chairman of the Swedish CLLL group and later vice chairman of ERIC (European LeukemiaNetwork). Dr Kimby has an Advisory role on the Board of European Network Mantle cell lymphoma. She is lecturer for students at the Karolinska Institute and at international meetings on CLL and lymphomas and a reviewer for journals as Haematologica, Leukemia, and Journal of Clinical Oncology.

Her main research interests are indolent lymphoma, CLL and the applications of immunotherapy. She is actively involved as a key investigator in several haematology trial groups and the principal investigator for two large Nordic rituximab +/- interferon trials and coinvestigator in the Stockholm CLL alemtuzumab studies. She has as published more than 100 papers and several reviews in peer-reviewed international journals.

Perspectives of New Drugs and Strategies for Chronic Lymphocytic Leukemia (CLL)

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Alkylating agents and purine analogues have remained good therapeutic options for patients with chronic lymphocytic leukemia (CLL). During the past decade also the monoclonal antibodies (mAbs) rituximab (anti-CD20) and alemtuzumab (anti-CD52), have shown to be effective in this disease. Chemoimmunotherapy regimens combining rituximab and purine analogues, mostly fludarabine in combination with cyclophosphamide, have improved response rates and progression-free survival in both newly-diagnosed and relapsed CLL patients, but it is still unclear whether overall survival has been improved. Patients who are not responding to purinanalogue-based therapy or have early relapse still have a poor prognosis, especially if clonal evolution with a high-risk chromosomal abnormality as del(17p13). Alemtuzumab is a good alternative in chemo-refractory CLL and has shown efficacy in patients with del(17p13). This mAb has been used also for consolidation and reduction of minimal residual disease (MRD) resulting in an improved long-term clinical outcome in some patients. The subcutaneous way of administration of alemtuzumab is beneficial, but the dosing is still not optimized, especially when used in combination with chemotherapy. The long-standing immunosuppression after therapy with alemtuzumab with risk for viral reactivation and opportunistic infections is an unsolved problem.

The clinical efficacy of therapy with mAbs has lead to an interest in development of new antibodies targeting distinct proteins on the surface of CLL cells. There are several such potential targets for immune-based therapies in CLL and in the last years interesting data has been obtained on the use of ofatumumab, veltuzumab, AME-133, GA101, epratuzumab, galiximab, lumiliximab, apolizumab, HCD122 and SGN-40. One of the second-generation anti-CD20 mAbs under clinical development. ofatumomab, binding to a CD20 extracellular loop close to the cell membrane, suggested to facilitate recruitment of cytotoxic effector cells. In-vitro studies of ofatumomab have shown enhanced binding and longer dissociation rate with possible activity also for low density CD20- expressing cells. Compared to rituximab, ofatumomab seems to have an enhanced complement-dependent cytotoxicity (CDC), but similar antibody-dependent cellular cytotoxicity (ADCC) activity. Cell-lysis of rituximab-resistant cells was also noted. In a clinical phase I/

II trial ofatomomab was well tolerated in CLL patients, also when administered in high doses intravenously (up to 2000 mg). Data on response was encouraging and confirmed in a phase II trial including heavily pretreated CLL patients with bulky disease. Veltuzumab is a another humanized, second-generation anti-CD20 mAb containing similar antigen-binding determinants to rituximab and >90 % human antibody sequences with identical antigen framework regions to epratuzumab (a humanized anti-CD22 mAb). In vitro studies have demonstrated that veltuzumab enhances binding avidity and CDC compared with rituximab in cell lines. This mAb is now undergoing clinical trials in several lymphoma types and in CLL. Interestingly, like alemtuzumab, a low-dose subcutaneous formulation of veltuzumab can be effective. AME-133 is another humanised anti-CD20 antibody, Fc-engineered, in early clinical development. GA-101 is a third-generation fully humanized, optimized glyco-engineered anti-CD20 mAb. No crosslinking is required and a stronger direct cell death induction and ADCC compared to rituximab has been shown in in-vitro studies. A good clinical efficacy has recently been described in clinical phase I/II trials in B-cell lymphomas and CLL.

Antibodies targeting other surface antigens on CLL-cells include apolizumab and lumiliximab. Apolizumab (HU1D10) is a humanized IgG1 antibody specific for a determinant on the HLA-DR beta chain and lumiluximab is an anti-CD23 IgG chimeric mAb with macaque variable regions and human constant regions. This later drug has been shown to be synergistic with fludarabine and rituximab in preclinical models. In a FCR ± lumiliximab phase I/II trial toxicity was limited and unrelated to dose. The combination seemed to be more effective, when compared with a cohort of FCR treated patients (historical controls) and a large controlled trial is ongoing.

SGN-40, a humanized IgG1 anti-CD40 mAb has been used in phase I/II clinical trials for different B-cell lymphomas. The CD40 antigen is expressed on normal- and tumor B-cells and SGN-40 seems to mediate both apoptosis and ADCC in CLL cells, predominantly through natural killer (NK) cells. HCD122, another anti-CD40 mAb, have been shown to induce cytotoxicity against CLL cells in vitro and a favorable safety profile and clinical activity was seen in pretreated CLL patients in a phase I trial.

Finally, anti-angiogenic mAbs, especially bevacimzumab, a VEGF inhibitor, and bispecific antibodies like blinatumomab (MT103/MEDI-538), a CD19-/CD3-bispecific antibody, might have a potential therapeutic role in CLL.

Drugs targeting the anti-apoptotic bcl-2 family of proteins and receptors, might be of interest in CLL, as bcl2 proteins are highly expressed in CLL cells. The bcl-2 antisense oligonucleotide oblimersen, and the Bcl-2 small-molecule inhibitor obatoclax have both been tested clinically in CLL. The addition of oblimersen to fludarabine/cyclophosphamide has shown a significant improvement in the rate of durable high quality responses. Obatoclax is a pan-Bcl-2 antagonist with in vitro activity against CLL cells and combination with other therapeutic agents is suggested. ABT-737 and its analogue, ABT-263, are designed inhibitors of BCL2 and BCL-XL. CLL cells are sensitive to ABT-737 in-vitro, with rapid induction of apoptosis in all patients tested, independent of previous clinical chemotherapy resistance. ABT-263, which is orally active, showed promising activity in early phase I clinical trials in B-cell malignancies, particularly in CLL and phase II trials are ongoing.

CLL cells within lymph nodes are mostly more resistant to therapy than tumor cells in blood, which might be explained by soluble factors and/or activity of other cells cells in the lymp hnode microenvironment. A trial on ABT-737 tried to mimic the lymph node microenvironment and CLL cells cultured in this milieu developed a rapid resistance to the drug, explained by de novo synthesis of antiapoptotic proteins as BCL-XL and BCL2A. Resistant CLL cells might also develop in lymph nodes following clinical therapy with ABT-737, and treatment strategies targeting multiple BCL2 antiapoptotic members with synergistic activity might be more effective.

The immunomodulating drug lenalidomide, a thalidomide analogue, has demonstrated clinical activity in CLL, both against genetically high-risk disease and in chemo-refractory patients. Toxicities such as tumor lysis syndrome and tumor flare reaction are more common with lenalinomide compared to established chemotherapy regimens and the dosing of lenalidomide has to be optimized. Some studies have shown that lenalidomide upregulates CD40 expression on B CLL cells and also activates NK-cells, why clinical trials of SGN-40 and lenalidomide in combination might be justified. A potential use of lenalidomide in combination with chemotherapy or as maintenance therapy is also being tested.

Inhibitors of cyclin dependent kinases (Cdks) have been reported to have activity in CLL. Flavopiridol

is one such inhibitor of Cdk , that is highly active in CLL also in chemo-resistant patients and independent of p53 activity. Due to high risk of tumor lysis syndromes more safety data is needed.

Cdks inhibitors have been reported to have an effect on Cdk7 and Cdk9, controling transcription. The Cdk inhibitor SNS-032 exhibits selective inhibitory activity against Cdk2, Cdk7 and Cdk9 and prevents tumor cell-induced angiogenesis. The Vascular Endothelial Growth Factor (VEGF), SNS-032, has been shown to effectively kill CLL cells in-vitro regardless of prognostic indicators and treatment history. Compared to flavopiridol, SNS-032 was more potent, both in inhibition of RNA synthesis and induction of apoptosis.

Another drug with shown efficacy in refractory CLL is fostamatinib disodium, an inhibitor of the spleen tyrosine kinase (Syk). This kinase is an important molecule in B-cell signaling, identified from gene array studies. The rationale for using a syk inhibitor is based on the importantance of the B-cell receptor (BCR)–mediated survival pathways in B-cell cells. A tonic stimulation of the BCR is an important survival pathway, in which Syk is a major component. Certain malignant cells, like CLL, are overexpressing Syk and might be sensitive to inhibition of this kinase. Fostamatinib has been used as an oral medication in a phase II-trial, including also CLL patients. The safety profile was acceptable, with the most common toxicities being reversible hematologic adverse events. Several heavily pretreated patients with CLL and large lymphadenopathy had a rise in white blood cell count with simultaneous and dramatic lymph node shrinkage in response to the drug. However, when the drug was stopped, the opposite occurred; the lymph nodes regained their original size, and the white cell count decreased. A recirculation phenomenon might explain these findings. Fostamatinib athus ppears to be an interesting compound that has activity in subtypes of CLL patients and might be effective in combination with other drugs.

New cytotoxic agents with novel mechanisms of action have been tested for the treatment of patients with CLL. One of these drugs, bendamustine is in fact an old drug used in Germany since many years, but has recently shown efficacy in CLL in randomized trials and is approved in the United States for treatment of CLL. Bendamustine is a cytotoxic agent with structural similarities to both alkylating agents and antimetabolites, but is non-cross-resistant with alkylating agents and other drugs both in-vitro and in the clinic. The optimal dose and schedule of bendamustine and combination with other drugs as well as management of toxicities are now being investigated. Other nucleoside analogs with potential activity in CLL are forodesine, clofarabine and nelarabine.

Curcurmin (diferuloylmethane), an active ingredient in the spice turmeric, has been shown to inhibit tumor metastasis and angiogenesis in tumor cell lines. Curcumin in combination with the green tea extract epigallocatechin-3 gallate (EGCG) has been shown to induce apoptosis in CLL B cells, especially if sequential administration.

In summary, most CLL patients treated with conventional therapy will progress and require subsequent therapy.The majority of patients are are aged and many show comorbidities. Moreover, over time resistantce to conventional therapy mosly evokes, sometimes related to clonal evolution and accumulation of negative prognostic features. Agents with novel mechanisms of action are therefore needed. Several new drugs are in various stages of development from Phase I to Phase III trials. These includes cytotoxic agents, monoclonal antibodies, immune modulators, inhibitors of CDK , BCL-2 family members, and PKC, as well as small modular immune pharmaceutics (SMIP). The use of these new agents provides an opportunity to develop risk-adapted therapeutic strategies to optimize response and quality of life in patients with CLL. For some drugs a chronic or maintenance regimen, might be the best for the control of the disease, contrasting to the way of giving standard chemotherapy. Further studies are needed to define biologic mechanism of action of these new agents, their safety and clinical activity, particularly for patients with high-risk genetic features.

Dr. Peter Dreger

Peter Dreger started his scientific career in 1985. After 3 years of basic research in experimental bone marrow transplantation he joined the Second Department of Medicine at the University of Kiel in 1988. Together with Norbert Schmitz he established a scientific program of experimental and clinical blood stem cell transplantation. Significant contributions were made in the fields of allogeneic peripheral blood stem cell transplantation and allogeneic and autologous transplantation for lymphoma and CLL. After heaving headed the Stem Cell Unit at the AK St. Georg Hamburg for 3 years, in 2005 he accepted the position of a Professor and Head of the Division of Allogeneic Stem Cell Transplantation at the University of Heidelberg. Peter Dreger is founding member of the German CLL Study Group (Responsibility: Transplant studies) and chairman of the CLL subcommittee of the EBMT Chronic Leukemia WP.

Stem Cell Transplantation in Chronic Lymphocytic Leukemia

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Efforts to develop curative treatment strategies for chronic lymphocytic leukemia (CLL) have focused on autologous and allogeneic stem cell transplantation (SCT) during recent years. Whereas the efficacy of autologous SCT (auto-SCT) relies exclusively on the cytotoxicity of the myeloablative regimen administered, the crucial antileukemic principle of allogeneic SCT (allo-SCT) in CLL appears to be the immune-mediated anti-host activities conferred with the graft (GVL effects).

Allo-SCT from matched related or unrelated donors can be highly effective in otherwise resistant CLL. Therefore it is regarded as a standard treatment option for eligible patients who fufil accepted criteria for poor-risk disease. Prospective trials are underway to prove if allo-SCT indeed can change the natural history of poor-risk CLL. This presentation will review the evidence for the efficacy of allogeneic stem cell transplantation in CLL and discuss indications and timing.

Although in the vast majority of cases auto-SCT will not cure CLL, the results of prospective trials suggest that it is capable of exerting profound disease control. However, currently auto-SCT in CLL has to be considered as an experimental procedure which should not be performed outside of a clinical trial protocol.

Other Aggressive Lymphomas

Welcome to the Session on other aggressive lymphomas. Lymphoma is one of the most heterogenous types of cancer and aggressive lymphoma has many subtypes beside diffuse large B-cell lymphoma, each with its own characteristics, biology and treatment. This year we focus on three diseases. I will open the session with a discussion on the treatment of primary CNS lymphoma. Dr. Wyndham Wilson from the National Cancer Institute, Bethesda, MD will discuss the management of Burkitt's lymphoma, the most aggressive form of lymphoma, but highly curable with modern combination chemotherapy. Dr. Owen O'Connor from Columbia University in New York will discuss advances in Mantle Cell lymphoma. Mantle Cell Lymphoma was recognized only relatively recently, and initially associated with a poor prognosis. Thanks to a focused research effort, much of the biology of this disease has been elucidated and great strides made in its treatment. Enjoy the session!

Dr. Koen van Besien

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Advances in the Management of Primary CNS Lymphoma

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CNS involvement by lymphoma can occur as a disease restricted to the CNS (primary CNS lymphoma, PCNSL) or as a complication of systemic lymphoma (secondary CNS lymphoma). Primary CNS lymphoma in severely immunocompromised patients particularly those with AIDS is often EBV related.[1,2] The etiology of PCNSL in the immunocompetent is unclear and EBV is not usually involved. Its incidence like that of other types of lymphoma has been steadily increasing.

The large majority of cases of immunocompetent PCNSL are diffuse aggressive B-cell lymphomas. They share many similarities with systemic DLBCL but have a unique gene expression signature. Presenting symptoms are varied and include focal neurologic deficits, headaches, neuropsychiatric changes including dementia and commonly ocular involvement. On CT and MRI, the disease is often multifocal. Response to systemic steroids can be swift (vanishing tumor). Staging should include CT/MRI of the craniospinal axis, CSF examination unless medically contraindicated, and eye exam.[3,4] Systemic staging including PET/CT and bone marrow aspirate and biopsy should be included. Hepatitis should be excluded. Generally accepted prognostic features include age and performance status.[5] Others also have found predictive value to location of lesion, spinal fluid protein level and serum LDH.[6]

Radiation therapy has long been the cornerstone of treatment for PCNSL and induces complete remission in 40-60% of patients but is rarely curative, even with modern radiation techniques. One study conducted in the 1990's showed a median survival of 18 months and a 5 year survival of only 18% in patients treated with radiation alone.[7] Many of the recurrences are in-field, indicating the relative radioresistance of primary CNS lymphoma compared with systemic lymphoma. It is customary to administer whole brain radiation; focal radiation has only rarely been investigated but in one study was associated with a high failure rate.[8]

Because of the high failure rate with radiation therapy, combined modality therapy has been investigated. CHOP or similar chemotherapeutic regimens do not offer any benefit, and high dose systemic methotrexate with leucovorin rescue has emerged as the single most effective treatment modality.[5] Methotrexate based chemotherapy followed by radiation has resulted in median survivals of up to five years. Decreasing the dose of radiation has resulted in some series in increased relapse rates.[9] But many have omitted radiation in older patients nevertheless. Such an entirely chemotherapy based approach results in lower cure rates, but also in lower rates of dementia among survivors. Furthermore,a retrospective review of the Sloan Kettering experience did not show a survival benefit from consolidation with radiation in those who achieved CR with chemotherapy.[10] On the other hand, a recent randomized study shows a remarkable event free survival benefit from consolidation with high dose cytarabine.[11] Those who received 4 courses of high dose MTX combined with high dose AraC had a 38% 5 year EFS. A control group receiving high dose MTX alone had fewer complications but lower CR rates and only 20% 5 year EFS. The combination of MTX and high dose Ara-C may therefore emerge as a new standard for chemotherapy based treatment of primary CNS lymphoma.

Alternative approaches include consolidation with high dose chemotherapy for patients in remission. This has resulted in durable remission in some patients with recurrent lymphoma. Its definitive role in consolidation of patients in first remission remains to be established.[12] Blood brain barrier disruption with intraarterial chemotherapy is a complex procedure that has yielded encouraging results and has limited neurocognitive impact.[13] It is technically demanding, requires general anesthesia and has not yet found widespread use.

Intrathecal chemotherapy has often been used as part of the treatment, based on data from treatment of meningeal leukemia. Its impact in PCNSL is rather limited and intrathecal treatment has considerable morbidity whether or not Ommaya reservoirs are used. Many limit its use to the approximately 20% of patients with primary CNS lymphoma who have CSF involvement.5 Intraocular lymphoma oc-

curs in approximately 20% of patients with PCNSL. Radiation to the eye, high dose systemic methotrexate, intraocular methotrexate and high dose chemotherapy with autologous stem cell transplant have all been advocated in cases of ocular involvement. A recent retrospective study failed to show a survival benefit for localized eye treatment, but did show an improvement in local control.[14]

Overall, the outcome of patients with PCNSL remains unsatisfactory with low cure rates and a high rate of neurocognitive sequelae. Research is hampered by the relative rarity of the disease. Ongoing efforts focus on the incorporation of novel drugs such as intrathecal rituximab2 or radiolabelled monoclonals in the salvage setting.[15] Temozolomide and topotecan are examples of promising chemotherapeutic approaches.[5;16]

Several other forms of PCNSL exist. Dural lymphomas are often indolent and of MALT type. They sometimes involve the spinal axis, respond well to involved field radiation or surgery and have an excellent prognosis.[17] Intravascular lymphoma is a rare form of lymphoma with a fulminant course and involving CNS, lungs and/or kidneys.[18;19] Prognosis used to be poor, but with modern rituximab based chemotherapy results have much improved.

Thanks to HAART therapy EBV driven CNS lymphoma in the AIDS patients has become a rare disease. Its diagnosis can sometimes be established without biopsy, based on EBV detection in the CSF. Prognosis remains poor, although it may have improved in the era of HAART therapy.[20]

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A Prospective Study of Dose-Adjusted (DA) Epoch with Rituximab in Adults with Newly Diagnosed Burkitt Lymphoma: A Regimen with High Efficacy and Low Toxicity

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Background: Burkitt lymphoma (BL) is a rare and very aggressive lymphoma, characterized by a high tumor proliferation rate. "Standard" therapy of BL is highly effective but involves intensive, multi-agent chemotherapy that is associated with high treatment related toxicity and mortality, particularly in older patients. We hypothesized that the DA-EPOCH-R regimen may be effective in BL, given its established efficacy in DLBCL and its ability to overcome highly proliferative tumors. **Methods:** We set out to investigate if DA-EPOCH-R could maintain the high cure rates of standard therapy in BL while minimizing treatment related toxicity. Eligible patients had untreated BL and could be HIV negative or positive - HIV negative patients (n=15) received 6 cycles of DA-EPOCH (with Rituximab) as previously described (Blood 99: 2685, 2002) and HIV positive patients (n=8) received 3-6 cycles of DA-EPOCH-R for 1 cycle beyond CR for a minimum of 3 cycles (Blood 106: #930, 2005). All patients received intrathecal methotrexate prophylaxis and outpatient therapy was instituted where possible. **Results:** Characteristics of 23 enrolled patients are: median age (range) 31 (18-66); male sex 18 (78%); median (range) ECOG PS 1 (1-3); stage III/IV 12 (52%); LDH > N 12 (52%); extranodal sites 17 (74%) and ileocecal disease 15 (65%). No patients had CNS involvement at diagnosis. Responses are CR/CRu in 100% with one patient receiving consolidative radiation to a site of residual disease. OS and PFS are both 100% and EFS 95% at a median potential follow-up of 27 months. Significant toxicities included tumor lysis syndrome (TLS) in one patient and fever/neutropenia in 16% of cycles. There were no treatment related deaths. **Conclusions:** DA-EPOCH-R is a very effective and well tolerated regimen in the treatment of newly diagnosed BL and is associated with low toxicity and low rates of TLS compared to "standard" high dose regimens used in BL. This regimen may significantly advance the therapeutic index in the treatment of BL. Accrual continues.

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2007-Present	Director, Lymphoid Development and Malignancy Program Herbert Irving Comprehensive Cancer Center. Columbia University – College of Physicians and Surgeons New York, N.Y. 10032-3789
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2007-Present	Associate Professor of Medicine Department of Medicine Division of Medical Oncology Columbia University – College of Physicians and Surgeons The New York Presbyterian Hospital New York, N.Y. 10032-3789
2002–2006	Head, Laboratory of Experimental Therapeutics for the Lymphoproliferative Malignancies Department of Medicine Division of Hematologic Oncology Lymphoma & Developmental Chemotherapy Services Memorial Sloan Kettering Cancer Center 1275 York Ave. New York, N.Y. 10021
2000-2006	Assistant Attending Physician Department of Medicine Division of Hematologic Oncology Lymphoma & Developmental Chemotherapy Services Memorial Sloan Kettering Cancer Center 1275 York Ave. New York, N.Y. 10021
2000-2007	Instructor Joan and Sanford Weil Medical College of Cornell University Medical Center The New York Presbyterian Hospital New York, N.Y. 10021

E. Professional Memberships

2006-Present	Member, American Society of Clinical Pharmacology and Therapeutics
1998-Present	Member, American Association for Cancer Research
1998-Present	Member, American Society for Clinical Oncology
1998-Present	Member, American Society for Hematology

1999-2002 Associate Member, American Society for Gene Therapy
1994-Present American College of Physicians
1984-1990 Member, American Chemical Society
1984-1990 Member, Society of Environmental Toxicology and Chemistry
1984-1990 Member, American Society for Microbiology

F. Honors and Awards

2008 Invited Plenary Lecture Introduction – American Society of Hematology
Abstract # 3
2008 Distinguished Jurkatt Scholar Lectureship – University of Vermont
2007-2012 U.S. Food and Drug Administration, Orphan Product Development Grant - RO1
A Multicenter Phase 2 Trial of Pralatrexate ((RS)-10-Propargyl-10-Deazaaminopterin) in the Treatment of Patients with Refractory or Relapsed Peripheral T-cell Lymphoma (PTCL).
2007 The Ellen Glesby Cohen Leadership Award from the Lymphoma Research Foundation, co-recipient with the Mantle Cell Lymphoma Executive Committee
2007 Co-Chair, The LRF North American Educational Symposium
2007 – Present Scientific Advisory Board, Lymphoma Research Foundation, N.Y., N.Y.
2007 – Present Senior Editor, Clinical Cancer Research
2007-2010 Editorial Board, Journal of Clinical Oncology
2006 Chair, Session on Germinal Center Lymphomas, American Society of Hematology (ASH)
2005 Chair, Session on New Therapies for the Treatment of Lymphoma, American Society of Clinical Oncology (ASCO)
2003 Chair, Session on New Drugs for the Treatment of Lymphoma, American Society of Hematology (ASH), San Diego, CA.
2002-2007 Scholar in Clinical Research – The Leukemia and Lymphoma Society, N.Y.
2002 Lymphoma Research Foundation, Clinical Investigator Award.
1999 Guy Forbeck Scholar Award - 'Targeted Gene Therapy'
William Guy Forbeck Foundation, Hilton Head, SC.
1999 Merit Award
American Society for Clinical Oncology
1997 Awarded the Dr. John Mendelsohn Medical Oncology Teaching Award for Housestaff Education
1997 Appointed Chief Medical Oncology Fellow
Memorial Sloan Kettering Cancer Center
New York, N.Y.
1993 William F. Groupe Scholarship for the Advancement of Medical Education
William F. Groupe Foundation
1991,1992 Who's Who Among Rising Young Americans
1991,1992 Awarded UMDNJ-RWJ Medical School Research Fellowship, UMDNJ-Robert Wood Johnson Medical School
1988 Awarded Doctoral Research Fellowship
Hudson River Foundation for Science and Environmental Research, New York, N.Y.
1988 Awarded Centennial Research Grant
School of Arts and Sciences
New York University
1984 Awarded Full Graduate Research Assistantship
Institute of Environmental Medicine
New York University Medical Center
New York, N.Y.
1982 Inducted into Sigma Xi
Manhattan College Chapter
1982 Magna Cum Laude
Manhattan College

G. Extracurricular Activities and Committees

9/2008 – Present Lymphoma Research Foundation – Chair, Bioinformatics Committee
1/2008 –-Present Senior Editor, Clinical Cancer Research
1/2007-Present Editorial Board, Journal of Clinical Oncology – Hematological Malignancies
1/2006-Present U.S. Food and Drug Administration (FDA) – National Institutes of Health (NIH) Consensus Panel on FDG-PET Imaging in Lymphoma Response Assessment.
1/2006-Present Editorial Board – Leukemia and Lymphoma
7/2005-Present NIH-CTEP Phase 3 Concept and Design Review Advisory Panel
7/2005-Present American Society of Clinical Oncology, Grants Selection Review Committee
7/2003-7/2007 Leukemia and Lymphoma Society
Translational Research Grant Review Committee
7/2002 – 2006 Investigational New Drug (IND) Committee
Memorial Sloan Kettering Cancer Center
8/2003 – Present Cancer and Leukemia Group B (CALG B)
• Lymphoma Committee
• Pharmacology and Experimental Therapeutics Committee (PET)
6/2003 – 2007 Lymphoma Research Foundation – Environmental Risk Assessment Task Force
1/2005 – Present Lymphoma Research Foundation – Mantle Cell Lymphoma Consortium – Executive Committee Appointment (Chair, Cell Bank Working Committee)
2/2008 – Present Lymphoma Research Foundation –– Executive Committee Appointment (Chair, Bioinformatics Working Committee)

I. Patents Pending: 3

1.

J. Editorial Responsibilities

2008 – Present Senior Editor, Clinical Cancer Research
2008 – Present Associate Editor, Journal of Hematology and Oncology
2008 – Present Editorial Board, Journal of Clinical Oncology
2008 - Present Editorial Board, Expert Review of Hematology
2005 – Present Editorial Board, Leukemia and Lymphoma
2004-Present Reviewer for the following journals:
- JNCI
- Cancer Research
- Cancer Biology and Therapy
- Cancer
- Clinical Pharmacology and Therapeutics
- Cancer Investigation
- American J. of Hematology
- Annals of Oncology
- Cancer Biology and Therapies

BIBLIOGRAPHY

A. Refereed Journal Articles: 60
B.Reviews and Editorials: 15
C.Book Chapters: 14
D.Published Proceedings and Abstracts: 113
E.Research Grants and Contracts (Owen A. O'Connor, M.D., Ph.D., Principal Investigator)

Mantle Cell Lymphoma

Dr. Owen A' O'Connor

Director, Lymphoid Development and Malignancy Program
Herbert Irving Comprehensive Cancer Center
Chief, Lymphoma Service
College of Physicians and Surgeons
The New York Presbyterian Hospital
Columbia University Medical Center

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Mantle cell lymphoma remains one of the more challenging sub-types of non-Hodgkin's lymphoma. This entity is characterized by response to a variety of different chemotherapy regimens like R-CHOP, HyperCVAd-R, and R- EPOCH, though none of these approaches are felt to cure the disease today. Typically, the duration of response to therapy remains quite short, especially for patients with relapsed disease. Retreatment with second and third line combination regimens results in shorter and shorter durations of response, with the rapid emergence of a very drug resistance phenotype. Despite these often frustrating clinical experiences, there is now a lot of new hope in managing patients with MCL. New insights into the molecular pathogenesis of MCL has revealed a plethora of new potential targets, while our continued efforts in novel targeted drug development has produced a host of agents that are already helping patients. The use of proteasome inhibitors for example, represents one example of a new strategy that has produced meaningful responses and duration of responses in patients with relapsed or refractory MCL.

Most recently, the development of other new agents targeting the PI3 Kinase – AKT – mTOR pathway, antiapoptotic Bcl-2 family members, and histone deacetylases is beginning to create new opportunities to develop truly novel, and potentially chemotherapy-free platforms, for the treatment of MCL. Recent biological insights have established that dysregulation of the AKT-mTOR axis may contribute significantly to the aggressiveness of the disease, and that HDAC inhibitors like vorinostat can essentially turn off cyclin D1 expression, possibly by inhibiting translation. During this lecture, the molecular pathogenesis of MCL will be reviewed, with an emphasis on how our evolving understanding of the molecular pharmacology of select new agents is affording us new opportunities to apply these new agents into specific diseases in a fashion that is completely complementary.

Diffuse Large B Cell Lymphoma

Dear friends and colleagues,

It is for me a pleasure to welcome all of you to the Symposium on diffuse large B-cell non-Hodgkin's lymphoma (DLBCL). The treatment of patients with DLBCL still represents a clinical challenge in our days. The widespread use of the anti-CD20 monoclonal antibody (Rituximab®) together with conventional chemotherapy as first line treatment has significantly improved both the progression-free and the overall survival curves. On the contrary, those patients primary refractory to first line therapy and those relapsing early after the completion of the treatment seem to constitute a somewhat highly resistant sub-population in whom new therapeutic approaches should be investigated. In addition, the impact of high-dose therapy with autologous stem cell transplantation (ASCT) – considered up to now the standard therapy for patients with relapsed chemosensitive disease – needs to be reviewed as well as its role as consolidation treatment after first line therapy in high-risk patients at diagnosis.

As more aggressive, but also potentially more toxic, treatments are now available, there is an increasing interest for early patient selection, assuming that rapid responders to a standard induction are likely to show better and more durable response, whereas non-responders could benefit from an early change of therapeutic orientation. Functional nuclear imaging provides metabolic tissue characterization; the emergence of 18F-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the clinical armamentarium and its increasing availability have recently provided an alternative to 67Ga-citrate scan. With FDG-PET, several studies have demonstrated that persistence of an increased glycolytic activity in lymphoma lesions at the end of first-line therapy, was associated with a 100% relapse rate, whereas the latter ranged from 16% to 20% in case of negative scan. If FDG-PET could also prove to be useful as an early indicator of tumour chemosensitivity, it may help refine therapeutic strategies.

Allogeneic stem cell transplantation (allo-SCT) has the potential advantages of the infusion of a tumour-free graft to the patient and the theoretical benefit of a graft versus lymphoma effect that can contribute to disease control after the intensive procedure over ASCT. Conventional allo-SCT has always been associated to significant non-relapse mortality (NRM). The improvement in supportive measures after the allogeneic procedure as well as the development of the "so-called" reduced intensity protocols have certainly been the major factors for the steady increment observed in the number of allogeneic transplant performed in patients with DLBCL. Allo-SCT can be considered a real treatment option for some DLBCL patients and several groups have reported their experiences regarding its therapeutic efficacy in this setting.

All these issues will be widely discussed by a panel of experienced physicians with a well-known expertise in the field.

Dr. Anna Sureda

Dr. Anna Sureda

Anna Sureda, 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. Since 1991 she has been working in the Clinical Haematology Division of the Department of Haematology at Hospital de la Santa Creu i Sant Pau in Barcelona where she was appointed Head of the Outpatient Department in 2002. She was a Visiting Physician at the University of Heidelberg, Germany in 1990 and at the Fred Hutchinson Cancer Research Center of Seattle in 1993.

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). Since then, her main focus of interest has been the analysis of the results and prognostic factors of autologous and allogeneic stem cell transplantation in lymphoid malignancies.

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

Allogenic Stem Cell Transplantation in Patients with Diffuse Large B Cell non-Hodgkin's Lymphoma

Dr. Anna Sureda

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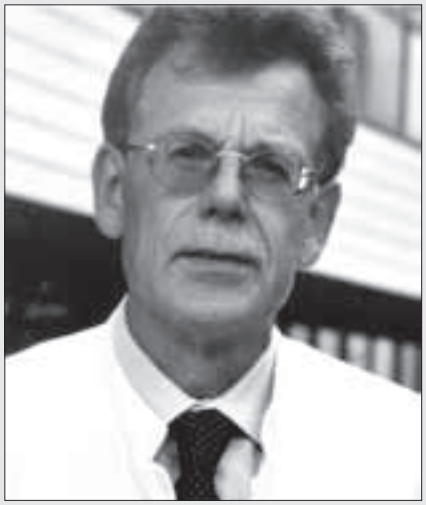
asureda@santpau.cat

Autologous stem cell transplantation (ASCT) is still considered the therapy of choice for those patients with diffuse large B-cell lymphoma (DLBCL) who present with a chemosensitive relapse after first line chemotherapy. Those patients with primary refractory disease, those in first relapse with a short first complete remission as well as those failing multiple therapy programmes including an ASCT have a very poor prognosis and can eventually be considered candiates for an allogeneic stem cell transplantation (allo-SCT). Potential advantages of allo-SCT in front of an autologous procedure are based in the theorical existence of a graft-versus-lymphoma effect (GvL) as well as the possibility to infuse healthy stem cells. Non-relapse mortality of allo-SCT was inacceptably high in the era of myeloblative conditioning regimens. The advent of the so-called non-myeloablative (or reduced intensity) conditioning protocols has significantly increased the number of allografts performed in lymphoma patients in the last years. Relapses after an ASCT constitute nowadays one of the major indications for an allo-SCT. In this sense, the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation has retrospective analyzed the outcome of a group of 101 adult patients



Dr. Norbert Schmitz

Professor Schmitz is Head of the Department of Haematology and Stem Cell Transplantation in the Asklepios Clinic St Georg in Hamburg, Germany, since 2001. He graduated as a medical doctor in 1976 and specialized in internal medicine in 1985 and in haematology 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 for 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 programme of the Department of Internal Medicine II 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 and more than 300 articles in peer-reviewed journals. In addition, he is an editorial board member of the Journal of Clinical Oncology.

Norbert Schmitz, M.D., born in Aachen, Germany, April 11, 1951.

Degrees

1976	Approval at the University of Darmstadt, Germany
1977	M.D. at the University of Giessen, Germany.
1989	Postdoctoral thesis (habilitation), title: Analysis of haematopoietic chimerism after allogeneic bone marrow transplantation in patients with chronic myelogenous leukaemia at the Christian-Albrechts-University Kiel, Germany.
1996	Professor of Medicine at the University of Kiel, Germany.

Positions

1976-1977	Resident in Internal Medicine at the District Hospital Braunfels/Lahn, Germany.
1978-1979	Resident at the Institute of Clinical Immunology and Blood Transfusion, University of Giessen, Germany.
1979-1980	Resident at the Department of Internal Medicine of the University of Giessen, Germany.
1981-1985	Resident at the 2nd Department of Internal Medicine of the University of Kiel, Germany.
1982	Visiting physician at the Department of Hematology and Bone Marrow Transplantation, City of Hope National Monument, Duarte, California, USA.
1983	Head of the Bone Marrow Transplant Unit of the Departments of Paediatrics and Internal Medicine II of the University of Kiel, Germany.
2001	Head of the Department of Hematology at the AK St. Georg, Hamburg, Germany

Board Certification (Germany)

1985	Specialist in Internal Medicine.
1988	Specialist in Hematology.

Society Memberships

German Society of Hematology and Oncology
German Cooperative Group for Blood and Bone Marrow Transplantation
European Group for Blood and Marrow Transplantation (EBMT)
American Society of Hematology (ASH)
European Haematology Association (EHA)
German Society for Internal Medicine

Other Important Functions

since 1989	Regular reviewer for the journals Bone Marrow Transplantation, BLOOD, Annals of Hematology, Haematologica, Annals of Oncology.
since 1992	Co-ordinator of studies for patients with relapsed Hodgkin's disease in Germany and Europe.
1992-1998	Secretary of the European Group for Blood and Marrow Transplantation (EBMT)
1998-2004	Chairman of the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT)
2002-2004 and since 2006	Chairman of the German High-Grade Non-Hodgkin-Lymphoma Study Group (DSHNHL)
2006	President of the Annual EBMT meeting 2006 in Hamburg, Germany
since 2006	Chairman of the T-cell subcommittee of the EBMT WP Lymphoma
since 01/2008	member of the Editorial Board for Journal of Clinical Oncology (JCO)

Scientific Publications

More than 250 articles in national and international journals, about 500 abstracts, about 60 book chapters

Treatment of DLBCL Patients in the Era of Monoclonal Antibodies

Dr. Norbert Schmitz

Asklepios Klinik St. Georg, Germany

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The combination of rituximab and cyclophosphamide, vincristin, adriamycin, and prednison (CHOP) is the new standard treatment for patients with aggressive B cell lymphomas. The studies by Coiffier et al. (N. Engl. J. Med.) and Pfreundschuh et al. (Lancet Oncol. 2008) showed substantial benefit of R – CHOP 21 or R – CHOP 14 over CHOP 21 or CHOP 14 , respectively in patients between 60 and 80 years of age. In young, good – risk patients the MINT study showed similar improvements in event-free and overall survival for patients treated with R and CHOP or CHOP – like regimens over chemotherapy alone. In young, high-risk patients formal proof of the superiority of R – containing regimens over chemotherapy alone is still lacking mostly because many of these patients are treated with high- dose chemotherapy and autologous stem cell transplantation. Several trials comparing conventional chemotherapy with high- dose chemotherapy , both in combination with rituximab, are ongoing. While results in young, good – risk patients and elderly patients with low IPI seem satisfactory and further improvement will be hard to achieve , results in young and elderly patients with high / intermediate and high IPI is certainly necessary. New studies are aiming to improve the treatment results by optimizing the administration of rituximab and incorporating new cytotoxic drugs.

For patients with relapsed disease high-dose therapy / ASCT remains the standard therapy. The major problem is the increasing difficulty to bring these patients into second remission. Various strategies to increase the percentage of patients achieving CR or PR are currently under investigation.

Personal Information

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Site address: (must match with the study site address)		
Institution name	Hôpital Henri Mondor Service Hématologie Clinique	
Street	51, avenue du Maréchal de Lattre de Tassigny	
Building/ House number		
Postal/Zip code	94010	
Town/City	Créteil	
Country	France	

Current position/job title: Hospital Practitioner and Professor of University in Clinical Haematology	Start Date (Year): 2001
CNOM registration Number: 05-781	

Professional Qualifications

Name of Granting Institution	Location (City, Country)	Degree	Obtained (Year)
Paris XII University of Medicine	Créteil, France	Doctorat in Medicine	1982
Paris XII University of Medicine	Créteil, France	Post-Graduate Specialized Degree in Haematology	1984

Experience/Previous Positions (in chronological order)

Job Title	Institution Name	Location	From (Year)	To (Year)
Assistant Physician	Clinical Hematology Department – Hôpital Henri Mondor	Créteil, France	1982	1991
Hospital Practitioner	Clinical Hematology Department – Hôpital Henri Mondor	Créteil, France	1992	Until today
Professor of University in Clinical Haematology	Clinical Hematology Department – Hôpital Henri Mondor	Créteil, France	2001	Until today

Clinical Trial Experience (Principal Investigator)

Start Date (Year)	Clinical Phase (I,II,III,IV)	STUDIES (Indication; ClinicalTrials.gov Identifier)
1999	III	LNH98B-3 (DLBCL = Diffuse Large B-cell Lymphoma, 1st line; NCT00169169)
2001	-	Pet-Scan (NHL, 1st line)
2003	III	LNH 03-B program (DLBCL, 1st line; LNH03-1B: NCT001140660;LNH03-2B: NCT00140595; LNH03-3B: NCT00144807; LNH03-6B: NCT00144755)
2003	II	R-GEMOX (DLBCL at relapse; NCT00169195)
2004	II	LNH 03-39B (DLBCL, 1st line; NCT00169143)
2005	II	RAIL (Angio-immunoblastic T-cell Lymphoma; NCT00169156)
2007	II	R-GEMOX-Enzastaurin (DLBCL at relapse; NCT00436280)
2007	I	VEGF – TRAP (DLBCL, 1st line; NCT00644124)

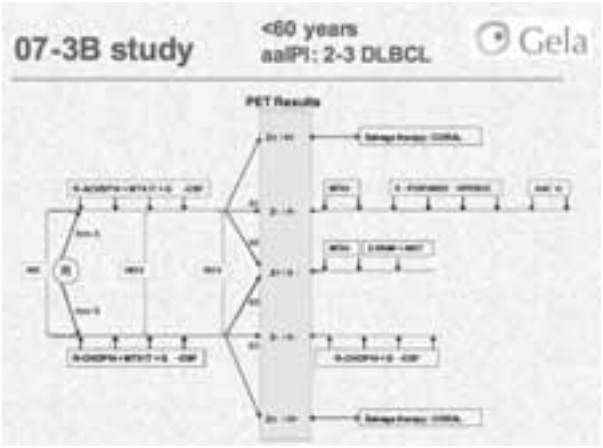
Investigator Signature

Signature:	Date: March 3,2009

The use of PET Scan for Risk Adapted Therapeutic Strategies in DLBCL

Dr. Corinne Haioun
Hôpital Henri Mondor, Créteil France and GELA
corinne.haioun@hmn.aphp.fr

Achieving a complete response to first-line therapy is an important goal in managing patients with aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL), as long-term outcome is greatly improved compared with those patients with residual disease. 18F- Fluorodeoxyglucose positron emission tomography (FDG-PET) is emerging as a powerful technique for the assessment of response in patients with DLBCL and also appears to be a valuable predictor of long-term outcome. A number of studies have shown that patients who have a negative PET scan (during the induction phase or after several cycles of induction chemotherapy) have a significantly better event-free survival (EFS) than those who have an abnormal PET scan. This suggests that it may be possible to use FDG-PET to identify poor responders during the course of induction therapy and modify their treatment accordingly. This approach is being investigated in an ongoing GELA (Groupe d'Etude des Lymphomes de l'Adulte) study (07-3B Study). Patients under the age of 60 years of age and with an age adjusted-IPI score of 2–3 were randomized to receive four cycles of either R-ACVBP14 + intrathecal methotrexate (MTX it) + G-CSF (group A) or R-CHOP14 + MTX it + G-CSF (group B) (Figure 1). PET assessments are performed at baseline and after the second and fourth cycle of therapy. Further treatment is then given according to response, as assessed by PET. Patients from either treatment group who are PET positive after the fourth cycle of treatment leave the study to receive salvage therapy. Those who are PET negative after both the second and fourth cycle of treatment continue to receive induction therapy (group A: MTX iv, R-ifosfamide-vepeside, cytarabine; group B: 4 cycles of R-CHOP14 + G-CSF), while those who are PET positive after the second cycle but PET negative after the fourth cycle receive more intense, consolidation therapy –MTX iv followed by Z-BEAM (90Y-ibritumomab tiuxetan plus BEAM) with autologous stem cell support. Indeed, for patients who are PET positive at the end of induction therapy, consolidation therapy involving 90Y-ibritumomab tiuxetan may be an appropriate option. The results of this study should help determine the value of using PET assessment during the course of induction therapy to modify the course of treatment and also the role of 90Y-ibritumomab tiuxetan as consolidation therapy in poor risk patients with DLBCL.



References

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2. Spaepen K, Stroobants S, Dupont P, Van SS, Thomas J, Vandenberghe P et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 2001; 19:414-9.
3. Spaepen K, Stroobants S, Dupont P, Vandenberghe P, Thomas J, de GT et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002; 13:1356-63.
4. Kostakoglu L, Coleman M, Leonard JP, Kuji I, Zoe H, Goldsmith SJ. PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. J Nucl Med 2002; 43:1018-27.
5. Haioun C, Itti E, Rahmouni A, Brice P, Rain JD, Belhadj K et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005; 106:1376-81.
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7. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007; 25:571-8.

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is characterized by the presence of the Philadelphia chromosome, a genetic aberration that codes for bcrabl, which plays a key role in disease pathophysiology. Following imatinib treatment, more than 90% of patients achieve complete hematologic response, and over 90% achieve a complete cytogenetic response. Within 7 years of follow-up, the results are still favorable, resulting in a major change in the natural history of the disease.

Routine cytogenetic analysis is still considered the gold standard for evaluating response in CML. As most patients achieve complete cytogenetic responses with modern therapy, there is a need to develop more sensitive and accurate monitoring tools to measure residual disease. It has been assumed that such increased accuracy might help better predict outcome.

Despite the benefit of imatinib over prior treatments, some patients may develop resistance, with a reported annual resistance rate of 2% to 4% in newly diagnosed patients in chronic phase, the incidence decreasing over time. Novel more potent tyrosine tyrosine kinase inhibitors such as dasatinib, nilotinib, and bosutinib have been developed to overcome imatinib resistance. These agents have shown significant activity after failure of imatinib therapy, with high rates of hematologic and cytogenetic responses.

Although, allogeneic stem cell transplantation is not anymore considered a frontline option for patients with CML in chronic phase, this strategy potentially remains the only curative approach in patients with advanced stage disease, particularly post imatinib failure, in patients not achieving an early cytogenetic response to second line tyrosine kinase inhibitors, and in patients harboring highly resistant kinase domain mutations such as the T315I mutation.

Dr. Elias Jabbour

Dr. Elias Jabbour

Dr. Elias Jabbour graduated from the Saint Joseph's School of Medicine in 1998 and joined, thereafter, the Hotel Dieu de France University Hospital as a resident. In 2001, he pursued in fellowship in Hematology-Oncology at the Gustave Roussy Institute. In 2003, he joined the University of Texas M. D. Anderson Cancer as a fellow in the Department of Hematology/ Leukemia and Stem cell transplantation. Thereafter, in 2007, he joined the faculty in the Leukemia department as Assistant Professor.

Dr. Jabbour is actively involved in research in both acute and chronic forms of leukemia. He was actively involved in clinical trials that lead to the approval of several drugs in chronic myeloid leukemia (CML) and myelodysplastic syndromes. His research on resistance to imatinib and mutations of the protein kinase domain were presented in several international; meetings and published in peer-reviewed journals. He is also developing tailored therapies to CML.

Dr. Jabbour has taken an active role in the medical community, participating in numerous scientific meetings. He has authored or co-authored more than 100 medical publications and abstracts and serves as a reviewer numerous scientific journals. In 2005, 2006, and 2007, he received the American society of Clinical Oncology and the American society of Hematology merit awards for Outstanding Clinical fellow, in addition to two similar awards from the American society of Bone Marrow Transplantation.
January 2009

PRESENT TITLE AND AFFILIATION
Primary Appointment
Assistant Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX
Dual/Joint/Adjunct Appointment/Ad Interim
N/A

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EDUCATION
Degree-Granting Education
Saint Joseph University, Beirut, Lebanon, MD, 1998, MD
Educational Committee for Foreign Medical Graduates, Philadelphia, PA, Certificate, 1999, MD
Saint Joseph University, Beirut, Lebanon, Masters, 1999, Biologic Sciences
University of Paris XI School of Medicine, Paris, France, University Diploma, 2002, Clinical Carcinology
University of Paris V School of Medicine, Paris, France, University Diploma, 2003, Hematology (Clinic and Biologic Options)
Saint Joseph University School of Medicine, Beirut, Lebanon, Fellow, Specialty Diploma, 2005, Hematology-Oncology
Postgraduate Training
Clinical Residency, Saint Joseph University, Beirut, Lebanon, Marwan Ghosn, M.D., 7/1998–10/2001
Clinical Fellowship, Hematology-Oncology, Gustave Roussy Institute, Villejiuf, France, Vincent Ribrag, M.D., 11/2001–10/2003
Clinical Fellowship, Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX, Hagop Kantarjian, M.D., 11/2003–10/2005
Clinical Fellowship, Blood and Marrow Transplantation, University of Texas M.D. Anderson Cancer Center, Houston, TX, Richard Champlin, M.D., 11/2005–10/2007

HONORS AND AWARDS
Merit Award, American Society of Clinical Oncolgy, 2005
Merit Award, American Society of Hematology, 2005
Merit Award, American Society of Blood and Marrow Transplantation, 2006
Merit Award, American Society of Clinical Oncology, 2006
Merit Award, American Society of Hematology, 2006
Merit Award, American Society of Clinical Oncology, 2007
Merit Award, American Society of Hematology, 2007
The Celegene Future Leader in Hematology Award, 2007
The Kimberly Patterson Fellowship in Leukemia Research Award, 2007
The Shannon Timmins Fellowship for Leukemia Research Award, 2007

Publications (n:65)

Invited Articles (n:2)

Editorials (n:1)

Abstracts (n:44)

Book Chapters (n:4)

EDITORIAL AND REVIEW ACTIVITIES
Editor/Service on Editorial Board(s)
N/A
Member of Editorial Review Board
N/A
Journal Reviewer
Reviewer, Proceedings of the Mayo Clinic, 2005–present
Reviewer, Cancer, 2006–present
Reviewer, American Journal of Hematology, 2007–present
Reviewer, Bone Marrow Transplantation, 2007–present
Reviewer, Leukemia, 2008–present
Reviewer, Oncology Briefings, 2008–present
Reviewer, The Leukemia & Lymphoma Society, 2008–present
Other Editorial and Review Activities
N/A

Treatment of CML Post Imatinib Failure

Dr. Elias Jabbour

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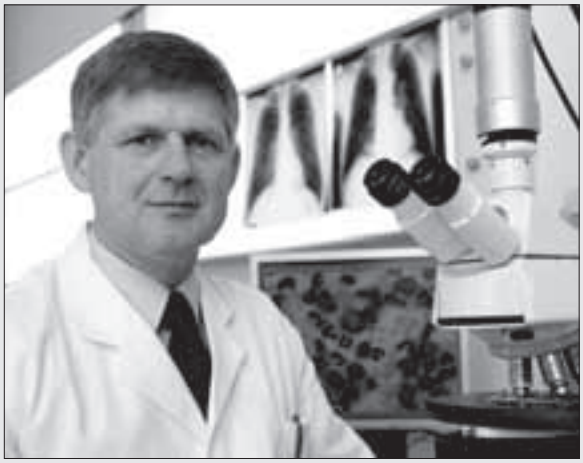
Chronic myelogenous leukemia (CML) is a progressive and often fatal hematopoietic neoplasm. The Bcr-Abl tyrosine kinase inhibitor imatinib mesylate represented a major therapeutic advance over conventional CML therapy, with more than 90% of patients obtaining complete hematologic response, and 70%–80% of patients achieving a complete cytogenetic response. Resistance to imatinib represents a clinical challenge and, is often a result of point mutations causing a conformation change in Bcr-Abl, which impair imatinib binding. Novel targeted agents designed to overcome imatinib resistance, include dasatinib, nilotinib, bosutinib, and others. Other approaches are exploring combination therapy, with agents affecting different oncogenic pathways, and immune modulation.



Dr. Andreas Hochhaus

Professor of Internal Medicine, Medizinische Fakultaet Mannheim
Ruprecht-Karls-Universitaet Heidelberg
Mannheim, Germany

Dr. Hochhaus is professor of internal medicine, hematology and oncology and head of the Department of Leukemia Research at the III. Medizinische Klinik, Medical Faculty Mannheim of the Heidelberg University in Germany. He received his medical degree from the Medical Academy of Erfurt and served as a research fellow at Hammersmith Hospital in London with Professor John M. Goldman.

He has been interested in treatment optimization of chronic myelogenous leukemia (CML) and has been involved in the management of the randomized CML Studies I-IV of the German CML Study Group for more than 17 years. His special interests are the molecular monitoring of minimal residual disease and mechanisms of resistance in CML.

Dr. Hochhaus is investigator for the dasatinib, nilotinib, INNO-406 and bosutinib phase II and phase III studies, has been participating in imatinib phase II and III studies and is conducting trials of imatinib combined with pegylated interferon alpha, and everolimus.

He is a member of the European Haematology Association, the American Society of Hematology, the American Society of Clinical Oncology, the International Association for Comparative Research on Leukemia and Related Diseases, and the German Society for Hematology and Oncology. He has published over 200 peer-reviewed papers and is regularly invited to speak at national and international symposia.

Dr. Giuseppe Saglio

Professor of Internal Medicine
Department of Clinical and Biological Sciences
University of Turin
Turin, Italy

Dr. Giuseppe Saglio is Professor of Internal Medicine and Haematology at the University of Turin. He is also responsible for the 2nd division of Internal Medicine and Haematology at San Luigi Hospital (University of Turin). He graduated from the University of Turin in 1975. Since then he has studied Internal Medicine at the University of Turin (1975–1980), Haematology at the University of Milan (1980–983) and Molecular Biology at the University of Leiden (1976), Inserm-Creteil, Paris (1979) and the University of California (1983).

Dr. Saglio is co-ordinator of the PhD programme in molecular medicine at the University of Turin, past-president of the Italian Society of Experimental Haematology (SIES) and is a member of the Academy of Medicine of Turin. He has published more than 280 peer-reviewed articles in the fields of molecular pathogenesis of haematological malignancies (1986–present), molecular medicine applied to clinical medicine (1978–1990) and the molecular basis of thalassemia and related haemoglobinopathies (1978–1990).

Dr. Saglio has been on the editorial board of Haematologica (the official journal of the European Haematology Association). He acts as a referee for a range of medical journals including Blood, British Journal of Hematology, Leukemia, Bone Marrow Transplantation, European Journal of Hematology and Haematologica. He has also been involved in numerous grant reviews including for the Leukemia Research Fund (U.K.), MIUR, CNR and for various Italian and European Universities including Padova, Siena, Southampton, Salamanca and Cordoba.

Giuseppe SAGLIO - Curriculum Vitae	
Name **Giuseppe SAGLIO**	Position **Full Professor of Internal Medicine University of Turin**

Date of Birth 17/05/50	Date of Doctoral Degree 23/07/1975
Doctoral Degree Medical Doctor	

Education and Training (include degrees and post-doctoral training)			
Institution and Location	Degree	Years	Field of Study
University of Turin	M.D.	1969-1975	Medicine
University of Turin	Residency	1975-1980	Internal Medicine
University of Milan	Residency	1980-1983	Hematology
University of Leiden	Fellow	1976	Molecular Biology
Inserm-Creteil, Paris	Fellow	1979	Molecular Biology
Universityof California, San Francisco	Fellow	1983	Molecular Biology

Research And Professional Experience:
NAME : Giuseppe SAGLIO
TITLES : MD, Professor of Internal Medicine

Professional Experience :

1975	Degree in Medicine at the University of Turin
1975-1980	Residency in Internal Medicine at the University of Turin
1980-1983	Residency in Hematology at the University of Milan
1983-1990	Assistent Professor in Internal Medicine – University of Turin
1990- present	Full Professor in Internal Medicine – University of Perugia (90/91), University of Turin in Novara (91/98), University of Turin in Turin (98-present)
1996-1999	Director of the I School in Internal Medicine of the University "Amedeo Avogadro" of Eastern Piedmont (formerly University of Turin in Novara) .
1996-1999	Coordinator of the PhD program in Molecular Medicine of the University "Amedeo Avogadro" of Eastern Piedmont (formerly University of Turin in Novara)
2000 – 2004	Vice-Dean of the Faculty of Medicine of the University of Turin
2001-2006 -	President of the II School of Medicine of the University of Turin

Present Appointments
Director of the Division of Internal Medicine and Hematology at the San Luigi Hospital– University of Turin.

Honors:
President (1996-98) and past-president (1998-2000) of the Italian Society of Experimental Hematology (SIES).
Member of the Academy of Medicine of Turin

Research Activity:
Focused in molecular biology applied to clinical medicine in haematology. More that 300 peer reviewed publications with a total IF of 2000

Editorial Activity
- Editorial Board of Journal of Clinical Oncology:
- Referee for Blood, British Journal of Hematology, Leukemia, Bone Marrow Transplantation, European Journal of Hematology, Haematologica and others;
- Reviewer for grants for the Leukemia Research Fund (UK), for MIUR, CNR and several Italian and European Universities (Padova, Siena, Jerusalem, Southampton, Salamanca, Cordoba etc...)

Pubblications in the Last 5 Years (n:90)

CML History and Update of Imatinib Experience

Dr. Giuseppe Saglio
University of Turin, Italy

Chronic Myeloid Leukemia (CML) has always been an ideal model to understand the molecular pathogenesis of human leukaemias and the way to cure them. This can be ascribed to the fact that CML was the first human cancer demonstrated to be strongly associated to the presence of a recurrent chromosomal translocation (the t(9;22)(q34;q11) that creates the Philadelphia (Ph)-chromosome) and to a specific molecular defect, the formation of a hybrid BCR-ABL gene that generates new fusion proteins endowed with a constitutive tyrosine-kinase (TK) activity, strongly implicated in the pathogenesis of the disease. The introduction into clinical practice of imatinib, a potent tyrosine kinase inhibitor of the Bcr-Abl protein as well as of a restricted number of other TKs, has not only produced a substantial improvement in the treatment of CML, but represents a major break-through in the perspective of opening a new era, that of molecularly targeted therapy, in the management of other types of leukemia, lymphoma and cancer in general. The impressive response rates and the good tolerability allowed imatinib to become the golden standard frontline therapy for all CML patients in early chronic-phase. This conclusion has been mainly reached through the results of the IRIS trial. In fact, in the IRIS trial-arm in which the patients were assigned to receive imatinib 400 daily, after 7 years of follow-up 60% of patients are still on treatment and almost all of them in stable complete cytogenetic remission (CCyR). The remaining patients (40%) discontinued treatment because of inadequate response, loss of response, adverse events or protocol violation. All together, the overall survivors (OS) after 6 years are 86%, and only 5% of patients had died due to CML-related causes. These data have been deduced so far from a single study and await definitive confirmation from other important ongoing trials, but there is a general consensus about the optimal outcome of more than two thirds of the CML cases treated with standard dose imatinib (400 mg daily). A higher dose of imatinib (800 mg per day) has been suggested to accelerate to achievement and to improve the rates of the cytogenetic and molecular responses. If High Dose Imatinib is really beneficial for all CML patients in early chronic phase or at least for some specific risk subgroup of patients is still matter of investigation and important answer are waited in the near future. Criteria to establish failure and suboptimal responses to imatinib have been defined and will be updated during this year. At present, hematologic resistance (rare, 2–3% of all cases) at 3–6 months, lack of any degree of cytogenetic response at 6 months, lack of a major cytogenetic response at 12 months (>35% Ph-positive metaphases) and absence of a complete cytogenetic response at 18 months, are all considered failures and other treatment strategies are justified in these cases as the residual probability of achieving optimal response in such patients are scarce. This type of failure occurs in approximately 15% of all patients, but in the "failure" group we must also include those patients (14% in the IRIS) who initially achieve the responses expected at the established timepoints, but subsequently lose them. In some of these cases (6–7%) progression to accelerated or blast phase of CML is observed. Failure must be distinguished from what has been defined "suboptimal response", an intermediate situation between optimal response and failure, in which the response is slower than expected, but there is still a substantial chance for the patient to achieve the awaited response at a later time point. In some cases, suboptimal responses and also failures may simply be due to a too low imatinib plasma level, than may be explained by e.g. poor compliance to daily oral therapy, drug–drug interactions, food interaction or concomitant diseases. In other cases, genetic polymorphisms of the genes involved in the cellular drug influx–efflux processes may be responsible for insufficient (too low) imatinib concentrations within the cells. Dose escalation of imatinib could overcome resistance in some patients with CML initially treated with standarddose therapy.

Dr. Richard E. Champlin

PRESENT TITLE AND AFFILIATION
Primary Appointment
Chairman, Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, TX
Dual/Joint/Adjunct Appointment/Ad Interim
Professor, Division of Internal Medicine, The University of Texas
M. D. Anderson Cancer Center, Houston, TX

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Fax: (713) 792-4346
Email: rchampli@mdanderson.org

EDUCATION
Degree-Granting Education
Purdue University, W. Lafayette, IN, BS, 1971, Engineering Sciences
University of Chicago Pritzker School of Medicine, Chicago, IL, MD, 1975, Internal Medicine
Postgraduate Training
Internship/Residency, UCLA School of Medicine, Los Angeles, CA, Williams ODell, M.D., 7/1975–6/1978
Fellowship, UCLA Center for the Health Sciences, Los Angeles, CA, Martin Cline, M.D., 7/1978–1/1980

CREDENTIALS
Board Certification
American Board of Internal Medicine, Internal Med, 1978
American Board of Internal Medicine, Hematology, 1980
American Board of Internal Medicine, Med Oncology, 1981
Licensures
Active
TX, H7397, 1990
CA, G31983, 1991
Inactive
N/A

EXPERIENCE/SERVICE
Academic Appointments
Assistant Professor, Department of Blood and Marrow Transplantation, UCLA Center for the Health Sciences, Los Angeles, CA, 1981–1985
Associate Professor, Department of Blood and Marrow Transplantation, UCLA Center for the Health Sciences, Los Angeles, CA, 1985–1990
Chairman, Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 1990–present
Professor, Division of Internal Medicine, The University of Texas
M. D. Anderson Cancer Center, Houston, TX, 2004–present
Administrative Appointments/Responsibilities
Director, Leukemia and Bone Marrow Transplant Service, UCLA Center for the Health Sciences, Los Angeles, CA, 1983–1990
Director, Transplantation Biology Program, UCLA - Jonsson Comprehensive Cancer Center, Los Angeles, CA, 1983–1990
Director, Hematology/Oncology Fellowship Program, UCLA - Center for the Health Sciences, Los Angeles, CA, 1984–1990
Chief, Sections of Blood and Marrow Transplantation & Apheresis, UT M.D. Anderson Cancer Center, Houston, TX, 1990–1997
Department Chair ad interim, Department of Hematology, UT M.D. Anderson Cancer Center, Houston, TX, 1995–1997
Associate Head, Division of Cancer Medicine, UT M.D. Anderson Cancer Center, Houston, TX, 1997–2007
Department Chair, Department of Stem Cell Transplantation, Division of Cancer Medicine, UT M.D. Anderson Cancer Center, Houston, TX, 1998–present
Institutional Committee Activities
Surveillance Committee (IRB), Member, 1992–2000
Clinical Research Committee, Member, 1994–1998
Division of Cancer Medicine Executive Committee, Member, 1997–present
Clinical Faculty Review Committee, Member, 2000–2003
Promotions and Tenure Committee, Member, 2001–2003
Clinical Council, Member, 2001–2006
President's Advisory Board, Member, 2001–present
Promotions and Tenure Committee, Co-Chair, 2003–2004
Division of Cancer Medicine Advisory Committee, Member, 2003–present
Revenue Utilization Committee, Member, 2006–present
M.D. Anderson Cancer Center Management Committee, Member, 2006–present
Executive Committee of the Medical Staff, Member, 2006–present

HONORS AND AWARDS
G.A. Ross Scholarship Award, 1968
Alpha Omega Alpha, University of Chicago Pritzker School of Medicine, 1975
Giannini Foundation Fellowship, 1979
Giannini Foundation Fellowship, 1980
Giannini Foundation Fellowship, 1981
National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, 1982 New Investigator Research Award, 1982
National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, 1983 New Investigator Research Award, 1983
National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, 1984 New Investigator Research Award, 1984
Robert C. Hickey Chair in Clinical Cancer Care, MD Anderson Cancer Center, 1998
Faculty Achievement Award in Clinical Research, MD Anderson Cancer Center, 2002
Thomas Lecture Award, American Society for Blood and Marrow Transplantation, 2004

PUBLICATIONS
Articles in Peer-Reviewed Journals: more than 500
Invited Articles: 129
Editorials: 5
Abstracts (past 5 years): 68
Book Chapters: 100
Books (edited and written): 11

EDITORIAL AND REVIEW ACTIVITIES
Editor/Service on Editorial Board(s)
Associate Editor, Biology of Blood and Marrow Transplantation, 1999–present
Regional Editor, Cytotherapy, 1999–present
Editorial Board, Blood, 2002–present
Editorial Board, Bone Marrow Transplantation, 2002–present
Associate Editor, Experimental Hematology, 2002–present
Executive Editor, The Oncologist, 2005–present
Editorial Board, Clinical Cancer Research, 2007–present
Journal Reviewer
Manuscript Reviewer, Biology of Blood and Marrow Transplantation, 1990–present
Manuscript Reviewer, Blood, 1990–present
Manuscript Reviewer, Bone Marrow Transplantation, 1990–present
Manuscript Reviewer, British Journal of Haematology, 1990–present
Manuscript Reviewer, Cytotherapy, 1990–present
Manuscript Reviewer, Experimental Hematology, 1990–present
Manuscript Reviewer, International Journal of Hematology, 1990–present
Manuscript Reviewer, Journal of Clinical Oncology, 1990–present
Manuscript Reviewer, Journal of Hematotherapy, 1990–present
Manuscript Reviewer, Lancet, 1990–present
Manuscript Reviewer, Nature Medicine, 1990–present
Manuscript Reviewer, New England Journal of Medicine, 1990–present
Manuscript Reviewer, Oncology, 1990–present
Manuscript Reviewer, Transplant Proceedings, 1990–present
Manuscript Reviewer, Transplantation, 1990–present

PROFESSIONAL MEMBERSHIPS/ACTIVITIES

Professional Society Activities, with Offices Held
National and International
American Association for Cancer Research
American College of Physicians
American Society for Blood and Marrow Transplantation
American Society for Clinical Oncology
American Society of Hematology
Institute of Medicine
International Society for Cell Therapy
International Society for Experimental Hematology
International Society for Hematotherapy and Graft Engineering (ISHAGE), Vancouver, BC, Canada
The Transplantation Society
United States Food and Drug Administration, Washington, DC
Local/State
American Autologous Bone Marrow Transplant Registry (ABMTR), Milwaukee, WI
American Board of Internal Medicine Hematology Board (ABIM), Philadelphia, PA
American Society for Blood and Marrow Transplantation (ASBMT), Arlington Heights, IL
American Society of Blood and Marrow Transplantation (ASBMT), Arlington Heights, IL
American Society of Clinical Oncologist (ASCO), Alexandria, VA
Autologous Bone Marrow Transplant Registry, Milwaukee, WI
Autologous Bone Marrow Transplant Registry (ABMTR), Milwaukee, WI
Autologous Bone Marrow Transplant Registry (ABMTR), Milwaukee, WI
Foundation for Accreditation of Cellular Therapy, Omaha, NE
International Bone Marrow Transplant Registry (IBMTR), Milwaukee, WI
International Bone Marrow Transplant Registry (IBMTR), Milwaukee, WI
Leukemia Society, White Plains, NY
National Cancer Center Network, Rockledge, PA
National Marrow Donor Program (NMDP), Minneapolis, MN
National Marrow Donor Program (NMDP), Minneapolis, MN
National Marrow Donor Program (NMDP), Minneapolis, MN
Richard E. Champlin, M.D.

Nonmyeloablative Stem Cell Transplantation for Chronic Myelogenous Leukemia

Dr. Richard Champlin

MD Anderson Cancer Center, Houston, TX USA

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Allogeneic stem cell transplantation (BMT) is an established, potentially curative therapy for patients with CML. Its use has declined related to concerns related to toxicities and GVHD and because of the favorable results of imatinib and other tyrosine kinase inhibitors. Minimal residual disease is detectable in most patients treated with tyrosine kinase inhibitors and some have overt progression of their leukemia.

The efficacy of allotransplantation in CML is largely derived from the immune graft-vs-leukemia effect mediated by donor T cells. Nonmyeloablative conditioning has reduced the toxicity and treatment related mortality with allotransplantation, and allowed treatment of older and medically infirm recipients. Post transplant treatment with imatinib and donor lymphocyte infusions can produce durable molecular complete remissions in substantial fractions of patients who have persistent or recurrent disease.

•We hypothesized that sequential treatment using a nonmyeloablative preparative regimen followed by post transplant imatinib and later by DLI if necessary for residual disease would reduce the risk of treatment related mortality and achieve molecular complete remission and long term survival in patients with CML. Patients received a reduced intensity preparative regimen involving fludarabine 40 mg/m2 x 4 days, busulfan 130 mg/m2 x 2 days, and antithymocyte globulin (Thymoglobulin) 2.5 mg/kg daily x 3 days followed by allogeneic stem cell transplant from an HLA identical or one antigen mismatched related or unrelated donor. The regimen was designed to achieve engraftment with a low rate of GVHD and treatment related mortality. Patients with residual disease after 3 months by quantitative polymerase chain reaction analysis for Bcr-Abl received imatinib and those who did not achieve molecular CR within 3 months received escalating doses of donor lymphocyte infusion (DLI).

38 patients were entered, 33 have more than 6 months of follow up and are evaluable. Median age was 41 (22-69) years. All were previously treated with imatinib, 11 were in cytogenetic CR, 32 had detectable disease by PCR. 16 had early disease (in chronic phase or with isolated clonal evolution) and 17 had advanced disease (with prior accelerated phase or in second chronic phase after blast crisis). Median follow up time is 2.4 (.3 - 4.2) yrs. The regimen was well tolerated. One patient required a second transplant for rejection. 7 patient (21%) developed reversible grade 2-3 acute GVHD. None died within 100 days post transplant. At 3 months, all 16 early patients and 12 of the 17 advanced patients achieved cytogenetic CR and 4 and 2 had molecular CR respectively. 18 patients with residual or recurrent molecular residual disease after 3 mo and received treatment with imatinib; molecular CR was achieved in 8 of 9 early patients and 2 of 9 with advanced CML. 8 patients subsequently received DLI; 2 early patients achieved molecular CR. Of 6 advanced patients receiving DLI, 2 have a molecular CR, and 4 still have detectable disease by quantitative polymerase chain reaction. 25 patients are alive, including 15 of 16 with early disease (94%), all currently in cytogenetic CR, 10 in molecular CR. Of the 17 patients with advanced disease, 10 are alive (58%), 8 in cytogenetic CR and 5 in molecular CR. 6 advanced patients succumbed to blast crisis. We conclude that sequential therapy including nonmyeloablative allotransplantation, post transplant imatinib, and DLI was well tolerated and capable of prolonged cytogenetic remissions and survival.

2nd International Congress on Leukemia – Lymphoma – Myeloma

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ABSTRACTS

TURKISH SOCIETY OF HEMATOLOGY

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Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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AN OVARIAN MALIGNANT TERATOMA WITH PERIFERAL BLOOD AND BONE MARROW EXPRESSION MIMING ACUTE LEUKEMIA

[1]Borsaru Gabriela, [1]Barbu Doina, [1]Angelescu Silvana, [2]Ardeleanu Carmen, [1]Muraru Minerva

[1]Coltea Clinical Hospital Bucharest, Romania, [2]V. Babes Institute, Bucharest, Romania

ACUTE MYELOBLASTIC LEUKEMIA (149–156)

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Barbaros Şahin Karagün, İhsan Yüksekkaya, İlgen Şaşmaz, Bülent Antmen, Yurdanur Kılınç, Göksel Leblebisatan

Çukurova University Faculty of Medicine Deparment of Paediatric Haematology, Balçalı, Adana, Turkey

P14

UPREGULATION OF HERG1B GENE AND PRESENCE OF THE FUNCTIONAL HERG VARIANT K897T IN PEDIATRIC ACUTE MYELOID LEUKEMIA

[1]Merve Erdem, [2]Tuğçe Ayça Tekiner, [2]Arta Fejzullahu, [3]Sema Anak, [4]Uğur Özbek, [5]Fatmahan Atalar

[1]Yeditepe University, Genetics and Bioengineering Department, İstanbul, Turkey, [2]İstanbul Technical University, Molecular Biology and Genetics Department, İstanbul, Turkey, [3]İstanbul University, İstanbul School of Medicine, Department of Pediatric Hematology and Oncology, İstanbul, Turkey, [4]İstanbul University, Institute of Experimental Medical Research (DETAE), Genetics Department, İstanbul, Turkey, [5]İstanbul University, İstanbul Medical Faculty, Child Health Institute, Pediatric Endocrinology Department, İstanbul, Turkey

P15

EXPRESSION OF ADIPONECTIN AND ITS RECEPTORS IN PEDIATRIC ACUTE MYELOID LEUKEMIA: HIGH LEVELS OF T-CADHERIN AND LOSS OF ADIPONECTIN

[1]Arta Fejzullahu, [1]Tuğçe Ayça Tekiner, [2]Merve Erdem, [3]Sema Anak, [4]Uğur Özbek, [5]Fatmahan Atalar

[1]İstanbul Technical University, Molecular Biology and Genetics Department, İstanbul, Turkey, [2]Yeditepe University, Genetics and Bioengineering Department, İstanbul, Turkey, [3]İstanbul University, İstanbul School of Medicine, Department of Pediatric Hematology and Oncology, İstanbul, Turkey, [4]İstanbul University, Institute of Experimental Medical Research (DETAE), Genetics Department, İstanbul, Turkey, [5]İstanbul University, İstanbul Medical Faculty, Child Health Institute, Pediatric Endocrinology Department, İstanbul, Turkey

P16

RESULTS OF TREATMENT IN CHILD ACUTE MYELOID LEUKEMIA IN TUNISIAN PATIENTS

Aissaoui Lamia, Ben Naji Hend, Ben Amor Ramzi, Jeddi Ramzi, Kacem Karima, Bouteraa Walid, Ben Lakhal Raihane, Bel Hadj Ali Zaher, Ben Abid Hela, Meddeb Balkis

Aziza Othmana Hospital, Tunisia, Africa

P17

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[1]Tuğçe Ayça Tekiner, [2]Fatmahan Atalar, [1]Arzu Karabay, [4]Sema Anak, [3]Uğur Özbek

[1]İstanbul Technical University, Molecular Biology and Genetics Department, İstanbul Turkey, [2]İstanbul University, İstanbul Medical Faculty, Child Health Institute, Department of Pediatric Endocrinology, İstanbul, Turkey [3]İstanbul University, Institute of Experimental Medical Research (DETAE), Genetics Department, [4]İstanbul University, İstanbul Medical Faculty, Department of Pediatric Hematology and Oncology, İstanbul, Turkey

P18

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[1]Mehmet Sönmez, [1]Nergiz Erkut, [2]T. Songül Tat, [3]Figen Celep, [4]Ümit Çobanoğlu, [5]H. Önder Ersöz
[1]Karadeniz Technical University, School of Medicine, Department of Haematology, Trabzon, Turkey, [2]Karadeniz Technical University, School of Medicine, Department of Internal Medicine, Trabzon, Turkey [3]Karadeniz Technical University, School of Medicine, Department of Medical Biology and Genetics, Trabzon, Turkey, [4]Karadeniz Technical University, School of Medicine, Department of Pathology, Trabzon, Turkey, [5]Karadeniz Technical University, School of Medicine, Department of Endocrinology and Metabolism, Trabzon, Turkey

P19

EXPRESSION ANALYSIS OF THE MITOGENIC GROWTH FACTOR RECEPTORS IN CHILDHOOD ACUTE MYELOID LEUKEMIA; INCREASED EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-1 AND THE LOSS OF ESTROGEN RECEPTOR

[1]Fatmahan Atalar, [2]Tuğçe Ayça Tekiner, [3]Sema Anak, [4]Uğur Özbek
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P20

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[1]Mesut Ayer, [1]Banu Kılıçdaroğlu Dane, [1]Tülay Çalışır Omma, [1]Ömer Aydın Yıldırım, [1]Eray Atalay, [1]İsmail Cengiz, [1]Meryem Tahmaz, [1]Ayşegül Zobi, [1]Fatma Aylin Ayer, [1]A. Kadir Ergen, [1]A. Baki Kumbasar, [1]Makbule Ulusoy, [1]Yeşim Gürkan, [1]Naciye Demirel Yıldırım
[1]Haseki Training and Research Hospital, İstanbul, Turkey, [2]Okmeydanı Training and Research Hospital, İstanbul, Turkey

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[1]Meral Beksaç, [2]Rıdvan Ali, [2]Tülay Özçelik, [1]Muhit Özcan, [3]Osman Özcebe, [4]Mahmut Bayık, [5]Semra Paydaş, [3]Yahya Büyükaşık, [1]Osman İlhan, [2]Fahir Özkalemkaş, [1]Günhan Gürman, [1]Akın Uysal, [1]Hamdi Akan, [1]Ender Akçağlayan Soydan, [2]Ahmet Tunalı
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LAMIVUDIN PROPHYLAXIS IN HBSAg POSITIVE STEM CELL RECIPIENTS

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MISCELLANEOUS (181, 182)

P84

THE ROLE OF BODY MASS INDEX AND OTHER BODY COMPOSITION PARAMETERS IN EARLY POSTTRANSPLANT COMPLICATIONS IN PATIENTS WHO UNDERWENT ALLOGENEIC STEM CELL TRANSPLANTATION WITH THE CONDITIONING REGIMEN BUSULPHAN- CYCLOPHOSPHAMIDE

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ACUTE LYMPHOBLASTIC LEUKEMIA

P11

ADULT ACUTE LYMPHOBLASTIC LEUKEMIA: 10 YEARS OVERVIEW IN NORTHWEST OF IRAN

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Objective: Interest has recently been paid to adolescents and young adults with Acute Lymphoblastic Leukemia, particularly because all reports so far published indicate that these patients have a better outcome. Patterns describing incidence and survival rates for Adult Acute Lymphoblastic Leukemia documented in most of the world over the last 3 decades. Flow cytometry is the preferred method of diagnosing and immunophenotyping Acute Lymphoblastic Leukemia. The purpose of this retrospective study was to illustrate the spectrum of subtypes and the Immunophenotypic features of cases referred as ALL, aged 10 to 73 years in Tabriz Hematology and Oncology Research Center. Methods: Data of 102 adult ALL patients hospitalized in our institute between March 1998 and February 2008 were retrospectively reviewed. Bone marrow specimens were detected by FACS caliber, Becton Dickenson Flowcytometry method using of T, B cell series and myeloid and non lineage markers. The results were analyzed with the SPSS 13 software. Results: of the 102 (58 males and 44 females) diagnosed cases of ALL, 5 cases (4.9%) had L1 Morphologic subtype; 81 cases (79.4%) had L2 Morphologic subtype and 5 cases (4.9%) had L3 Morphologic subtype. The mean age at diagnosis was 25.49 year-old, 49 cases (48.0%) had Splenomegaly and 31 cases (30.4%) had Hepatomegaly. Tumor Lysis Syndrome has been seen in 12 cases (11.7%) . The mean Leukocyte count was 28.75 × 109/L, Hemoglobin mean 8.83 g/dl and Platelet count mean range was 76.60 ×103/µl. According to the results, CD19 in 34 cases (33.3%) and CD20 in 20 cases (19.6%) have been gathered. The most frequent positive T-cell marker was CD7 in 37 (36.3%). For Myeloid markers, CD13 in 12 (11.8%) was the most common, and CD33 in 14 (13.7%), and CD10 in 19 (18.4%), CD34 in 32 (31.1%), TdT in 14 (13.6%) and HLA-DR in 33 (32.0%) were positive. Conclusions: Multiparameter Flow Cytometry can not only provide data of cell lineage and differentiation status but also detect phenotypic aberrancies, which is helpful for analyzing the origin and differentiate status of lymphoblastic leukemia.

P12

AN OVARIAN MALIGNANT TERATOMA WITH PERIFERAL BLOOD AND BONE MARROW EXPRESSION MIMING ACUTE LEUKEMIA

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Malignant teratoma is a type of cancer that involves cysts that contain one or more of the three main types of cells found in a developing embryo. The ovarian teratoma is the most frequent abdominal teratoma described in women. We present here a case of 44 years old women who is been recovered with initial diagnosis-acute idiopathic thrombocytopenia but the clinical examination show an abdominal tumor. The peripheral blood show moderate leucocytosis (15100/µl) with the presence of big young cells with blast aspect (36%), with anemia (8g/dl) and sever thrombocytopenia (6.10°9/l). The coagulation analysis indicated disseminated intravascular coagulation. The same cells are present in the bone marrow in a significant percent (33%). The flow-cytometric examination of peripheral blood and bone marrow did not evidence any myeloid or lymphoid markers. The MRI examination of the abdomen and pelvis put the problem of a malignant teratoma. The surgical intervention performed confirms the MRI suspicion and the anatomopathological and immunohistochemical examination of tumor indicated a high grade of malignity. After the surgical intervention the peripheral blood aspect was maintained with the decrease number of young blast cells, anemia and thrombocytopenia. The patient died one month after surgical intervention by cerebral bleeding due to the thrombocytopenia by bone marrow failure and disseminated intravascular coagulation. We consider particular this case for the presence of bone marrow infiltrate with peripheral expression of teratoma cells with high grade of malignity miming acute leukemia.

ACUTE MYELOBLASTIC LEUKEMIA

P13

UNUSUAL PRESENTATION OF GRANULOCYTIC SARCOMA

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Granulocytic sarcoma is an unusual variant of myeloid malignancy in which there is an extramedullary tumor mass composed of myeloblasts and mature neutrophils. It may be found in any location throughout the body; however, intrathoracal and intracranial occurrence is extremely rare. It clinically may resemble lymphoma. This report describes a case of intratoracal and intracranial granulocytic sarcoma that developed secondary to MDS in a 10-year-old male. Case: The patient was diagnosed as having granulocytic sarcoma based on clinical, radiological, and histological findings. The intracranial tumor regressed significantly after two induction chemotherapy courses. But intathoracal mass that developed 9 months after bone marrow relapse. Granulocytic sarcoma diagnosed after the performing transthrosic biopsiy. The patient had been refracter to treatment and subsequently died due to anal abscess and sepsis. This case report affirms the importance of granulocytic sarcoma in the differential diagnosis of all sites of body like our case that have intracranial and intrathoracal mass. It is most common in the pediatric population and may present at any time in the course of the disease, either concurrently with the onset of leukemia or during a remission or relapse.

P14

UPREGULATION OF HERG1B GENE AND PRESENCE OF THE FUNCTIONAL HERG VARIANT K897T IN PEDIATRIC ACUTE MYELOID LEUKEMIA

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Expression of K^+ channels encoded by human ether-a-go-go related gene (herg) is reported to be deregulated in cancer cells compared to the healthy counterparts. HERG K^+ channels belong to multigene family of voltage activated K^+ channels and are significant in the regulation of cell proliferation. There are two HERG protein isoforms, HERG1 and HERG1B; a truncated form of the full length HERG1 protein encoded by herg1 gene, which are preferentially expressed on the plasma membrane of the tumor cells. Structurally and functionally compared to each other, the alternative transcript, HERG1B protein, displays a short N terminus and has different gating properties than HERG1. The herg gene is expressed in myeloid leukemia cell lines and in the majority of Acute Myeloid Leukemia (AML) cases. The activity of HERG K^+ channels is found to be effective in mitotic cycle in hematopoietic progenitor cells and herg up-regulation has been determined in leukemic cells but not in proliferating normal lymphocytes. K897T mutation in herg gene has been suggested leading to inhibition in the channel activity. The aim of the present study was to determine the expression levels of herg1 and herg1b genes by the quantitative real-time PCR (QRT-PCR) together with the analysis of a common HERG polymorphism (K897T) in 35 pediatric AML (pAML) patients. Our results suggest that herg1 expression is lower in pAML patients compared to the control group which is composed of CD33+ cells isolated from healthy bone marrows (2.5 fold). Herg1b expression was found to be higher in pAML patients (20 fold, $p<0.01$) compared to CD33+ control cells. The presence of HERG1 and HERG1B proteins in pAML patient samples was also confirmed by western blot analysis. We also studied the K897T polymorphism in 35 pAML patients by PCR analysis followed by an enzymatic digestion. We found the prevalence of 897K/T variant 37% in patients, where the presence of the common variant 897K/K was 63% among patients. Gene and protein expression studies showed the increased level of HERG1B expression in pAML patients. This increase confirms the previous findings about HERG currents displaying fast deactivation kinetics that may be attributable to expression of an N-terminal truncated HERG in cancer cells. Our result also revealed the presence of K897T variation in 37% of pAML patients. Interestingly, this polymorphism at codon 897, which is read as a Thr instead of a Lys, is known to create a phosphorylation site for the Akt protein kinase on the HERG channel protein. The studies about the role of this polymorphism in pAML are still ongoing. In conclusion, our results suggest the oncogenic potential of HERG K^+ channels and herg gene may be a molecular target for both prognosis and pharmacological therapy of pAML.

P15

EXPRESSION OF ADIPONECTIN AND ITS RECEPTORS IN PEDIATRIC ACUTE MYELOID LEUKEMIA: HIGH LEVELS OF T-CADHERIN AND LOSS OF ADIPONECTIN

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Adiponectin induces PI3K/Akt and Wnt/β-catenin pathways which regulate the growth and/or survival of cancer cells. Adiponectin works through its three cell surface membrane receptors AdipoR1, AdipoR2 and glycosylphosphatidylinositol-anchored extracellular protein, T-cadherin. Cadherins are shown to form complexes with β-catenin, being one of major components of Wnt/ β-catenin pathway, and this complex is known to be involved in the regulation of cell adhesion. This study aims to determine the expression level of adiponectin, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6); two major regulators of adiponectin production, AdipoR1 and AdipoR2 together with its third receptor T-cadherin in 24 pediatric acut myeloid leukemia (pAML) patients with quantitative real-time PCR (QRT-PCR). Our findings showed that the expression of the adiponectin was not detected in pAML patients compared to control group, CD33+ blasts isolated from healthy bone marrows. The expression of TNF-α was observed to be lower in patients than in control group. Contrary, the expression of IL-6 was detected to be significantly higher in pAML patients compared to controls ($p<0.01$). The expression of the AdipoR1 compared to controls was observed to be lower in pAML patients whereas the expression of AdipoR2 was found to be higher ($p=0.03$ and $p<0.01$). Besides, T-cadherin overexpression was determined in pAML patients compare to controls ($p<0.01$). The overexpression of T-cadherin led us to investigate its interaction with the β-catenin. Therefore, we studied the expression of β-catenin and its controlling proteins adenomatosis polyposis coli (APC) and glycogen synthase kinase 3 beta (GSK-3β). Interestingly, the expression of β-catenin was found to be significantly higher compared to controls ($p<0.01$). Whereas, the expression of APC was not detected. GSK-3β was observed to be three times higher than the control group. To our knowledge this is the first study showing the loss of adiponectin mRNA expression and the overexpression of T-cadherin in pAML patients. The loss of adiponectin expression was further confirmed by the altered level of TNF-α and IL-6 mRNA expressions, suggesting their role in the regulation of adiponectin. The high level of T-cadherin and β-catenin expressions

might lead us to speculate their possible role in cell-cell adhesion in pAML. The cross talk between adiponectin and β-catenin need to be further investigated in order to understand the interaction between PI3K/Akt and Wnt signaling pathways in the progression of pAML.

P16

RESULTS OF TREATMENT IN CHILD ACUTE MYELOID LEUKEMIA IN TUNISIAN PATIENTS

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Introduction: Acute Myeloid Leukemia (AML) is a relatively rare malignancy in the pediatric population, comprising only 15 to 20% of the acute leukemia diagnosed in this age group. It remains a challenging disease with an inferior treatment outcome compared with pediatric acute lymphoblastic leukemia. Despite high-dose cytarabine consolidation and allogenic bone marrow transplantation (BMT), about 40% of the children with AML still died of their disease. Patients and Methods: In department of hematology (pediatric and adult) of Aziza Othmana Hospital, among 156 children acute leukemia enrolled between January 2003 and June 2008, 26 (16.6%) de novo AML (Down's syndrome and FAB M3 excluded) were noted. The median age was 12 years (2.2-17); WBC was > 20x109/L in 11 patients. The diagnosis of AML was done by BM smears and immunophenotyping (CMF) using EGILE scoring. Karyotype was done in all patients and it was informative in 22 cases (85%). According to the Medical Research Council's Trial (MRC): 8 patients were classified into favorable or CBF leukemia,13 into intermediate group and only 1 into unfavorable. All patients were treated according to the French multicenter protocol ELAM02 with a common induction treatment by cytarabine and mitoxantrone than 3 courses of consolidation therapy among them 2 courses with high dose cytarabine. Patients in CR with HLA identical family donor have allogenic stem cell trasnsplantation. Results: Twenty two patients (85%) achieved CR after one course and 23 (88.5%) after 2 courses. Toxic death and induction failure were both at 7.7% . Fourteen patients had a matched sibling donors, but stem cell transplantation was done only in 6 patients because of problems of feasibility. Two of them died by GVHD but no relapse occurred in this group. Relapse occurred in 8 patients (36%) in median period of 9 months. EFS (18 months) was 65% . When studied separately, the patients with CBF leukemia who were treated by chemotherapy alone and all the other group who were treated by chemotherapy alone or chemotherapy with stem cell transplantation, the EFS (18 months) were respectively 83.5% vs 46.5% . OS (3years) was 59% . Conclusion: Despite of the low number of patients, our results seem to be near those reported in large studies, and to improve them more we had to indicate stem cell transplantation to more patients with a better management of graft complications.

P17

A SIGNIFICANT LOSS OF LEUCINE RICH REPEAT DOMAIN IN A NOVEL CANDIDATE TUMOUR SUPPRESSOR GENE PHLPP IN CHILDHOOD ACUTE MYELOID LEUKEMIA: MOLECULAR ANALYSIS AND EXPRESSION STUDIES

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The constitutive activation of PI3K/Akt signaling pathway has been implicated in both pathogenesis and progression of Acute Myeloid Leukemia (AML). Two key proteins control the termination of Akt signaling: PTEN, and PH domain and leucine rich repeat protein phosphatase, PHLPP. It has been previously shown that PHLPP levels are markedly reduced in a number of cancer cell lines. Human PHLPP contains four major functional domains; an amino-terminal PH domain, a leucine-rich repeat region (LRR), a PP2C-like catalytic core and a PDZ binding motif. So far, there are no described mutations in PHLPP gene. In this study, the architecture of PHLPP gene variations and the expression of four major functional domains of PHLPP gene together with PI3K/Akt pathway genes; Akt, PTEN and caspase-3 were examined. Mutation secreenings of 11 exons covering the four domains of PHLPP gene were performed in 38 pediatric AML (pAML) patients by DHPLC analysis. Mutation detection was accomplished by direct sequencing. The sequence variations are presented in Table1. The expression studies were performed by QRT-PCR in 35 pAML patients and in controls, CD33+ blasts isolated from healthy bone marrows. The results revealed that Akt was up-regulated in pAML patients (OR=4.4 95% CI=0.04-2.9, p=0.06). PTEN, PHLPP and caspase-3 were found to be decreased in pAML patients compared to controls (3 times (p>0.05), 10 times (p>0.05) and 3 times (p>0.05) respectively). Expression of PH domain, PP2C-like catalytic core domain and PDZ binding domain were detected both in pAML patients and in controls. Interestingly, expression of LRR domain in pAML patients was not detected. Amplification of PHLPP mRNA covering the region between exon 2 to exon 17 by conventional PCR in pAML samples lacking LRR domain expression resulted in identification of three different transcript variants. Direct sequencing results revealed a single nucleotide change in exon 5 at position 55 in those patients. Further studies were performed on the expression of four major functional PHLPP domains in various tumour tissues (colon, stomach, pancreas and breast tumours). In tumour samples, LRR domain expression could not be determined and PP2C like catalytic core expression was found to be lost. PHLPP mRNA transcript variants different than those observed in pAML samples were detected in tumour samples. Western blot analysis results also confirmed the loss of PHLPP expression in pAML patients and tumour samples. This is the first study evaluating sequence variations together with the expression of PHLPP functional domains. It can be

proposed that PHLPP gene might act as a tumour suppressor in AML leukomogenesis and tumorigenesis. This can provide an important guidepost for the development of appropriate diagnostic tools. The role of epigenetic regulation in cancer might explain the presence of PHLPP transcript variants in pAML and different tumour tissues. Therefore, the possible underlying mechanisms need further be studied.

Table 1. PHLPP gene sequence variations in pediatric AML

Exon	Base pair change	Amino acid change	Polarity change	Charge change	Frequency (%)	Reference
Exon 2	59insA	G→E	non-polar→ polar	neutral→ acidic	%5. 2	This study
Exon 2	60T>G	—	—	—	%2. 8	This study
Exon 2	77C>A	K→Q	—	neutral→ basic	%2. 8	This study
Exon 2	109A>T	K→STOP			%2. 8	This study
Exon 3	289C>A	P→T	non-polar→ polar	—	%7. 8	This study
Exon 3	352C>A	Q→K	—	basic→ neutral	%7. 8	This study
Exon 3	343insA	W→STOP			%2. 8	This study
Exon 5	599insA	S→R	—	neutral→ basic	%47	This study
Exon 14	1980T>C	—	—	—	%5. 2	This study
Exon 14	1992T>C	—	—	—	%5. 2	This study
Exon 17	3280C>A	L→M	—	—	%13. 1	This study
Exon 17	3302insA	—	—	—	%13. 1	This study
Exon 17	3303T>C	—	—	—	%13. 1	This study
Exon 17	3407insA	—	—	—	%5. 2	This study
Exon 17	3611insC	—	—	—	%7. 8	This study

P18

CAN A HIGH PLATELET COUNT BE RESPONSIBLE FOR DIABETES INCIPITUS IN ACUTE MYELOGENOUS LEUKEMIA WITH MONOSOMY 7 AND INVERSION 3 (q21q26)?

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Central diabetes insipidus (DI) and thrombocytosis are two rare events as a presenting symptom of acute myelogenous leukemia (AML). The mechanism of DI is not clear. Hemorrhage, thrombosis, infection or tumor cell infiltration of the pituitary or hypothalamus may be responsible factors for the etiology of DI. However, DI development is not observed in many patients with leukemic infiltration of the hypophyso-hypothalamic region. DI and AML with a high platelet count are usually associated with specific chromosome defects of monosomy 7 and/or inversion of chromosome 3 (3q21q26). A 26-year-old male patient was admitted to our hospital with polyuria, polydipsia, and fatigue. Physical examination was normal except pallor and dryness in his skin and mucosa. White blood cell count (WBC) was 3.500/μL with 32% blast. Hemoglobin (Hgb) level was 6.5g/dl and platelet (Plt) count was 1.788.000/μL. Bone marrow examination revealed hypercelluler marrow and infiltration with 37% blast cells plus micromegakaryocytes. Blastic cells were positive for especially CD13, 33. 34, HLA-DR, and myeloperoxidase (MPO) with immunophenotyping analysis. Diagnosis was AML with M2 morphology. Blood chemistry was as follows: sodium, potassium, creatinine, and lactate dehydrogenase were 146 mmol/L, 4.9 mEq/L, 1.1 mg/dl, and 466 IU/L, respectively. Serum osmolality was 295 mOsm/kg and urine osmolality was 112 mOsm/kg. Antidiuretic hormone (ADH) level was <0.5 pmol/L. DI diagnosis was confirmed after a water deprivation test. Oral desmopressin treatment, 0.1 mg twice daily, was begun and complaint of patient including polyuria and polydipsia promptly improved. Serum osmolality, urinary osmolality and serum sodium regressed to normal ranges. A Magnetic Resonance Imaging (MRI) scan of the brain showed no abnormality. Cytogenetic analysis of marrow blastic cells demonstrated 46, XY[10]/45, XY, inv (3) (q21q26), -7[3]. The remission induction regimen including idarubicin and cytarabine (3+7) was planned. After 8 days of induction chemotherapy, platelet count dropped to normal ranges and desmopressin requirement dissolved. Desmopressin was stopped. ADH levels raised to normal ranges. He had no laboratory or clinical evidence of DI in the following days of treatment period. Leukemic cells were observed persistently in bone marrow examination on day 28. He was accepted refractory to remission induction treatment and passed to salvage treatment regimes. In our patient, we observed that DI has improved when high platelet count, which is probably in a relationship with the defined cytogenetic abnormality, dropped to normal ranges. In conclusion, we think that high platelet count related to dysthrombopoiesis can interfere with the level of circulating arginine vasopressin.

P19

EXPRESSION ANALYSIS OF THE MITOGENIC GROWTH FACTOR RECEPTORS IN CHILDHOOD ACUTE MYELOID LEUKEMIA; INCREASED EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-1 AND THE LOSS OF ESTROGEN RECEPTOR

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Constitutive PI3K/Akt/mTOR signaling is upregulated by the activating mutations of receptor tyrosine kinases (RTKs), autocrine/paracrine secretion of growth factors (FGF, IGF-1, VEGF) and estrogens triggering the

binding of estrogen receptors alpha (ERa) to PI3K and estrogen receptor beta (ERβ) to AKT. Mutational analysis of FLT3 together with the expression analysis of vascular endothelial growth factor (VEGF) receptors (Flt-1, KDR [kinase domain receptor]), estrogen receptors (ERα and ERβ) and IGF system were performed in a group of newly diagnosed pediatric patients with AML. FLT3/ITD and FLT3/D835 mutations were performed on DNA material isolated from peripheral blood and/or bone marrow cells of 50 pediatric AML patients by PCR and enzyme digestion methods. Total RNA was also isolated from patients materials and the expression of FLT-1, KDR, ERα, ERβ and IGF system and the downstream target genes were analyzed by qRT-PCR and RT-PCR. FLT3/ITD and FLT3/D835 mutations have been identified in 12% and 2% of our study group, respectively. Flt-1 and KDR were expressed in 77.5% and 48.5% of pediatric AML patients, respectively. Flt-1 and KDR expression were significantly higher when compared with controls ($p>0.01$ and $p=0.02$ respectively). ERα expression was observed in 54.5% of the study group and diminished ERβ expression was determined in our study group. The expression of ERβ was also evaluated by western blot analysis in AML samples, in various tumours (breast, stomach, pancreas and colon tumours) and in healthy controls. IGF-1 expression was found to be 16.3 fold higher compared to CD33+ bone marrow cells. Expression of IGFBP-rP1 In AML patients was 10.48 fold lower compared to controls. IGF-1 was significantly higher in AML patients compared to peripheral blood cells ($p<0.001$) and CD33+ bone marrow cells ($p<0.01$). Conversely, IGF-2 and IGF-1R expressions were significantly lower compared to CD33+ bone marrow cells ($p<0.001$). Initiator caspases, Caspase8 and caspase9 expressions were also evaluated and the results revealed low level of expression of caspase9 compared to CD33+ bone marrow cells while caspase 8 expression showed 13.6 fold increase in AML patients compared to controls. B-catenin gene expression increased 5 fold compared to controls (OR=0.4; 95% CI=0.007-34.9 p= 0.02). In AML patients c-myc expression level was significantly higher compared to controls and cyclin D1 expression was not different in AML group as compared to normal controls ($p=0.3$). To our knowledge this is the first data representing the loss of ERβ gene expression in pediatric AML patients. Previous results of ERβ distruption in mice showed its important role in the development of myeloproliferative disease. The loss of ERβ in AML would shed the restrictive properties of this steroid receptor in the regulation of cell growth, death and motility. Our study showed that IGF-1 and caspase-8 could be potential antiapoptotic markers and IGFBP-rP1 is a new tumor suppressor for AML. Increased expression of β-catenin and C-myc and low expression of Cyclin D1 were also observed in AML patients. The increased expressions must be due to the phosphoinhibition of GSK3ß. The role of c-MYC in regulating Cyclin D-1 expression is complex, and its role need to be further studied in acute myeloid leukemia.

P20

PETHEMA PROTOCOL ADMINISTERED TO AN ACUTE PROMYELOCYTIC LEUKEMİA CASE IN THE SECOND TRIMESTER OF PREGNANCY

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A 29-year-old pregnant woman presented with gingival bleeding. At diagnosis, we established that 16 weeks of healty gestation and WBC: 3700/mm³, neutrophil: ‰57, lymphosit: ‰27, Hgb: 7.6gr/dl, Hct: ‰21, Plt: 20.000/mm³, LDH: 449 U/L, PT: 19.3 sc INR: 1.55 aPTT: 30.5 sc, fibrinogen: 33 mg/dl, D-Dimer: 4976 ng/ml. Peripheral blood smear evalution showed leukoerytroblastic viewing with atypical granular promyelocyts which contain Auer rods. Bone marrow examination of the patient who is considered Acute Promyelocytic Leukemia (APL) (AML-M3) +DIC syndrome; Discontinuance of myeloid series' maturation at promyelocyt phase, increased promyelocyts (‰50) that includes Auer rod, in addition to that by flowcytometric analysis determined CD13, CD33, CD117 and high ratio of MPO positiveness with the absence of HLA-DR, CD34 markers. FISH studies showed 96 of one hundred cells that were analysed had t (15; 17) (q22; q21.1) translocation. We referred to gynecology and genetic consultancy. ATRA and Idarubicine (PETHEMA) treatment commenced by approval of family. Pregnacy-related complications were not observed at weekly gynecological examinations and USG follow up. Bone marrow aspiration which was performed at 28th day of treatment of the patient who completed remission induction therapy determined hematologic remission and negativity t (15; 17) at FISH studies. We referred to genetic consultancy secondly and early consolidation therapy administered in accordance with PETHEMA protocol. There was not any complications related pregnancy during follow up. A healty female baby who had 2890 gr weight, 34cm head circumference was born at 37th week by normal spontaneous termination of pregnancy. About this case we considered that remission induction treatment which recommended to PETHEMA group can be achieve without complication at the APL cases that appearing during in second and third trimester of pregnancy.

P21

MULTIVARIATE ANALYSIS REVEALS BOTH FEMALE SEX AND GRANULOCYTE COLONY STIMULATING FACTOR USE DURING INDUCTION AS FACTORS THAT PROLONG SURVIVAL IN PATIENTS WITH DE NOVO ACUTE MYELOID LEUKEMIA: RESULTS OF A RANDOMIZED MULTICENTER PHASE III TRIAL

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Objectives: The effects of granulocyte colony-stimulating factors (G-CSF) on response and survival have been analyzed in many trials but roles of additional factors i. e patient gender and clinical prognostic factors have not been evaluated in a trial where G-CSF is given during remission induction therapy. This prospective multicenter clinical trial was designed, as a primary objective, to analyze the impact of G-CSF administered during and following induction chemotherapy on response and outcome. Methods: In this prospective phase III trial patients were randomized to receive induction therapy consisting of either cytosine arabinoside 100mg/m2/d, days 1-10 and idarubicin 12 mg/m2/d, days 1-3 (control arm) or plus G-CSF (Filgrastim, 5 µg/kg/d starting from day 8 until absolute neutrophil count over 0.5x109/L for two consecutive days) for a median duration of 14 days (G-CSF arm). Results: A total of 260 patients were enrolled in the study. Patients' characteristics, response, relapse and refractoriness rates were similar in both arms. Duration of fever and the use of antimicrobials did not differ between the arms. The duration of hospitalization was reduced by 4 days in the G-CSF arm compared to the control arm. Severity and duration of leukopenia was improved with G-CSF use; d 21 and d 28 leukocyte (x109/L) was higher in G-CSF arm [0.5 (0.1-9.6) vs 0.6 (0.1-37) p=0.08, 1.8 (0.1-9.3) vs 3.2 (0.1-55.9) p= 0.003]. The median survival in the G-CSF arm was longer than the control arm (239±81 vs 184±65 days, median) (Figure 1) (Tables 1 and 2). Conclusion: This study has shown that Filgrastim does not worsen the outcome. The results suggest that G-CSF, administered during induction therapy can decrease the time to neutrophil recovery, duration of hospitalization without adversely affecting toxicity or mortality. Subgroup analysis has shown some patients to benefit from G-CSF with a prolongation of survival. This possibility of better outcome in patients with AML-M2 and female gender, if confirmed by other groups may help to increase cost-effectiveness by limiting the use of GCSF to a subgroup of patients.

Table 1. Results of univariate and multivariate survival analysis

Parameter	p value Univariate[1]	p value Adjusted for G-CSF use[2]	p value Multivariate[3]	p value Multivariate[4]
M2	0. 013	0. 015	0. 63	NS
Induction cycle CR was achieved	<0. 0001	<0. 0001	<0. 0001	<0. 001
Gender	0. 006	0. 005	0. 87	0. 05
G-CSF	0. 38	-	0. 061	0. 049

Table 2. Impact of patient sex and G-CSF use on survival (C: Control arm, G-CSF: G-CSF arm)

Factors	Median OS days (SE)		P
All patients: male vs female	152 (35)	437 (150)	*P*= 0. 006
C: male vs female	136 (44)	407 (122)	*P*= 0. 037
G-CSF arm: male vs female	152 (60)	649 (NA*)	*P*= 0. 063
Male patients: C vs G-CSF	136 (44)	152 (60)	*P* = 0. 41
Female: CvsGCSF	407 (122)	649 (NA)	*P* = 0. 41

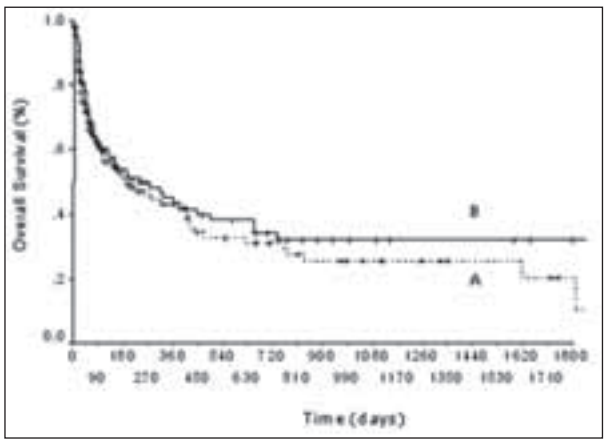

Figure 1. Overall survival of all patients in the G-CSF arm and control arm

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RECURRENT ACUTE PROMYELOCYTIC LEUKEMIA PRESENTING WITH HYPOPYON

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29-year-old male, fatigue, widespread body pain, gum bleeding and vision disorders, was admitted because of that. In the blood count, anemia, leukocytosis and addition that over the last 2 days to vision disorders, so the patient was admitted to hospital. At physical examination, common petechial rash on the limbs, decreasing vision, followed by focal intraretinal hemorrhage. WBC 32700, Hb: 5.1 gr/dl, Hct: ‰14.8, plt: 5000/mm3, PT, aPTT, Fibrinogen levels were normal deviation. Peripheral blood smear evaluation viewed ‰96 myeloblast/hypogranuler atipic promyelocytes. Bone marrow aspiration evaluation

viewed that hypogranuler atipic promyelocytes included rare auer rods. Flowcytometri as a resulted CD13, CD33, CD16+, CD56+, high ratio of MPO positiveness, with absence of HLA-DR and CD34 markers. With the highest rate in the myeloid markers, CD16+56+ and that the MPO positivity because of the findings were thought to be compatible with variant AML-M3. FISH studies was detected that t (15; 17) (q22; q21.1) translocation. These findings in patients with established diagnosis of APL was started PETHEMA protocol induction therapy. Treatment of the 30th day, the bone marrow examination in hematologic remission and FISH analysis in the t (15; 17) were negative deviation. Completed in accordance with the protocol of the early consolidation treatment of patients in the control FISH analysis t (15; 17) were negative deviation. Sustaining treatment on patients late 3rd month, in the bone marrow examination continue to remission and t (15; 17) was confirmed negative. In the ninth month of treatment the patient's right eye hypopyon examined, blood count were normal in this period. Peripheral blood and bone marrow evaluations findings did not belong to leukemia. In the morphological analysis of hypopyon, seen atypical hypogranuler promyelocytes similar to the cells 9 months ago diagnoses obtained from the bone marrow. FISH analysis of t (15; 17) were negative deviation. The case accepted extramedullary recurrence applied bilateral orbital radiotherapy after was started ATO (arsenic trioksit) treatment. The 7th day of treatment, patients who developed fever, dsypnea and in a short time has been lost because of respiratory insufficiency. Ocular lesions; menings and often appearing in the testis after the third is the localization of extramedullary involvement. These detected extramedullar involvement is very rare in hematologic and cytogenetic remission and with bad prognosis. Malignant cells, inoculated here at the beginning of the illness exist intraretinal bleeding, because of the blood-brain barrier chemotherapotics can not reach enough here and malignant cells in this region, was considered to be the source of later recurrence. Because of this case during to be recognized the eye findings may later provide extramedullar recurrence and it is thought to be appropriate will be provide extramedullar recurrence and it is thought to be appropriate will be prophylactic radiotherapy as an option would be to keep in mind.

P23

ISCHEMIC CEREBROVASCULAR EVENTS IN ACUTE LEUKEMIAS

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The risk of thrombosis is high in leukemia patients but thrombosis mechanism is not clear. These patients are generally presented with hypercoagulable state and disseminated intravascular coagulation without thrombosis and/or hemorrhage. The procoagulant state because of malignancy, cytotoxic treatments and infections are the factors causing coagulation activation. In acute leukemias, this situation is seen as localized venous/arterial thrombosis and serious thrombohemorrhagic syndrome. There is no guide for anticoagulant prophylaxis and treatment of these patients under high hemorrhage risk. Hemostasis disorders are generally seen in acute promyelocytic leukemia (APL). But arterial thromboembolism is seen rarely. We presented two acute leukemia patient with ischemic cerebrovascular event. First case, a 49 years old man with AML-M4 presented tonic-clonic convulsion and loss of consciousness. He had finished consolidation therapy with high dose cytosine arabinoside before 3 days. He had pancytopenia with hemoglobin 7.8 g/dl, white blood cell count 547/109/L, platelet count 13500/109/L. His serum glucose and electrolyte levels were normal. Cranial thomography revealed no hemorrhage. There was acute enfarkt in left precentral and postsantral gyrus, parietal and phrontal areas in cranial magnetic resonans examination. We gave him low molecular weight heparin with dose decrement because of thrombocytopenia. Dose adjusment was done according to daily platelet count. After antiepileptic treatment, his consciousness became normal. Motor deficit was determined in his right hand. We decided to investigate him for hereditary and aquired thrombophilia. Homocysteine was 16.15 u/mol, protein C 68 (% 70-140), protein S 121 (% 60-140), activated protein C resistance negative, antinuclear antibody negative, anticardiolipin IgG 5.9 (0-10) GPLU/ML, anticardiolipin IgM 2.2 (0-2) MPLU/ML, lupus anticoagulant 70 second (80-160), and antithrombine III 96 (% 80-120). His factor V leiden and prothrombin G20210A mutations were normal. Second case, a 45 years old man with AML-M1 complained numbness and weakness in the right half of body for 2 minutes. He had recieved consolidation therapy with high dose cytosine arabinoside before 10 days. He had pancytopenia with hemoglobin 10.5 g/dl, white blood cell count 1040/109/L, platelet. 21400/109/L. First neurologic examination revealed motor deficite in left upper and lower extremities and after a short time these findings became normal. His serum glucose and electrolyte levels were normal. Cranial thomography and magnetic resonance imaging revealed neither hemorrhage nor ischemia. Transthoracic echocardiography showed suspicious thrombus at the edge of jugulary central catheter. Transesophageal echocardiography revealed normal. We thought that he had transient ischemic attack and started low molecular weight heparin. We couldn't give antiagregant therapy because of thrombocytopenia. When platelet count increased, we gave him 1.

P24

TREATMENT OF EXTRAMEDULLARY RELAPSE IN ACUTE PROMYELOCYTIC LEUKEMIA WITH ARSENIC TRIOXIDE

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Extramedullary relapse (EMR) of acute promyelocytic leukemia (APL) is a rare clinical presentation. Central nervous system and skin are the major relapse areas. Here we present a patient who was in molecular remission for 2.5 years after treatment of APL and presented as an isolated mass in lomber spine. 46 years old female patient was diagnosed as APL in our clinic 3 years ago. WBC count was 780/mm3 and she had 80% t (15; 17) positivity in bone marrow aspiration sample. She had received 5 courses of all-trans retinoic acid (ATRA) ve idarubicin treatment. After the cession of therapy, peripheral blood samples obtained at every three months were negative for t (15; 17) with RT-PCR. After two and a half years, patient admitted to our hospital with back pain radiating to legs. Lumbar hernia was suspected and lumbar MRI

was performed. Beside a lumbar disc hernia, there were multiple nodular lesions in lomber spine located from L1 to S1. Tomography guided biopsy of L1 vertebra was reported as granulocytic sarcoma. Aspiration material from the same area revealed t (15; 17) positivity. Morphology of bone marrow aspiration and biopsy from iliac bone was normal but bone marrow sample was also positive for t (15; 17). Patient had no sign of other malignancy or mass lesion on systematic review of her body. According to these data, we cosidered the patient as extramedullary relapse of APL. The patient received concomitant oral all trans retinoic acid (ATRA) therapy and radiotherapy of effected areas. After radiotherapy ATRA was terminated and arsenic trioxide was started. At the end of the first month of treatment, lumbar lesions disappeared. EMR is a rare entity in APL. Metaanalysis are based on case reports. High leukocyte count on admission and receiving ATRA containing regimens as induction therapy are reported as risk factors for EMR in APL. In patients who received ATRA, overexpression of adesion molecules may be a possible mechanism of EMR. Systemic relaps occurs after a short period from EMR. Patients with recurrent EMR? s in different parts of their body are reported. There aren? t any guidelines for EMR in APL but general idea is to consider EMR as systemic disease. Radiotherapy of effected areas is recommended before or after systemic therapy. ATRA and chemotherapy or arsenic trioxide (ATO) with or without ATRA and gemtuzumab ozogamicyne added to these combinations are treatment alternatives. ATO is given at a dose of 0.15mg/kg/day for maximum 60 days. Complete remission rate is over 80% in systemic relapses. The complete response is observed usually on 30th day of the treatment. After first remission, consolidation treatment with ATO would be suitable in EMR as it is in systemic relapses.

P25

THE TELOMERE AND TELOMERASE SYSTEMS MAY PLAY A MAJOR ROLE IN THE ARSENIC-INDUCED CELL DEATH

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Objective: The exact mechanism of arsenic trioxide efficacy remains unknown, arsenic actions may result in the inhibition of growth and the induction of apoptosis. The aim of this study was to investigate the biological significance of the action of arsenic in regulating telomerase activity (TA) of leukemic cells and addressed whether the TA inhibition and telomere length (TL) shortening may play a role in the arsenic-induced cell death. Methods: The acute promyelocytic leukemia (APL) cell line NB4 was cultured in presence of different concentration of arsenic. Viability and growth inhibition of cell line were evaluated at different time points by morphology, cell count, and MTT cytotoxicity assays. Apoptosis effect of arsenic on NB4 model was evaluated by Fluorescent Microscopy and flowcytometery assays, using double-labeled Annexin-V/ PropidiumIodide (PI) and Hoescht-33342/PI dyes treatment, respectively. TA was assessed by TRAP-ELISA and –PAGE procedures. Terminal restriction fragment (TRF) length was determined by Southern blot analysis, using a Chemiluminescence-based assay. Results: During the therapeutic treatment of NB4 by arsenic, two levels of effects leading to the down-regulation of telomerase activity were identified. A slower repression of TA during longer-term treatment of NB4 cells by low dose of arsenic that lead to shortening of telomeres, growth arrest and cell death; a rapid down-regulation of telomerase activity after high dose of arsenic that lead to sudden growth arrest and cell death. Conclusion: These data suggest that arsenic trioxide at pharmacological concentrations exhibit anti-proliferative activities through the down regulation of telomerase, leading to telomere shortening and cell death.

P26

TELOMERASE ACTIVITY AND TELOMERE LENGTH IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA: CORRELATION WITH DISEASE PROGRESSION, PROGNOSIS AND OVERALL SURVIVAL

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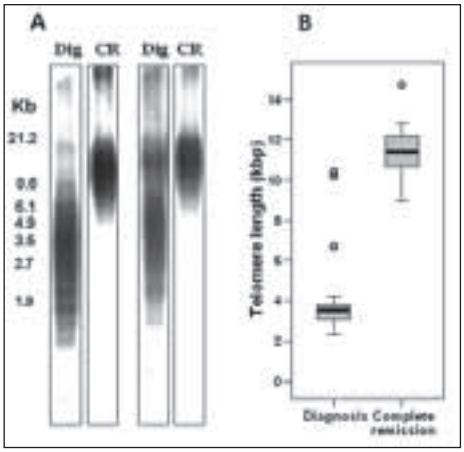
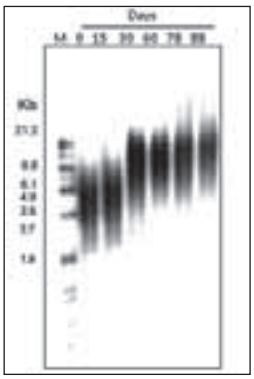
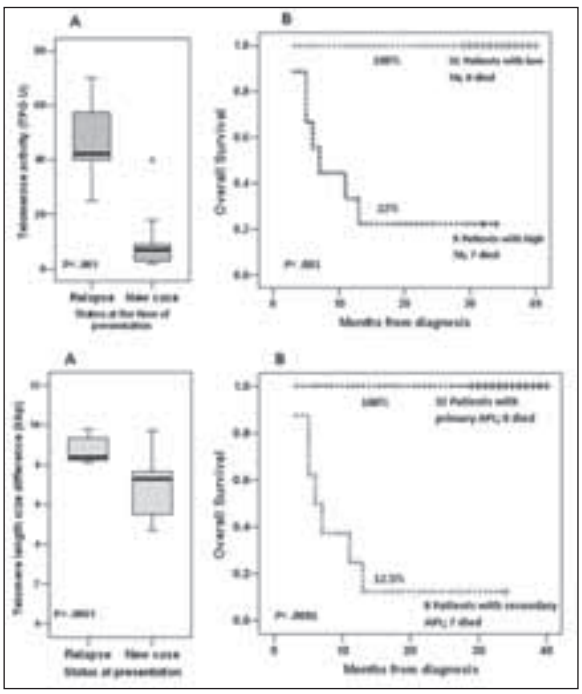
Objective: The telomeric DNA together with its associated proteins protects the chromosome ends from degradation or aberrant recombination. The progressive shortening of telomeres and the activation of telomerase have been considered to be one of the key mechanisms in cellular immortalization and tumor progression. The purpose of this study was to investigate the significance of telomerase activity (TA) and telomere length (TL) in patients with acute promyelocytic leukemia (APL). Methods: About 300 sequential peripheral blood mononuclear cell samples were collected from 40 patients with APL, at presentation, during and after therapy with Arsenic Trioxide. TA was assessed by TRAP and terminal restriction fragment (TRF) length was determined by Southern blot analysis, using a Chemiluminescence-based assay. PML-RARα/G6PDH transcripts were quantified by real-time PCR. Results: About 90% of the APL patients had a significant reduction in telomere length (TL) relative to the age-matched control or to that at the time of CR from the same patients (median 3.5 vs 11.37 kbp; $P<0.001$). A significance positive correlation between telomere length and PML-RARα expression was found in the APL patients ($P=0.001$). Telomerase was activated in all APL patients; however, significantly a higher level of TA was found in the group of relapsed patients than patient with newly diagnosed APL. The group of patients with shortened TRF and elevated telomerase activity had a significantly poorer overall survival. Conclusion: The shortened TL and elevated TA in APL patients are mainly indicative of extensive proliferative activity and they correlate with disease progression and relapse; thus, they may serve as prognostic factors for a subset of APL patients with more aggressive disease and poor outcome, those who may not respond favorably to arsenic therapy.



Telomere length in the APL patients at diagnosis and complete remission.



Profiles of telomere length changes in PB sample of patients with APL during and after treatment with arsenic trioxide.



Telomerase activity and Telomere length size difference and in PB samples of APL patients in relation to patient overall survival and patient status at the time of presentation (relapsed vs. new case).

CHRONIC LYMPHOCYTIC LEUKEMIA

P27

HLA-G EXPRESSION IN B CHRONIC LYMPHOCYTIC LEUKEMIA: A NEW PROGNOSTIC MARKER?

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Chronic lymphocytic leukemia (CLL) is characterized by a malignant clonal population of lymphocytes, which are usually of the B cell lineage. Classical Rai and Binet staging of CLL is being superseded by new prognostic markers. The mutational status of the immunoglobulin variable region heavy-chain genes segregates the disease into more benign and more malignant versions, and has been confirmed as an important prognostic marker in prospective clinical trials. A search for surrogate markers for this difficult-to-perform assay has led to flow cytometric assays for CD38 and ZAP-70 expression which are being widely used. The human leukocyte antigen G (HLA-G) molecule exhibits limited tissue distribution, low polymorphism that generate seven HLA-G isoforms. HLA-G exerts multiple immunoregulatory functions. Recent studies indicate an ectopic up-regulation in tumor cells that may favor their escape from anti-tumor immune responses. In this study we aimed to detect HLA-G with CD38 and ZAP-70 in B-cell chronic lymphocytic leukemia (B-CLL) patients. HLA-G expression was studied retrospectively in circulating B-CLL cells from 20 patients by flow cytometry using the anti-HLA-G specific monoclonal antibody MEM/G9. The proportion of leukemic cells expressing HLA-G varied from 1% to 34% . We detected a statistically significant correlation between HLA-G positive (>12%) and negative group with progression free survival (p=0.045), but no correlation in CD38 and ZAP-70. We also detected a statistically significant difference between Binet stage A; B and C (p=0.046) and a positive correlation between IL-10 and HLA-G (p=0.044). We conclude that positive HLA-G has an effect on progression - free survival, when compared with CD38 and ZAP-70.

P28

HEPATITIS B VIRUS REACTIVATION IN HBV-DNA NEGATIVE AND POSITIVE PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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Introduction: Reactivation of hepatitis B virus (HBV) is a frequent complication of chemotherapy (CT). We documented our prospective follow-up in 30 adult, HBsAg-positive patients with hematological malignancies. Patients and Metod: Patients were divided into two groups: baseline HBV-DNA negative (18 patients), and HBV-DNA positive (12 patients). Patients without viral replication were followed with HBV-DNA PCR and preemptive lamuvidine 100mg/day was commenced once HBV reactivation observed. Patients with viral replication received 100 mg/day lamuvidine at the initiation of the CT. Results: HBV-DNA negative group: The median number of CT

cycles was 5 (1-29). Eleven patients (61.1%) developed HBV reactivation after a median of 2 (1-15) CT cycles. Nine patients with HBV reactivation received lamuvidine treatment, and 2 patients were treated with famciclovir. Antiviral response was observed in 9 patients (81.8%). The median duration of antiviral therapy was 20.5 (2-64) months. During follow-up, CT regimen was interrupted in 3 patients due to HBV reactivation with elevated transaminase. Three patients developed HBV reactivation after lamuvidine withdrawal. HBV reactivation was not correlated with age, fludarabine and steroid containing regimens (p>0.05), but more frequent in CLL patients (p=0.008) and rituximab containing regimens (p=0.06). HBV-DNA positive group: At the baseline, HBeAg positivity was found in 4 patients, ALT elevation was determined in 4 patients, and median HBV-DNA titres was 1,1x107 (1x104-4.5x108). Patients received a median of 4.5 (2-17) CT. Eleven patients responded to lamuvidine (91.6%). The median duration of antiviral therapy was 7.5 (2-29) months. We observed that HBV reactivation based on regular follow-up of HBV-DNA titre developed during CT in 4 patients (50%) after a median of 3 (1-6) cycles, and after lamuvidin withdrawal in 2 patients. Three patients who experienced HBV reactivation during CT were positive for YMDD mutation, and they responded to adefovir. None of the patients interrupted CT due to HBV reactivation. HBV reactivation was not correlated with age, primary diagnosis, baseline HBV-DNA titres, HBeAg positivity, steroid, fludarabine and rituximab containing regimens (p>0.05). Discussion: HBV reactivation risk is frequent in patients with hematological malignancies receiving CT. The risk is increased in patients receiving rituximab containing regimens and in patients with CLL. Despite a high rate of HBV reactivation, mortality was low and there was a high response rate to lamuvidine in HBV-DNA negative group in our patients. HBV-DNA positive patients at the baseline also had a high response to lamuvidine, but reactivation during or after the cessation of lamuvidine is frequent. Nucleoside analogues with a lower risk of resistance like entecavir may improve the results in this patient group.

P29

CHOLESTEROL LEVELS IN UNTREATED PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Hypocholesterolemia is seen in solid tumors and some hematological malignancies such as multiple myeloma. In a few experimental studies, decrease in the levels of serum cholesterol was reported in chronic lymphocytic leukemia (CLL). Aim of the study: To evaluate the lipid parameters in untreated patients with CLL. Material and Methods: According to International CLL Working Group, thirty-eight patients with CLL (23 male with mean age 64 ± 10 years) were diagnosed. In control group, there were 71 healthy persons (42 female, mean age 55 ± 9 years). Lipid parameters including total cholesterol (TC), high-density cholesterol (HDL-C), very-low density cholesterol (VLDL-C), and triglyceride (TG) were studied in both groups. Student-t test was used for comparison of two groups. Values of p<0.05 were accepted as significant. Results: The levels of TC, LDL-C and HDL-C in patients with CLL were lower than control group (p<0.001). But the levels of VLDL-C and TG were not different (p>0.05). Conclusion: Hypocholesterolemia are seen in patients with CLL. Hypocholesterolemia may be due to increased LDL clearance and utilization of cholesterol by lymphocytes.

P30

A CASE OF SEVERE APLASTIC ANEMIA CAUSED BY A COMBINATION THERAPY OF FLUDARABINE AND CYCLOPHOSPHAMIDE IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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OBJECTIVES: Fludarabine and cyclophosphamide is one of the widely accepted most effective chemotherapy schemes used in chronic lymphocytic leukemia (CLL) 1. Although myelosuppresion and infections are observed frequently during treatment, severe aplastic anemias and pancytopenias refractory to growth factors are rare2. Here we report a patient with CLL who developed severe aplastic anemia during fludarabine and cyclophosphomide therapy. CASE REPORT: A 44-year-old male patient was diagnosed as chronic lymphocytic leukemia (Rai stage 2) in 2005. He was followed up at our outpatient clinic without any treatment until february 2007. On February 2007 he was admitted to the cardiology clinic with dyspnea and chest pain. Pericardial effusion was found. Pericardiocentesis and biopsy was performed and he was diagnosed as pericarditis due to CLL. The combination treatment with fludarabine (25 mg/m2/day for 5 days po) and cyclophosphamide (200 mg/m2/day for 5 days po) was initiated on April 2007. Leukopenias responsive to growth factors were observed on every course of therapy. The patient became pancytopenic after the fifth course. The complete blood count values were as follows, WBC: 1400/µL (with 1000 neutophils), hemoglobin: 7. g/dl, platelet count: 31000/µL. One week after the last neutropenic episode, the patient was hospitalized with neutropenic fever. Supportive therapy including antibiotherapy, growth factors and parenteral fluids were administered. He had still severe pancytopenia during his hospitalization period (WBC: 100/µL with 18% neutrophil, hemoglobin: 4.9 gr/dl, MCV: 93fl hemotocrite: 14.1% and trombocyte: 2000/µL). There was no sign of infection which could explain the pancytopenia. His viral markers including CMV, EBV, HIV and hepatitis viruses were all negative as well as direct and indirect coomb tests. Vitamin B12, folic acid and iron parameters were within normal limits. Bone marrow aspiration and biopsy showed aplastic bone marrow with a cellularity of 10% . The flow cytometric analysis were unremarkable for CLL. The patient died because of septic shock at the 77th day of the neutropenia despite he was in remission for CLL. He was not a good candidate for bone marrow transplantation since his performance status was poor. CONCLUSION: Leukopenias and infections due to myelosuppresion are frequent during fuludarabine therapy. But close attention must be paid for a possible aplastic anemia in case of prolonged cytopenias.

P31

ATYPIC PRESENTATION OF TUBERCULOSIS IN HAIRY CELL LEUKEMIA

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A 49 years old male patient refered to our clinic because of fever and pancytopenia. He had also elevated ESR (140mm/h) and hepatosplenomegaly. Bone marrow aspiration was dry-tap. Bone marrow biopsy and flow-cytometric analysis was resulted in hairy cell leukemia. Pulmonary infitration was seen at chest x-ray and there was a mass which was placed at left pulmonary lingular segment surrounding pulmonary artery and infiltrate to pleura and mediastenium at CT. Biopsy procedure from the mass applied two times and resulted nondiagnostic. We couldn't exclude lung cancer. Bronchoscopy, bronchoalveolar lavage cytology and mediastinal biopsy was negative for cancer and spesific infection. Tuberculosis history and sputum AARB was negative. The patient was treated with Cladribine. Fever and hepatosplenomegaly regressed and pancytopenia resolved. But pulmonary mass remained stabile after treatment. New biopsy was evaluated as nonspesific abscesses. One month later the patient admitted to our clinic with fever and neutropenia. Bone marrow examination was normal. There was progresion at pulmonary mass. Although sputum AARB result was (-), therapy for tuberculosis begun with 4 drugs because of clinically high suspicion of tuberculosis. M. tuberculosis was isolated at culture. The patient recovered and mass regressed at two months anti tbc treatment. Conclusion: Diagnosis of tuberculosis and/or mycobacteria infection is particularly difficult in immunocompromised patients. Because of this we must always remember tuberculosis in these patients evenif with atypic presentation.

P32

RETROSPECTIVE ANALYSIS OF 33 CLL CASES FOLLOWED BETWEEN 2006-2008 IN ANKARA ONCOLOGY HOSPITAL

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CLL is a malignant disease of bone marrow characterized by infiltration of hematolymhoid organs by small lymphocytes derived from relatively mature cellular period of B or T lymphocytes. In the present study, 33 cases followed with the diagnosis of CLL between 2006-2008 in our center were evaluated retrospectively. 15% (n=5) of the cases was female and 85% (n=28) male. Median age of diagnosis was 61 (35-80). All cases were evaluated as B-CLL immunophenotypically. In 9% (n=3) of the cases, Hbs Ag was present. Anti HCV and anti HIV was found to be negative in all cases. The number of cases who were in stage 0,1,2,3, and 4 according to RAI staging system were respectively n=6, n=10, n=13 and n=4. When the same cases were classified according to Binet system, the number cases who were in class A, B and C was respectively n=5, n=22 and n=6. In 9% (n=3) of the cases, hemolytic anemia was established. 30% (n=10) of the cases were followed without treatment and 70% (n=23) received chemotherapy. They were administered chemotherapy in mean 1 (0-5) steps. Chlorambucil+prednisolone, CVP, CHOP, fludarabine, fludarabine+cyclophosphamid, rituximab+fludarabine+cyclophosphamid, alemtuzumab regimes were administered in respectively, 39% (n=13), 33% (n=11), 21% (n=7), 9% (n=3), 27% (n=9), 3% (n=1) and 6% (n=2) of the patients. No patients was included in autologous or allogeneic stem cell transplantation programs. In the follow up period, 2 patient died because of progressive disease and one of CMV pneumonia developing during alemtuzumab treatment. CLL is malignant disease which can not be cured by methods other than allogeneic stem cell transplantation. Present treatments do not improve survival. In our clinic, present treatment approaches are taken into account and our studies on novel treatment approaches are in progress.

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NEUROTOXICTY WITH CEFEPIME IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Cefepime is a forth generation broad spectrum antibiotic used in pneumonia, febril neutropenia, urinary system infections, intraabdominal, skin and soft tissue infections. Side effects of cefepime are nause, vomiting, diarrhea, constipation, hypersensitivity reaction, headache and fever. Drug related neurotoxicity was reported with other cephalosporins such as ceftazidim, ceftriaxon, and cefuroxim more frequently than cefepime. Cefepime related convulsion was seen in 1/10000 of patients and confusion 1/1000. We presented a patient developed neurotoxicity after cephepime. A 55 years old man with chronic lymphocytic leukemia and chronic renal disease presented shortness of breath and caugh with sputum for 2 days. He had recieved 5th course of fludarabine and cyclophosphamide therapy. His oxygen saturation was found 83% and directly chest graphy showed pneumonic infiltration in upper lobes. We started ceftriaxon and increased dose of trimetoprim sulphometaxazole His complaints decreased after this treatment but after one week, his fever and sputum repeated. His directly chest graphy and thomography revealed new infiltration. We stopped ceftriaxon and started piperacillin tazobactam empirically. Because sputum culture revealed Acinetobacter boumanni, piperacillin tazobactam changed with cefepime. His renal function tests increased and he needed hemodialysis and ultrafitration. After 24 hours from cefepime, acute phase reactants decreased, his clinical condition improved but on the 3'th day of treatment his speech deteriored. Loss of cooperation, orientation and myoclonic convulsion were seen. He was recieving omeprasole, N-acetylcystein, granulocyte colony stimulating factor, theophilin, salmoterol, and fluticasone propionat. There was no pathology which could explain this situation in cranial thomography and magnetic resonans imaging. We thought that neurologic symptoms had developed because of cephepime and we stopped cephepime. Doxicyclin was started. After 24 hours interrupted cefepime, his neurologic condition changed normal completely. Neurotoxicty is a well known but rarely seen side effect of cephalosporins. However the mechanism of neurotoxicty is not exactly known. Increase in endotox-

ins, and cytokines, depletion of inhibitor mediators like gama aminobutyric acid are thought to be reponsible. Neurologic symptoms related to cefepime was reported as confusion, convulsion, agitation, tremor, delirium and coma. These symptoms were reported generally patients with renal failure. Duration from drug using to symptoms was reported as 1-10 days, from drug stopping to normalisation of symptoms was 2-7 days. Clearance of cefepime is from kidneys and it should be given with dose adjustment in renal failure. Generally cliniceans don't recognize cefepime induced neurotoxicty and diagnosis is delayed. This advers effect should keep in mind especially patients with renal failure, cefepime should be given with dose adjustment and when neurotoxicty is

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ELEVATED INTRACELLULAR CYTOKINE LEVELS IN A PATIENT WITH SEVERE PRURITUS DURING THE COURSE OF CHRONIC LYMPHOCYTIC LEUKEMIA: A CASE REPORT

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Pruritus during the course of chronic lymphocytic leukemia (CLL) has various causes, and leukemic infiltration of skin and autoimmune skin disorders are common among the others. This report describes a patient with CLL who developed severe pruritus without any primary skin changes and had a complete response to chemotherapy. Intracytoplasmic cytokine levels of CD20+ B lymphocytes were evaluated by flow cytometry. Compare to the healthy subject the levels of IL-4, IL-5, IL-13, IL-10 and IFN gama were increased in the patient. IL-4, IL-5, and IL-13 are known to be effective in the class switch to IgE during antibody response. These findings suggested that increased expression of these cytokines by leukemic lymphocytes might play a role in the development of pruritus as a paraneoplastic syndrome in this patient with CLL.

CHRONIC MYELOID LEUKEMIA

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A CASE OF CHRONIC MYELOGENOUS LEUKEMİA IN BLASTIC CRISIS PRESENTING WITH UNUSUAL CLINICAL FEATURES

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Chronic myeloid leukemia (CML) is a clonal hematological stem-cell disorder characterized by the Philadelphia chromosome (Ph) which is present in about 95% of CML patients. The natural history of the disease is progression from a chronic phase to an accelerated and/or blast phase within 2 to 5 years of the initial diagnosis. Cytogenetic abnormalities in addition to the Ph chromosome develop in about 80% of CML patients in blast crisis. We report here a 26-year-old woman without a history of hematological disease. . The patient was referred to our Centre for leucocytosis and fever. She reported excellent health before two weeks. She was reported to have fever (38-38,5 0C) for ten days. She had no signs or history of hematological diseases. On physical examination showed significant bilateral multiple cervical (4 cm), submandibular (2cm), axiller (3 cm) lymphadenopathies. There were no hepatosplenomegaly on physical examination and ultrasonography. On Admission blood counts showed marked leucocytosis: WBC 66.9 × 109/l hemoglobin 81 g/l, platelets 257×109/l. The initial peripheral blood smear revealed 25% stabs, 65% neutrophils, 8% lymphcytes, 1% monocytes, and 1% eosinophils. Myeloblasts were not noted. Routine chemistry tests were unremarkable. Bone marrow evaluation revealed hypercellular, with 33% of blasts. Immunophenotypic analysis of blasts showed positivity for CD11b (92%), CD13 (59%), CD33 (93%), CD34 (32%), MPO (42%) and HLA-DR (80%) and negativity for CD2, CD3, CD7, CD19, CD20, and TDT. Cytogenetic analysis showed the presence of Philadelphia-chromosome 46 XX, t (9; 22) (q34; q11) in 100% of metaphases studied. Classical bcr–abl rearrangement. (210 kDa protein) was detected by reverse transcription polymerase chain reaction (RT-PCR). There was not additional genetic changes. According to these findings a diagnosis of CML in blastic phase was made. She was treated with standard 3+7 (anthracycline/ cytosine arabinoside) induction regimen plus imatinib (600mg daily) . After the first course of chemotherapy the patient achieved a complete remission with less than 5% blasts in thebone marrow and normalized peripheral cell counts. In conclusion, we have presented a case of Philadelphia positive CML in blast crises lacking the typical clinical and laboratory features of CML.

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CHRONIC MYELOCYTIC LEUKEMIA: SINGLE CENTER IMATINIB MESYLATE EXPERIENCE

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Chronic myelocytic leukemia (CML) is a clonal stem cell disease and is characterised by uncontrolled proliferation of mature granulocytes and their precursor forms. It is associated with characteristic chromosomal translocation termed as Philadelphia chromosome. Imatinib mesylate is bound with amino acids at the region of ABL kinase and leads BCR-ABL protein to remain inactive by preventing the binding of adenosine triphosphate. 12 patients who were newly diagnosed with CML between June 2006 and December 2008 and followed regularly were evaluated retrospectively in terms of clinical course and response to treatment. of 12 patients, 9 was female and 3 male. Median age of the patient was found to be 52 (Range 21-74). Mean duration of follow up was 12 months (3-18). In all of the 12 cases, complete hematological remission was obtained. 3 patients are being followed in complete molecular remission and 5 in major molecular remission. 4 patients are on the 4th month of treatment, being followed with complete hematological remission. Intolerance developed in 2 of the patients in whom molecular remission was achieved. Nilotinib was initiated

in one and dasatinib in the other. In both cases, hematological and molecular remission was obtained. Imatinib mesylate is a safe and reliable agent in the treatment of CML. However, the most important problem seems to be the development of intolerance and resistance.

HODGKIN'S LYMPHOMA

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IMMUNE THROMBOCYTOPENIA IN HODGKIN'S DISEASE

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Autoimmune complications like immune thrombocytopenic purpura may be seen during the course of lymphoproliferative disorders most prominently secondary to chronic lymphocytic leukemia and other non-Hodgkin lymphomas. Here we describe a rare case of a-21-year-old woman who had developed autoimmune thrombocytopenic purpura one year after completion of Hodgkin lymphoma therapy for stageIIA disease. She was treated with pulse prednisolone and intravenous IgG with no response. During hospitalization period she experienced intracranial bleeding with mild mental changes. Splenectomy dramatically normalized her platelet count. Searching few similar reports in the literature we observed that conventional first-line treatment modalities as applied in idiopathic thrombocytopenic purpura cases are not usually effective in cases with immune thrombocytopenia in the setting of Hodgkin's disease and splenectomy might be considered more earlier in these patients.

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AUTOLOGOUS TRANSPLANTATION FOR HODGKIN'S LYPHOMA: A SINGLE CENTER EXPERIENCE

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High dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is now the accepted therapy for most patients with Hodgkin's lymhoma (HL) that is not controlled by conventional chemotherapy and can result in long term progression free survival (PFS) in a significant proportion of patients. A retrospective study was carried out in a group of 25 patients with relapsed and refractory Hodgkin's lymphoma who underwent high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) at our institution between 1/2007 and 12/2008. M/F ratio was 15/10, median age was 32.6 (range 17-46). According to Rye classification frequency of hystologic subtypes was as follows; 60% nodular sclerosis, 36% mixed cellularity,% 04 lymphocyte predominant. Median time from diagnosis to transplant was 46 months except one patient. This time was 204 months in one patient. The disease was sensitive to the chemotherapy administered immediately prior to transplantation in 17 patients and resistant in 8 patients. The mobilization regimen was cyclophosphamide + G-CSF in 15 patiens, G-CSF in 5 patients, ICE + G-CSF in 3 patients and DHAP + G-CSF in 2 patients. Conditioning regimen consist of high dose ICE in 15 patients and BEAM in 10 patients. Toxicities were similar in two regimens. The median time to neutrophil and thrombocyte engraftment was not different between two conditioning regimens. We evaluated the patients after 3 months from ASCT. There were 6 (40%) complete response, 2 (13%) partial response and 7 (46%) stable disease in 15 patients treated with high dose ICE regimen and 3 (30%) complete response, 4 (40%) partial response and 2 (20%) stable disease in 10 patients treated with BEAM regimen. One patient (10%) died on + 7'th day because of GIS bleeding. 5 of the 9 patients (56%) with stable disease after ASCT were evaluated as chemorefractory disease before high dose chemotherapy. We obtained 47% complete response, 24% partial response in patients with chemosensitive disease and 1 (12%) complete response and 2 (25%) partial response in 8 patients with chemorefractory disease.5 of 8 patients with complete response after ASCT were still disease free after 6 months. Conclusion: High dose chemotherapy followed by autologous stem cell transplantation is an effective treatment for chemosensitive Hodgkin's lymphoma. HDC also may be a therapeutic approach for chemorefractory Hodgkin's lymphoma.

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ALLOGENEIC STEM CELL TRANSPLANTATION FOR HODGKIN'S LYMPHOMA

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Prognosis of Hodgkin's lymphoma patients who showed early relapsed after autologous hematopoietic stem cell transplantation is dismal. In this study, we retrospectively analyzed eleven refractory/relapsed Hodgkin's lymphoma patients who underwent allogeneic hematopoietic stem cell transplantation (AHSCT) in our unit. Median age of the patients were 29 (24-46). Female/Male ratio was 8/5. Three patients were in chemosensitive relapse and 8 were chemorefractory before the transplant. All patients had autologus hematopoietic stem cell transplantation before AHSCT. Median number of chemotherapy regimens before AHSCT including high dose therapy/autologous stem cell support was 5 (range 3-8) Median time from diagnosis to AHSCT is 40 (11-135) months. Median time from autologus transplantation to AHSCT is 14 (3-27) months. Nine patients had reduced intensity (fludarabine+melphalan) and two had myeloablative conditioning regimens. Stem cell source was either HLA matched sibling (8 patients) or HLA matched unrelated (3 patients) donors. Except two, stem cell collection was performed from the peripheral blood. Median number of CD34+ cells infused was 6.7x10e6/kg (range,3.31-9.60x10e6/kg). Cyclosporine+ Mycophenolate mophetile was the main regimen used for GVHD prophylaxis (5 patients). Median follow up period was 9 (2-24) months. Five patients (45%) died during the follow up (one had CMV pneumonitis and sepsis, three had disease progresssion and one had bronchiolitis obliterans) . Six patients are stil alive. Three had complete remission, one had partial remission (CR+PR; 36%), one had stable disesase. The last patient had disease progression at day +60. Five patients had acute GVHD (45%) and 4 had (36%) chronic GVHD. This limited data shows us that AHSCT is a viable option for younger Hodgkin's lymphoma patients who relapsed after autologous transplantation.

NON-HODGKIN'S LYMPHOMA

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PULMONARY EMBOLISM AS THE FIRST SIGN OF PRIMARY PERITONEAL LYMPHOMATOSIS: CASE REPORT

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Introduction: In patients with a malignant disease the risk of thromboembolic complications are demonstrably increased Fatal venous thromboembolism (VTE) in high grade non-Hodgkin's lymphoma (HG-NHL) is rare, but VTE is associated with an unfavourable clinical course of HG-NHL In this report we aimed to demonstrate a fatal pulmonary embolism as the first sign of primary peritoneal lymphomatosis. Case report: A 56 year-old male admitted to our emegency department with sudden-onset dyspnea, tachypnea and tachycardia with retrosternal pain. His shortness of breath and chest pain continued throughout the night. There was no history of trauma, fever, cough, asthma, or travel. Examination showed a heart rate of 102 bpm, a respiratory rate of 17 breaths per minute, blood pressure of 135/79 mm Hg, a temperature of 36.6°C, The arterial blood gas showed a pH of 7.43, PaCO2 of 27 mmHg, PaO2 of 87 mmHg, SaO2 of 97% on room air. He was in mild to moderate distress, breathing through pursed lips intermittently; he was ambulatory and talking. The cardiovascular examination was normal. The lungs were clear to auscultation.. There was no extremity tenderness or swelling. Specifically, there was no calf tenderness, and Homan's sign was negative bilaterally. Chest radiographs and electrocardiogram were normal. A computed tomography (CT) scan showed bilateral pulmonary emboli. Doppler ultrasonography revealed bilateral deep venous thrombosis of the common femoral, superficial femoral, and popliteal veins. Anticoagulation with low molecular weight heparin (LMWH) was initiated. On the third day he suffered from adbominal distension and tenderness. Abdominal examination showed hardness and distension. Ascites and thrombosis of the vena cava inferior revealed by sonographic examination. Parasynthesis revealed a haemorragic fluid. Vena caval interruption was performed preventing from recurrent emboli. The diagnosis was first established by cytologic examination of ascit fluid, which showed neoplastic cells consistent with malignant lymphoma. Flowcytometric examination showed CD 20 (+) diffuse large B-cell lymphoma. A CT scan of his abdomen demonstrated colonic wall thickening and oedema. Colonoscopy revealed no mass or mucosal abnormality. The final diagnosis was primary peritoneal lymphomatosis. We planned to apply the patient R-CHOP protocol. But the patient did not live long enough to receive chemotherapy. Discussion: The relationship between cancer and abnormalities of blood coagulation has been recognized for well over a century. Deep venous thrombosis (DVT) of the lower extremities is the most common cause of thromboembolic disease, but pulmonary embolism, upper extremity vein thrombosis, disseminated intravascular coagulation, and other, more unusual, clinical events, may occur. Clinical analysis documented a 6.6% incidence of VTE, and 77% of all cases occured before or within the first 3 months of chemotherapy in HG-NHL. Conclusion: This report describe an uncommon clinical presentation of HG-NHL. Pysicians should be careful with unexplained VTE. Because this may be harbinger of an occult malignancy.

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PRIMARY NON-HODGKIN LYMPHOMA OF SPINE: A CASE REPORT

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Introduction: Primary bone lymphomas (PBLs) comprise about 3% to 7% of all malignant bone tumors, less than 5% of extranodal lymphomas, and less than 2% of all lymphomas in adults, respectively. PBLs occur most often in the femur, spine and pelvic bones, but in rare cases can also affect the small bones of the limbs. The incidence of a single vertebral lesion is thought to be% 1,7 of all PBLs. Diffuse large B-cell lymphoma makes up the majority of PBLs cases. We present a 31 year old male patient admitted because of progressive norological deficit. Magnetic resonance imaging (MRI) showed severe destruction of the body of thoracal 6 vertebrae, with a bulky mass growing into paravertebral area. Diagnosis is established on histopatological examination of the tissue sample obtained during the operation. Case report: A 31-year old previously healthy man was admitted to our orthopaedy clinic with torachal pain and progressive norological deficit. This condition had been present for 5 months before his admission. Examination showed severe motor weakness, sensory loss was found below his nipple (T4), furthermore his biceps, triceps and brachioradial reflexes were decreased. There was no B symptoms. Except high LDH lactic dehydrogenase level routine biochemistry and hemogram were normal. Magnetic resonance imaging (MRI) showed severe destruction of the body of T6, with a bulky mass growing into paravertebral area The patient had undergo surgery with the preoperative diagnosis of spine tuberculosis. During the operation an open biopsy was taken. The histopathological diagnosis revealed diffuse large B-cell lymphoma with LCA+, EMA-, HLA-DR+, CD20+++, CD30+. Technetium-99m methylenediphosphorate nuclear medicine study of the skeloton and thorax-abdomen-cranium computerized tomography scan were performed. There was no evidence of any other systemic involvement. And there wasn't bone marrow involvement. A CHOP (cyclophosphamide, adriablastina, vincristin, prednisolon) protocol combination with rituximab treatment modality was planned and six cycles of R-CHOP had been aplied after surgical stabilization. Treatment modality has been tolerated very well and physical examination findings resolved completely. 6 months after therapy beginning, 18F-FDG PET/CT imaging was performed. Any pathological activity were obtained. The treatment lead to complete responce with the improvement of performance status and total remission of Primary bone lymphoma.. The patient who has been followed up with complete remission for more than 10 months showed no evidence of recurrence. Discussion: When a non-Hodgkin's lympoma of the bone is diagnosed, it usually is a secondary deposit in patients who already have known lymphoma in bone marrow, lymph nodes, or other extranodal sites. A PBLs (i. e., without any systemic involvement within months after the first diagnosis) is very rare. The incidence of a single vertebral

lesion is thought to be% 1,7 of all PBLs. The radiologic diagnosis of a PBL is not simple. It can be missed easily on plain radiographs. Therefore, a histopathological diagnosis is necessary, usually requirring biopsy to obtain tissue for further analysis. Therapy for PBLs is potentially curative. Treatment usually consists of chemotherapy, radiotherapy or both. Patients with primary bone lymphoma have the best survival rate among patients with primary malignant lymphomas of bone. Conclusion: This report describe an uncommon location of PBLs localized on a single spine. Furthermore, this report stresse the importance of histopathological examination at the correct diagnosis. Misdiagnosis and delay in treatment would result otherwise.

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THE TREATMENT RESULTS OF PATIENTS WITH NON-HODGKIN'S LYMPHOMA FOLLOWED BY PEDIATRIC ONCOLOGY IN CUKUROVA REGION IN ADANA.

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The third most common cancer in children <15 years of age is lymphoma which is accounted for 10-15% of childhood cancers. Non-Hodgkin lymphoma (NHL) is a malignant disease of lymphoid system. As a result of prolipheration of lymphocytes metastatic involvement, including BM, CNS and/or bone occurs. We investigated 82 patients diagnosed with NHL in between June 1996 and January 2009. Cases included 23 (28%) girls and 59 (72%) boys. Mean age was 81.5±44.6 (8-205) months. 53 (64.6%) of patients were Burkitt lymphoma, 18 (22%) were lymphoblastic lymphoma, seven (8.5%) was diffuse large B cell lymphoma, three (3.7%) was anaplastic large cell lymphoma and one (1.2%) was maltoma. While one of these cases (1.2%) was stage I, 12 (14.6%), 41 (50%) and 28 (34.2%) of patients were stage II, III and IV, respectively. 61 (74.4%) of NHLs were presented in the abdomen. Nine (13.4%) of which was located in the thorax and 9 (% 13.4) of which was in the head and neck. Other locations were skin (one) and central nervous system (two). One case with unknown origin was disseminated. Pleural effusion, bone marrow infiltration and ascites were found in 16 (19.5%), 16 (19.5%) and 9 (13.4%) of patients, respectively. 61 (74.4%) of cases were diagnosed with mass biopsy. NHL was diagnosed in totally or partially resected mass in 13 (15.9%) and 8 (9.7%) of cases operated with the findings of intestinal obstruction or suspicion of appendicitis. 64 (% 78) of cases received BFM-90 and 18 (22%) were given LSA2L2 treatment protocol. We found five-year overall survival of 74% and event-free survival of 70% . In conclusion, although the stages of patients with NHL were reported histopatologically as stage III-IV and Burkitt lymphoma in our clinic, the treatment results correlated with recent literatures.

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MEGALIN AND ITS LIGAND METALLOTHIONEIN ARE DIFFERENTIALLY EXPRESSED IN ABC AND GCB SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA

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Objective. To identify the expression profile of metallothionein (MT) and its receptor Megalin in lymph nodes of Diffuse Large B-cell Lymphoma (DLBCL) subtypes and to assess the expression profile with the clinical course. Methods. Lymph nodes of 11 patients diagnosed with DLBCL and subclassified in activated B-cell (ABC) and germinal center B-cell (GCB) types were evaluated histopathologically and correlated to the clinical and paraclinical findings. The median age of DLBCL patients was 67 years (range 49 to 79 years). Lymph node histopathology was characterized by using immunohistochemistry for MT, Megalin and a panel of antibodies (CD3, CD20, CD10, CD68, CDC47, MUM1P, Bcl-2, Bcl-6) in order to classify the lymphoma subtypes, proliferation rates and macrophage infiltration. The cellular sources of MT and Megalin were identified by using double immunofluorescence with a B-cell marker (CD20cy) and proliferation marker (CDC47). Data were evaluated by microscopy and by quantification. Results. MT expression was significantly increased in ABC lymphomas relative to healthy controls. No differences in lymphatic MT levels were observed between GCB subtypes versus controls. MT was predominantly expressed in CD20+ B-cells and in not expressed in proliferating cells with CDC47 immunoreactivity. The numbers of megalin positive cells were unaltered in DLBCL patients versus healthy control groups, but the distribution pattern of megalin expression was clearly different in DLBCL relative to controls. Megalin expression in control lymph nodes showed a nodular pattern, whereas in both ABC and GCB subtypes of DLBCL, a diffuse expression pattern of megalin was observed throughout the lymph node tissue. Megalin was not confined to any specific subtype of lymphatic cells. Conclusion. High expression levels of MT are considered as a predictor of an unfavourable prognosis in DLBCL, because MT provides cellular resistance to apoptosis and anti-cancer treatment. In agreement with this, the data presented here found increased MT in the more aggressive ABC subtype. Megalin, an endocytic receptor, and also the receptor for MT were also observed in subtypes of DLBCL, although the quantitative levels of megalin were unaltered relative to controls. However, we show for the first time that the morphologic distribution of megalin is different in DLBCL relative to control lymph nodes. The exact role for megalin in DLBCL still needs further elucidation.

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HAIRY CELL LEUKEMIA WITH ATYPICAL CD23 EXPRESSION: A CASE REPORT

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Background: Hairy Cell Leukemia (HCL) has a characteristic immunophenotypic profile and the tumor cells express B-cell associated markers, CD19, CD20, CD22, CD79a, and are characteristically positive for CD103, CD11c, and CD25, and usually negative for CD10, CD5, and CD23. Immunophenotypic variations in HCL can

be seen. CD23 positivity has been reported in 17-21% of HCL. The distinction between HCL and other small B cell lymphomas is clinically important because patients with HCL do not respond well to conventional lymphoma chemotherapy but are highly sensitive to purine analogues as Cladribine. Therefore, accurate diagnosis of HCL is critical for appropriate treatment, and abberant expression of CD23 may present difficulty for making correct diagnosis. Case Presentation: A 30-year-old male was admitted to our hospital with the complaint of fatigue and dyspnea which was initially mild in nature and then gradually progressed to increased severity with total duration of two months. On physical examination, massive splenomegaly was found. Examination of the peripheral blood revealed pancytopenia. Bone marrow aspiration was hypocellular consisting 58 percent atypical lymphocytes with hair-like surface projections. Flow cytometry detected a CD11c+, CD25+, CD103+ population of hairy cells. Bone marrow trephine biopsy confirmed the diagnosis of HCL. Neoplastics cells were CD20+, CD79a+, CD23-, CD43-, CD5-, and CD10-. The patient underwent splenectomy. On gross examination the spleen weighed 1700 grams and had a fairly smooth intact capsule. The cut surface was homogenously dark red and with inconspicious white pulp. Microscobic examination revealed diffuse infiltration of neoplastic B cells with characteristic blood lakes. Immunophenotype of the neoplastic cells was same as the ones in the bone marrow. The patient was treated with Cladribine for 6 months and control bone marrow was found to be infiltrated with neoplastic cells. Bone marrow trephine biopsy revealed diffuse and interstitial infiltration of neoplastic lymphoid cells wih characteristic morphologic features, but immunophenotype was different from the first biopsy. Neoplastic cells expressed CD23 which was negative both at the initial bone marrow biopsy and the splenectomy material. Conclusion: CD23 positivity has been reported in approximately 20% of HCL cases in some studies. It is not uncommon for HCL to display immunophenotypic variation, and recognition of these variations and correlation with morphologic findings and clinical information are essential for accurate diagnosis of HCL. A case of HCL which gained CD23 positivity on control bone marrow trephine biopsy specimen is presented, the role of aberrant expressions in differential diagnosis of small B cell lymphomas is discussed, and the literature is rewieved.

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CLINICAL FEATURES AND TREATMENT OUTCOMES IN B CELL NON-HODGKIN'S LYMPHOMA IN CHILDHOOD: A SINGLE CENTER EXPERIENCE

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Malignant non-Hodgkin's lymphomas (NHL) of childhood and adolescence are a heterogeneous group of diseases originating from the lymphoid cells. The aim of this study was to evaluate and compare the clinical characteristics of the B-cell NHL patients and therapeutic efficacy of modified NHL German Berlin Frankfurt Munster (BFM) protocols in our center. From January 1990 to December 2008, 66 new diagnosed children with B-cell NHL were enrolled to the study. The patients were stratified by risk factors and treated either with a modified B-NHL BFM-90 (before 2004) or BFM-95 (after 2004) protocols. The use of 1 or 3 g/m2 of methotrexate instead of 5 g/m2/24 h was the only important modification in BFM-90 protocol. Sixty six children (19 girls, 47 boys) with a mean age of 80 months (range: 24-168) were treated in the center with 59 months follow-up. There were 2 patients (3%) in stage 1, 11 patients (17%) in stage II, 37 (56%) in stage III, and 16 (24%) in stage IV. The most common initial primary tumor sites were abdomen (68%), head and neck (11%) and thorax (9%). The 5-year overall survival (OS) for all patients was 72%, and event-free survival (EFS) was 67% . The 5-year OS rates in modified BFM-90 (45 patients) and in BFM-95 (21 patients) protocols were 66% and 94% ; the 5-year EFS rates in these 2 protocols were 60% and 94%, respectively (p=0.061 for OS, p=0.049 for EFS). Factors associated with lower EFS by univariate analysis were risk groups (p=0.03) and stage (p=0.005). Surrenal carcinoma was detected as a seconder malignity in a patient after 36 months of therapy and this patient died due to surrenal carcinoma after 59 months of therapy. In conclusion, the treatment results in this study showed that improvement results similar to those of BFM group with intensive supportive care and therapy modalities.

P46

IRON DEFICIENCY ANEMIA AS AN INITIAL PRESENTATION OF BURKITT'S LYMPHOMA

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Iron deficiency anemia is the most common type of anemia, which is characterized by symptoms like pallor, fatigue and weakness. In postmenopausal women and men the most important cause is the loss from gastrointestinal tract. We report a 29 year old male patient who presented with fatique, palpitation and abdominal pain for the last one month. His physical examination revealed paleness of the conjunctiva pansystolic murmur on the apex and pain in the lower quadrant of abdomen by deep palpation. His first complete blood count revealed WBC 5.200/mm^3, hemoglobin 5.8gr/dl MCV 58.5fl, platelets 277.000/mm^3 and LDH 828U/L. Further examination showed a very low ferritin level (1.7 ng/ml). In abdominal ultrasonography right iliac conglomerated lymphadenopathies largest 7.5 x 4 cm in diameter were detected. Colonoscopy was performed and biopsies from the ulcerovegetative mass in ceacum revealed CD20 positive B cells with LCA expression and with massive Ki-67 activity. Hemicolectomy and ileotransversostomy were done and the final pathological diagnosis was Burkitt lymphoma. We want to imply the importance of careful evaluation of iron deficiency anemia especially in such a young male patient.

P47

OROPHARYNX PERFORATION AFTER TREATMENT IN DIFFUSE LARGE B CELL LYMPHOMA

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Diffuse large B cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin's lymphoma, with a rate of approximately 40% in adults. It is an heterogeneous group clinically, morphologically and genetically. It is marked by malignant proliferation of mature lymphocytes. They appear as nodal or extranodal. At least 40% of them are extranodal in onset. Aproximately 15% of NHL present with extranodular involvement in oropharyngeal region. Oropharynx perforation is a rare occurrence in the course of lymphoma and is reported hence. Case presentation: A 66 year old man presented with swelling in the neck and was diagnosed with DLBCL upon cervical lymph node biopsy. In computed tomography, mucosal thickening was found in oropharynx but biopsy not performed. Patient was evaluated as Ann Arbor stage 3B. After first course of CHOP treatment, difficulty in swallowing developed and in physical examination perforation in oropharyngeal region was observed and oral mucosa was seen to be covered with membranous white plaques. Systemic antifungal involving mucormycosis and antibiotic therapy was instituted. Total parenteral nutrition was supplied. In microbiological cultures, Klebsiella spp. was isolated. Biopsy obtained from three different regions in oropharynx was assessed as inflammatory changes. Mucosal membranous lesions improved with treatment. However, perforation did not regress. After the completion of chemotherapy, reconstructive intervention to oropharynx was planned. Immunosuppression developed to in relation to primary disease and the chemotherapy administered and perforation was thought to becaused by tumor necrosis and accompanying secondary infection.

P48

PRECURSOR B-CELL LYMPHOBLASTIC LYMPHOMA PRESENTING AS A SOLITARY BONE TUMOR

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OBJECTIVES: Precursor B-Cell Lymphoblastic Lymphoma (B-LBL) is a rare disease, accounts for less than 10% of cases of LBL. In contrast to LBL of T-cell lineage, B-LBL may present as an extranodal disease, with a propensity to involve skin and may present as a solitary bone tumor (1). In the literature, fewer than 10 cases of primary bone B-LBL have been reported (2). CASE REPORT: A 46 year-old woman, with progressive right elbow pain and a palpable mass on her right arm admitted in October 2007. The MRI showed a destructive lesion of low signal intensity on T1-weighted images; a diffuse medullary high signal intensity on T2-weighted images and adjacent soft tissue involvement in the right distal humerus. The biopsy of involved area revealed a diffuse dense proliferation of small to intermediate sized neoplastic cells showing scant cytoplasm, fine chromatin and irregular nuclei with inconspicuous nucleoli infiltrating the venous structures and fibroadipose tissue. Immunohistochemical stains showed strong positivity for CD34, CD43, CD10 and CD79a and TdT, lacking of MPO, CD99 and CD56. CD20, CD3, CD7 was positive in 5% of the tumor cell population. The proliferative index of the neoplasm with Ki-67 was 90% . A diagnosis of B-LBL was made. The neck, chest, abdominopelvic CT and bone marrow biopsy, revealed no other involvement site. A positron emission tomography (PET) study demonstrated extensive FDG accumulation in the area of the dominant mass in the right ½ distal arm (SUVmax=4,8) and along the right axillary lymph nodes (SUVmax=4.9). The patient subsequently underwent local radiation to the right humerus and elbow followed by 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy between January and May 2008. Since partial remission was noted, she was treated with combination chemotherapy, with Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate and cytarabine). FDG-PET was repeated after the chemotherapy and showed a complete remission with total regression of the tumor and pathological lymph nodes. CONCLUSION: Although it is a rare disease, B-LBL should be kept in mind in the differential diagnosis of small round blue cell tumors of the bone.

P49

BLASTOID MANTLE CELL LYMPHOMA MISDIAGNOSED AS A DIFFUSE LARGE B CELL LYMPHOMA: A CASE REPORT

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Background: Although the WHO classification requires a great deal of morphologic, immunophenotypic, genetic, and clinical features for making diagnosis of various types of lymphoma, it is still feasible to misdiagnose under limited resources, especially a limited panel of antibodies used for immunophenotyping. One of the reasons why diagnosis and classification of lymphoma at times are not properly given is the general pathologists' being unaware of the pitfalls in classifying lymphoma. Most of the lymph node biopsies from patients clinically suspected of lymphoma are first evaluated by general pathologists. Hematopathologists generally are the ones from whom second opinions are requested. In classifying lymphomas, knowledge of morphologic features influences and greatly enhances the accuracy of the interpretation of immunophenotypic findings. Immunophenotypic findings improve the accuracy of interpretation of histological findings when diagnosis cannot be made from morphologic feature alone. Mantle cell lymphoma (MCL) is frequently misdiagnosed, and blastic variant has to be distinguished from lymphoblastic lymphoma, diffuse large B cell lymphoma or high grade follicular lymphoma. Case Report: a 44-year-old male presented with bilateral axillary lymphadenopathy, and an excisional biopsy was performed. The biopsy material was first evaluated at an outside pathology laboratory by a general pathologist and the diagnosis of diffuse large B cell lymphoma was made. Immunohistochemical antibodies applied was

restricted to only CD20 and CD3. The patient was clinically evaluated as stage 4S with bone marrow and spleen involvement. Paraffine blocks of the lymph node was consulted to our pathology laboratory, and by using an appropriate set of antibodies immunohistochemical studies helped us to prove that the case was infact a MCL with blastoid features. Neoplastic cells were pleomorphic and expressed CD5, CD20, CD43, and CyclinD1. Conclusion: MCL is a rare group of mature B cell neoplasia, which is difficult to discriminate from other lymphoma subtypes in morphologic appearance. 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 MCL. In order to enhance the understanding of MCL, we present a case of blastoid MCL first diagnosed as diffuse large cell lymphoma by a general pathologist, and highlight the morphologic and immunohistochemical properties of MCL.

P50

THE EFFICACY OF SUBEROYLANILIDE HYDROXAMIC ACID IN COMBINATION WITH INTERFERON ALPHA AND EXTRACORPOREAL PHOTOPHERESIS IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME

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Purpose: To evaluate the activity of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in combination with interferon alpha and extracorporeal photopheresis in persistent, progressive advanced stage mycosis fungoides (MF) and Sezary syndrome (SS). Patients and Method: Three patients with stage IIB, IVA MF and one patient with SS were treated with 400 mg of oral vorinostat daily at least six months. Among three patients who were already receiving extra corporeal photopheresis (ECP) and interferon (IFN) alpha 2a, all of them continued receiving therapy with IFN-alpha-2a 3 million unit three times/week and ECP two consecutive day/month. Two patients with MF stage IIB and IVA received local electron beam radiotherapy (RT) one month before initiation of vorinostat. Evaluation of response was performed every 2 months and after the completion of 6 months of treatment. Partial responding patients were maintained on therapy with vorinostat, IFN- alpha-2a and ECP while treatment was discontinued in non responders and in complete responders after completion 6 months of therapy. Complete and partial response (PR) rate, time to response (TTR), time to progressive disease (TTP), response duration (DOR), pruritus relief and safety were determined parameters. Haematological response was determined by comparing the absolute numbers of atypical lymphoid cells on peripheral blood smears, peripheral blood flow sytometric analysis before, 6 months and after treatment. Results: Patient with stage IIB MF achieved a complete response. Patient with SS showed a stable disease as less than 50% improvement in body surface area (BSA) with reduction in lymph node. Over the course of the following 6 months of PR of the patient with stage IVA MF, the disease rapidly progressed to new tumoral lesions. The most common drug related adverse effects were thrombocytopenia, nausea and elevation of blood creatinine levels. Thrombocytopenia required dose reduction in one patient. Conclusion: Oral vorinostat is an effective and safe treatment in combination with ECP and IFN-alpha in advanced and refractory MF/SS. Three patients with stage IIB, IVA and SS were treated with 400 mg oral vorinostat daily at least six months.

P51

CASTLEMAN DISEASE PRESENTING WITH AUTOIMMUN HEMOLYTIC ANEMIA

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We presented 53 years old patient admitted to our hospital because of weakness, pallor and exersize dyspnea. Physical examination revealed pallor but any palpable lymphadenopathy and organomegaly. Laboratory finding demonstrated autoimmune hemolytic anemia value of Hb: 4.7 gr/dL, Htc: 14.7%, MCV: 88 fL, RDW: 27%, Direct Coombs Test (++++) positivity. LDH: 450 U/L, Haptoglobulin was normal, Total Bilirubin: 1.4 mg/dl, Direct Bilirubin: 0.6 mg/dL, Indirect Bilirubin: 0.8 mg/dL, reticulocyte was 16% . Metilprednisolon treatment, 1 mg/kg, administreated. During treatment there was no improvoment in hemolysis. CT scan demonstranted supraclaviculary, mediastinal and bilateral hilar lympadenopathy. Right supraclavicular excisional lymph node biopsy revealed castleman disease (C. D.), plasma cell types. Six cycles of CHOP chemotherapy administered After treatmnet clinical and laboratory findings were improved value of Hb: 12 gr/dl, Htc: 32%, MCV: 88 fL, LDH normalized direct coombs positivity persist. One should keep in mind that C. D. may present with autoimmun hemolytic anemia without any palpabl lymphadenopaty.

P52

CLINICAL CHARACTERISTICS AND TREATMENT OUTCOME OF PEDIATRIC NON-HODGKIN LYMPHOMA PATIENTS IN A SINGLE CENTER

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Objectives: This study was designed to evaluate the clinical presentation and survival rates of children with non-Hodgkin lymphoma (NHL) treated in our institution. Methods: We evaluated 55 patients with NHL who were followed up between June 1998 and December 2008 and treated according to the APO, SJBC-2, LMB 89, LMB 96, BFM 90 protocols at Department of Pediatric Oncology. Procedure: Fifty-five patients (15 girls, 40 boys) with a median age of 5 years (range: 1-14) were treated in our center. Median follow up time was 14 months (0.1-126). The most common localizations of the primary tumor were abdomen (72.7%) and neck (9.1%). Eight patients were admitted with disseminated disease (14.5%), one patient with inguinal lymph node involvement (1.8%) and one patient with a mass adjacent to spinal cord (1.8%). There were more patients (89%) in stage III and IV (1

patient in stage I, 4 in stage II, 35 in stage III and 15 in stage IV). of these patients with stage IV, 13 (23.6%) had bone marrow involvement, 1 (1.8%) had central nervous system (CNS) involvement and 1 had both of them at diagnosis. Thirty patients were treated with BFM-90 (54.5%), 8 patients with LMB 89 (14.5%), 14 patients with LMB 96 (25.5%), 1 patient with APO (1.8%) and 1 patient with SJBC (1.8%) regimens. Twelve patients (21%) were lost of follow up. In rest of 43 patients, overall survival (OS) was 66%, and event-free survival (EFS) was 58% at 5 years. Results: The OS and EFS values were low. It may be related to the high proportion of the advanced stage of the patients. However, it was interesting the rate of lost patients as high as 21% .

P53

PRIMARY PANCREATIC LYMPHOMAS

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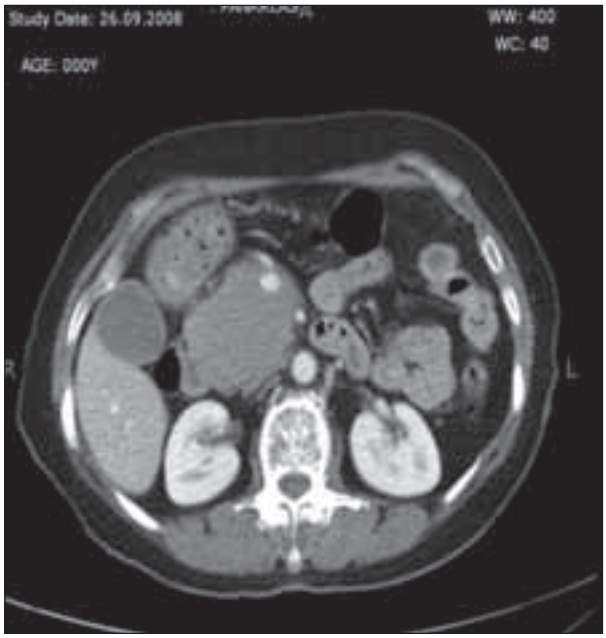
Primary pancreatic lymphomas (PPL) are rare tumors of the pancreas. Comprising 2% - 4.9% of all pancreatic malignancies and less than 1% of Non Hodgkin Lymphomas (NHL). Symptoms, tumor markers and imaging findings can mimic pancreatic adenocarcinoma but treatment and prognosis of these tumors is different. The diagnosis of PPL is very difficult. Many patients are diagnosed as having lymphoma only after invasive radical resection. Therefore biopsy of all pancreatic masses is essential. Combined treatment, utilizing chemotherapy and radiotherapy, without any surgical resection will provide curative therapy. Case 1: A-58-year-old female was admitted to our hospital because of abdominal pain in September 2007. Physical examination revealed a palpable nontender epigastric mass and icteric sclera. The abdominal ultrasound demonstrated a hypoechoic 48x 40 mm sized mass located at the head of pancreas. Abdominal computed tomography showed a well defined mass located at the head of pancreas with the dimension of 5x6.5 cm. Microscopic examination of the mass revealed a malignant lymphoma which consisted of large and atypical lymphocytes. Tumor cells showed strong staining B cell marker protein (CD 20) and CD 79 alpha, Ki 67 index was focal strong positive and were negative for the T cell marker protein (CD3). She was diagnosed as diffuse large B-cell lymphoma and stage I E disease. Chemotherapy protocol was designed as six cycles of CHOP and eight cycles of Rituximab. Case 2: A 61-year old female was admitted to hospital with the complaint of abdominal pain and jaundice in September 2008. A palpable mass in the epigastric region, icteric sclera and skin was detected in the physical examination. The abdominal ultrasound showed a hypoechoic 6x5,5 cm sized mass located at the head of pancreas. Computed tomography (CT) of the abdomen revealed 7x5 cm sized mass located at the head of pancreas. CT guided biopsy was performed. Microscopic examination revealed a malignant lymphoma. Tumor cells showed positive membrane staining for CD 20, CD 10 and LCA. Ki 67 index was 80% positive. She was diagnosed as Diffuse Large B-cell Lymphoma and stage I E disease. Six cycles of CHOP and eight cycles Rituximab chemotherapy were planned. PPL are rare disease and they can present as an isolated mass mimicking pancreatic carcinoma. However, unlike carcinomas, PPL are potentially treatable. The tru-cut biopsy of all pancreatic masses is essential before radical surgical approach, because treatment and prognosis of PPL is significantly different from those for adenocarcinoma.



Pancreatic lymphoma CT image

P54

THE EFFECT OF RITUXIMAB IN FIRST LINE THERAPY ON RESULTS OF AUTOLOGUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN RELAPSED NON HODGKIN's LYMPHOMA PATIENTS

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INTRODUCTION: The response rates to salvage therapy and high dose chemotherapy with autologus hematopoietic stem cell transplantation (AHSCT) of relapsed non Hodgkin's lymphoma (NHL) patients treated with rituximab in first line therapy, are still inconclusive. PATIENTS AND METHOD: We retrospectively analyzed 76 patients (median age 42 y, range 17-63), M/F: 48/28) who relapsed or progressed after first line therapy and received AHSCT. We grouped them as patients treated with rituximab [R (+) n: 21] and without rituximab [R (-) n: 54] in first line therapy. The majority of the patients was diffuse large B cell lymphoma (DLBCL). Median time from diagnosis to transplantation was12 months (range, 5-151) in R (-) group and 20 months (range, 5-54) in R (+) group. RESULTS: The median age of R (+) patients was significantly older than R (-) patients (p=0.02). Overall response (CR+PR) to salvage therapy before transplantation was 62% in R (+) group and 44% in R (-) group, p=0.448. Overall response after transplantation was 76% in both groups. Posttransplant 2 years survival of all patients was 50% ±7% in 21 months of median follow

up. Posttransplantation 2 years survival according to groups was not different between R (+); 35% ±26% and R (-) 51% +8% patients (p=0.72). If DLBCL patients were analyzed separetely; rituximab was found to have no effect on post AHSCT response and survival rates; 1 year survival was 71% ±14% in R (+) group and 61% ± 8% in R (-) group, (p=0.838). Twenty nine patients (RR+) treated with rituximab both in first and second line therapy were compared with 46 patients (RR-) who did not; 2 years survival was 40% ±15% in RR (+) group and% 55±8% in RR (-) group (p=0.72). CONCLUSION: We did not find a positive impact of rituximab in first line treatment on response of both salvage therapy and post AHSCT. Our R (+) group was older and had less patients than rituximab negative group. Further randomized, prospective studies with larger patient groups are needed.

	Rituximab negative n: 55	Rituximab positive n: 21	P
Male/Female (n)	36/19	12/9	0. 502
Age (years)	34 (17-61)	48 (28-68)	0. 02*
Diagnosis			
DLBCL	39	12	0. 838
Others:	16	9	
Folicular	5	3	
Anaplastic	3	1	
Mantle cell	3	5	
Marjinal Zone	2	0	
Burkitt-like	3	0	
Median time from diagnosis to transplantation	12 months (5-151)	20 months (5-54)	0. 372
Pretransplantation responses			0. 118
Overall response (CR+PR)	33 (%59) (16+8)	16 (%76) (11+2)	
Refractory	22 (%41)	5 (%24)	
Posttransplantat response			
Overall response (CR+PR)	41 (%76) (34+7)	16 (%76) (12+4)	
Refractory	11 (%21)	2 (%9)	0. 345
NA	2 (%3)	3 (%14)	
2 years overal survival (log rank)	%51±8	%35±26	0. 72

P55

LONG-TERM FOLLOW-UP OF PATIENTS WITH HAIRY CELL LEUKEMIA AFTER CLADRIBINE TREATMENT

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Hairy cell leukemia (HCL) is a rare chronic B cell lymphoproliferative disease that mainly involves the bone marrow and spleen. While there are several treatment options available for HCL when therapy is indicated, purine analogs such as pentostatin and cladribine are currently the preferred first-line therapies and can induce long-lasting complete responses in the vast majority of patients with HCL. We retrospectively reviewed 20 patients (7 female, 13 male) with hairy cell leukemia who were treated with cladribine. Median age at diagnosis was 53 years (range 28-68). All of the patients received seven-day continuous intravenous infusion program at a dose of 0.10 mg/kg/day as a standard therapy. Cladribine was the first line agent in 9 of the patients. In 10 of the patients cladribine was used as a second line therapy either after splenectomy (4 patients) or interferon treatment (5 patients). In two of the patients cladribine was used after splenectomy and interferon therapy as a third line agent. Bone marrow biopsy was performed in the third month of cladribine therapy and remission was confirmed in all of the patients. Overall survival of the patients was 8.1 years (range: 286 days-23 years). Median follow-up of was 4.8 years (223 days-10.8 years) after cladribine therapy and only one patient relapsed in his second year. This patient had been diagnosed as hairy cell leukemia for 12 years and cladribine was used as a third line agent after splenectomy and interferon therapy. Cladribine therapy was repeated after his third relaps and remission was achieved second time with cladribine. We observed bone marrow suppression in almost all patients but febrile neutropenia was seen in only 7 patients. We have also seen autoimmune hemolytic anemia in one of the patients at 28th day of cladribine therapy. Other than these 8 patients, cladribine was well tolerated without any life threatening complications. We conclude that single agent cladribine therapy is very effective in achieving long term remissions in patients with hairy cell leukemia without serious side effects and could be used as a first line therapy.

P56

IMMUNOHISTOCHEMICAL PROFILING OF DIFFUSE LARGE B-CELL LYMPHOMAS ARISING IN THE BRAIN AND ANALYSIS OF THE B-CELL PHENOTYPE

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Aim: Lymphomas of the central nervous system (CNS) are rare, and among the lymphomas presenting in CNS, diffuse large B-cell lymphoma (DLBCL) is the most common type. In the last WHO 2008 classification, primary diffuse large B-cell lymphoma of the CNS is recognized as a distinct subtype of DLBCL. The purpose of this study was to determine the expression of a panel of immunohistochemistry (CD10, Bcl-6, MUM-1, Bcl-2, CD30, Ki67) in cases of DLBCL arising in the brain; to subdivide these cases into the germinal center B-cell (GCB), or activated B-cell-like phenotype (ABC) according to the expression of CD10, Bcl-6 and MUM-1 (IRF-4) by immunohistochemistry. Patients and methods: This study included 20 cases diagnosed as lymphoma, arising in the brain, between 2000-2009 in our department; for whom archival tissue is available. The patients having CNS lymphoma with a history of known previous nodal lymphoma or transplantation were excluded from the study. Results: The male/female sex ratio was 1 (10/10), and the mean age was 50.9 (range 21-76). Nuclear MUM-1 and Bcl-6 expression were significantly high; 90% and 95%, respectively. Only two cases showed CD10 expression (10%). Bcl-2 and CD30 positive cases were 80% and 20%, respectively. Mean Ki-67 positivity was 68% (range 30-100%). Among the 20 patients, 18 were classified ABC, suggesting activated B-cell-like

phenotype, only 2 were classified in GCB. Conclusion: DLBCL of CNS are almost homogenously ABC type, regarding to be a distinct subtype. The coexpression of Bcl-6 and MUM-1 positivity and Bcl-2 expression in most of our cases may be the result of high load of mutations in both immunoglobulin genes and protooncogenes. The aggressive behaviour of these lymphomas may be explained by the high Ki-67 proliferation index values.

P57

CLASSIFICATION OF LYMPHOID NEOPLASMS ACCORDING TO WHO CLASSIFICATION 2008: ANKARA ONCOLOGY RESEARDH AND EDUCATION HOSPITAL EXPRIENCE

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AIM: To classify the patients newly diagnosed Non Hodgkin lymphoma (NHL) and Hodgkin Lymphoma (HL) according to WHO 2008 classification of lymhoid neoplasms and to compare the percentages with WHO 2001 and Turkish data. PATIENTS AND METHODS: Patients who admitted to our hospital between May 2006 and January 2009 were evaluated. 258 patients were recorded, female n=109 (42,2%) male n=149 (57.7%). N=180 (69.8%) and n= 78 (30.2%) were diagnosed NHL and HL respectively. RESULTS: Table 1 shows the characteristics of patients according to lymphoid classification of WHO 2008. In NHL group distribution of the neoplasms according to cell origin was B cell n=167 (92.8%) T cell n=12 (6.7%) NK cell n=1 (0.5%). Excluding plasma cell myeloma and hairy cell leukemia the percentage of subtypes were evaluated and the results were compared with those of WHO (1) and Turkish data (2) . The results are summarised in table 2. DISCUSSION: Diffuse large B cell lymphoma is the most common type in all series. The follicular lymphoma is the third most common type after CLL/SLL and its percentage is similiar to Turkish data.

DIAGNOSIS	N	F/M	AGE MEDIAN
B cell Neoplasms			
Precursor B cell leukemia lymphoma	1	1/0	58
CLL/SLL	17	3/14	60 (39-74)
Hairy cell leukemia	4	0/4	37, 39, 44, 63
Plasma Cell myeloma and plasmocytoma	29	8/21	57 (41-72)
Waldenström Macroglobulinemia	1	0/1	57
Splenic Marginal Zone lymphoma	1	1/0	51
Extranodal marginal zone lymphoma	2	2/0	61, 67
Nodal Marginal zone lymphoma	2	1/1	37, 48
Follicular Lymphoma	14	7/7	54 (30-77)
Mantle cell llymphoma	5	1/4	48, 57, 57, 63, 79
Diffuse Large B cell Lymphoma	86	43/43	55, 5 (17-81)
Mediastinal large B cell lymphoma	2	2/0	19, 26
Burkitt Lymphoma	3	2/1	40, 42, 45
T/NK cell neoplasms			
Precursor Tcell lymphoblastic leukemia/ lymphoma	1	0/1	23
Enteropaty type T cell lymphoma	1	0/1	58
Hepatosplenic T cell lymphoma	1	0/1	18
Blastic NK cell lymphoma	1	1/0	49
Primary cutaneous CD30+ T cell lymhoma	1	1/0	27
Peripheral T cell lymphoma	3	1/2	36, 62, 60
ALK (-) anaplastic large cell lymphoma	2	0/2	56, 67
Anaplastic large cell lymhoma	3	0/3	29, 61, 74
HODGKIN LYMPHOMA			
Nodular Lymphocyte predominant HL	2	2/0	22, 46
Classical HL	6	3/3	32 (21-56)
Nodular Sclerosis	43	20/23	41 (15-64)
Lymphocyte-rich	6	2/4	48 (21-69)
Mixed cellularity	18	7/11	37, 5 (26-57)
Lymphocyte depleted	3	1/2	32, 45, 55

WHO subtype	AOERH (%)	(WHO) %*	(TURKEY) %**
Diffuse Large B cell Lymphoma	47, 3	30, 6	30, 1
CLL/SLL	9, 34	6, 7	13, 2
Follicular Lymphoma	7, 7	22, 1	6, 84
Mantle cell llymphoma	2, 8	6, 0	3, 2
Anaplastic large cell lymhoma	2, 8	2, 4	3, 6
Peripheral T cell lymphoma	1, 7	7, 6	3, 2
Extranodal marginal zone lymphoma	1, 1	7, 6	3, 7
Mediastinal large B cell lymphoma	1, 1	2, 4	1, 8
Nodal Marginal zone lymphoma	1, 1	1, 8	0, 8
Burkitt Lymphoma	1, 7	2, 5	3, 3
Precursor Tcell lymphoblastic leukemia/ lymphoma	0, 5	1, 7	2, 9
Precursor B cell leukemia lymphoma	0, 5	OTHERS %8. 6	0, 9
Enteropath type T cell lymphoma	0, 5		0, 2
Hepatosplenic T cell lymphoma	0, 5		0, 1
Blastic NK cell lymphoma	0, 5		0, 08
Primary cutaneous CD30+ T cell lymhoma	0, 5		0, 5

MULTIPLE MYELOMA

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IN VITRO AND IN VIVO ANTINEOPLASTIC ACTIVITY OF NF-KB INHIBITOR DHMEQ ON MULTIPLE MYELOMA

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Objective and Rationale: The constitutive activation of NF-κB is often observed in lymphomas, leukemias and solid tumors. Excess activation of NF-κB may contribute to the increased malignancy including the acquisition of drug resistance. Multiple myeloma (MM) is an incurable disease derived from monoclonal malignant plasma cells. Treatment of MM with conventional chemotherapeutic drugs and an approved proteasome inhibitor (bortezomib, Velcade) resulted in improved clinical response rates; however, with modest improvement in overall survival. Therefore, a more effective inhibitor of NF-κB may improve overall survival. Hence, we have designed and synthesized a specific NF-κB inhibitor, dehydroxymethylepoxyquinomicin (DHMEQ) for analysis (1). Hypothesis: Since MM cells exhibit constitutive and strong activation of NF-κB, we hypothesized that inhibition of the NF-κB pathway by DHMEQ would attenuate drug resistance and may save patients from tumor recurrences. This hypothesis was tested in the present study and we examined the role of DHMEQ in vivo in the suppression of the growth of MM cells in mice and in vitro on the sensitization of drug-resistant MM cells to CDDP-apoptosis. Experimental Designs and Methods: The MM KMM-1 cells were inoculated subcutaneously into NOG mice and DHMEQ was administered intraperitonally. The drug-resistant IM-9 and 8226 MM cells were analyzed for their in vitro sensitization by DHMEQ. The cells were treated with DHMEQ for 24 h and followed by the addition of CDDP (10 ug/ml) for an additional 24 hours and apoptosis was determined by the PI/Annexin-V method. Results: DHMEQ completely suppressed the constitutively activated NF-κB of KMM-1 cells. It also decreased the size and weight of the KMM-1 tumor in mice without any detectable toxicity. The combination treatment of DHMEQ and CDDP resulted in a synergistic enhancement of apoptosis compared to single treatment with DHMEQ or CDDP. The chemosensitizing activity of DHMEQ was the result of the inhibition of anti-apoptotic gene products regulated by NF-κB, such as Bcl-xl, cIAPs, and XIAP. Conclusions: DHMEQ directly binds to NF-κB components (2) and is a very specific inhibitor of NF-κB activities. DHMEQ exhibited a potent anti-tumor effect in mice bearing KMM-1 tumor xenografts. Further, treatment of MM cells with DHMEQ increased significantly their sensitivity to drug-induced apoptosis. We propose that DHMEQ is a useful and novel chemotherapeutic/sensitizing agent against MM and supports its clinical investigation in patients with MM.

P59

INTRACEREBRAL PLASMACYTOMA AS AN INITIAL PRESENTATION OF MULTIPLE MYELOMA

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Cerebral involvement is an uncommon complication of multiple myeloma. We report a 68-year-old woman hospitalized for acute renal failure, vertigo and headache. MRI revealed two and a half and 3cm length intra-cerebral lesion, which proved to be plasmacytoma. After complete staging, we retained the diagnosis of immunoglobulin G lambda-type multiple myeloma with CNS involvement. Cytogenetic analysis of plasma cells detected no change. She is a regular hemodialysis patient now. She is planned to have both systemic therapy with 40mg dexamethasone and cranial radiotherapy. Involvement of the CNS in multiple myeloma is very rare. Diagnosis of multiple myeloma subsequent to initial cerebral involvement is confined to exceptional cases. Despite aggressive systemic treatments, including autologous stem cell transplantation and local treatments such as cerebral radiotherapy, the prognosis for patients with CNS myeloma is extremely poor. Our unique case implies that physicians should be alert in case of vertigo or headache in cases with acute renal failure.

P60

MALIGN PLEURAL EFFUSION WITH MULTIPLE MYELOMA

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INTRODUCTION: Multiple myeloma (MM) is a malign disease characterized by proliferation of plasma cells and subsequent overabundance of monoclonal paraproteins. An intriguing feature of MM is the malign cells producing antibodies which results in unusual manifestations. The presentation of disease can range from asymptomatic to symptomatic with complications requiring emergent treatment. Systemic ailments include bleeding, infection and renal failure, whereas local catastrophes are pathologic fractures and spinal cord compression. Exramedullary manifestations are relatively rare. Pulmonary and pleural involvement has only been described as case reports. Pleural effusion may develop in the setting of MM due to various reasons, and myelomatous pleural effusion is rare. We report a case of myelomatous pleural effusion in a patient with advanced MM. CASE: A 74 year old man was admitted to our hospital complaining of lomber pain, weakness, and weight loss. Past medical history did not reveal any other diseases. On physical examination; his temperature was 36.5ºC, heart rate 88 beats/min, respiratory rate 16 breaths/min, blood pressure 117/72 mm-Hg. Laboratory data showed that; WBC: 3920/uL, Hb: 8,12 g/dl, Plt: 227000/uL and sedimentation rate: 119 mm/h, creatinin: 0.72mg/dl, BUN: 17.3mg/dl, Na: 142mmol/L, total calcium: 8.2 mg/dl, ionised calcium: 1.04mmol/L, albumin: 3.2 g/dl and total protein: 10.55 g/dl. Bone marrow aspirate was obtained and biopsy samples revealed nearly% 80 plasma cell infiltration. There was a monoclonal IgG kapa band in immunoelectrophoresis of both serum and urine samples. According to these findings the diagnosis of multiple myeloma was established and he received one course of VAD chemo-

therapy (vincristine+adriamycin+dexamethasone). After the fist dose of chemotheraphy the patient had cough, fever and dyspnea. On physical examination; his temperature was 39.2ºC, heart rate 112 beats/min, respiratory rate 20 breaths/min, blood pressure 123/84 mm-Hg and there was diffuse bilateral rales on chest oscultation. The chest radiograph showed bilateral multifocal areas of infiltration. Computed tomography of thorax showed bilateral pleural effusion and pneumonic consolidation on the left side. Ultrasonography guided thoracentesis yielded 8 cc of bloody exudative effusion. Pleural effusion and sputum culture was negative, Protein electrophoresis of the pleural fluid showed monoclonal protein, and cytology demonstrated monoclonal plasma cells., and cytology demonstrated monoclonal plasma cells. DISCUSSION: Pleural effusion (due to pulmonary infection or hypoalbuminemia) is a relatively infrequent complication of multiple myeloma and malign effusions caused by plasma cell involvement is extremely rare which may indicate poor prognosis. This effusion is due to plasma cells secreting numerous immunoglobulins and thereby increasing oncotic pressure of pleural space. In addition, if exists, malign pleural effusion is more frequent in Ig A type than IgG type of MM. Our case is unique with its having malign effusion in association with Ig G type MM. Since cytopathologic analysis is the gold standart for diagnosis, it should absolutely be done for such cases of MM with pleural effusion.

P61

GASTRIC ADENOACARCINOMA MIMICKING PLASMOCYTOMA DURING THE COURSE OF MULTIPLE MYELOMA

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Introduction. Multiple myeloma (MM) is characterized by a proliferation of malignant plasma cells originating in the bone marrow.1 The disease results in a number of organ dysfunctions and symptoms of bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia and occasionally clotting abnormalities, neurologic symptoms and manifestations of hyperviscosity.2 The association between multiple myeloma and secondary malignancies is already well established.3 In literature, co-existence of MM and gastrointestinal tract tumors has rarely been reported.4 It is unclear whether MM itself is a risk factor for the incidence of secondary solid neoplasms.5 The use of alklyating agents and immunologic tolerance have been suggested as a possible mechanism accounting for the development of a secondary primary tumor in patient with MM.5 In this case we reported a patient who was followed as multiple myeloma and treated with VAD therapy. During the third cycle of therapy, gastric solid mass was determined incidentally at abdominal ultrasound imaging and after abdominal CT. She was referred to esophagogastrodudenoscopy. Low-differentiated adenocancer was diagnosed at gastric biopsy and she had partial gastrectomy operation. Case. A 68 years-old-woman was presented with fatigue and shortness of breath for one month. The routine investigations revealed the presence of anemia, high erythrocyte sedimantation rate and high levels of globulins (Figure 1). She did not have a history of chronic drug use or any other disease. Her blood pressure was 120/80 mm Hg and phsyical examination was normal. At laboratory tests; erythrocyte sedimantation rate: 135 mm/h, total protein: 8.9 g/dL, albumin: 3.8 g/dl, globulin 5.1 g/dl, red blood cells: 3.35 M/Ul, hemoglobin: 7.6 gr/dL, hematocrit: 25.5%, Ig G: 3720 mg/dL, Ig G A 398 mg/dL, Ig E: 19.5 mg/dL, Ig M: 63.7 mg/dL, Calcium: 8.9 mg/dL, creatinin: 1.1 mg/dL, lactat dehydrogenase: 492 U/L. The peripheral blood smear showed hypochromic and mycrositic erythrocytes. The lytic bone lesions were determined on the cranial X-ray graphies. The bone marrow aspirate showed 30% plasma cells (Figure 2). She was diagnosed with MM and VAD (vincristine, doxorubicin, dexamethasone) chemotherapy was planned. She received four cycles of VAD therapy. During the third cycle an epigastric mass was determined incidentally with ultrasound imaging. The abdominal CT scan showed a mass of 5*6 cm on the corpus of stomach. The esophagogastroduodenoscopy was performed. The biopsy taken from the solid mass demonstrated low differantiated adenocarcinoma (Figure 3,4). During this period chemotherapy was applied properly. After the fourth cycle her sedimantation rate was 53 mm/h, Ig G: 678 mg/dL, protein electrophoresis and repeated bone marrow aspirate was normal (Figure 5). She was accepted to be in complete remission. After the consultation with medical oncology the patient was given to surgery. Total gastrectomy was performed. The pathological examination of the solid mass after surgery also showed low differantiated tubuler adenocarcinoma. After one year, the control computered tomographies of thorax and abdomen showed no significant lesions nor lymphadenopathies. At laboratory tests; erythrocyte sedimantation rate: 31 mm/h, total protein: 7 g/dL, albumin: 4.2 g/dl, globulin 2.8 g/dl, red blood cells: 4.01 M/Ul, hemoglobin: 12.6 gr/dL, hematocrit: 37.2%, Ig G: 1270 mg/dL, Ig G A 280 mg/dL, Ig M: 62.9 mg/dL, Calcium: 8.9 mg/dL, creatinin: 0.6 mg/dL, lactat dehydrogenase: 571 U/L. We wanted to report this case because co-existance of MM and gastrointestinal tract tumors is rarely seen. Here we reported a case with multiple myeloma which time of occurrence of second malignancy and type of presentation are very unusual.

P62

MYELOMA CELL INTERACTION WITH MESENCHYMAL STEM CELLS, GENOMIC PHENOTYPES AND RISK SCORES

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Gene expression profiling of myeloma plasma cells (MMPC) divides myeloma patients into 7 distinct phenotypic groups, also associated with prognosis (Zhan, Blood 108; 2020, 2006), and into high and low risk disease on the basis of a 70 gene risk assessment model (Shaughnessy, Blood 109: 2276, 2007). The bone marrow microenvironment has been recognized to play an important role in the disease process, being responsible for manifestations like osteolytic bone disease, drug resistance, and

other manifestations. The OBJECTIVE: to determine if the interaction between MMPC and cellular components of the bone marrow microenvironment can shed light on the phenotype-derived risk groups. METHODS: MMPC purified from bone marrow aspirates obtained from 15 consenting patients were co cultured with mesenchymal stem cells (MSCs) from healthy individuals, and their survival in comparison to MMPC cultured alone was measured. The results were then correlated with Affymetrix U133Plus2.0 GEP-defined molecular subgroups and risk, as well as signaling networks using Ingenuity software. MSCs were selected because, unlike osteoclasts, they interact heterogeneously with MMPC. RESULTS: Co culture with MSCs supported survival of MMPC from 11 patients and resulted in reduce survival of MMPC from 4patients (ratio 1.2 and ≤0.8, respectively). ≥of viability co culture: MMPC alone Analysis of Microarray data of MMPC at diagnosis revealed that a total of 369 probesets, representing 307 genes, were significantly differentially expressed between the two groups (p≤0.05, Mann Whitney 1.24 fold (median 1.67, 1.24-4.17) ≥test). Expression of 150 genes was higher in MMPC supported by MSC, including ERK, AKT, Cyclin A, Cyclin E, Insulin, retinoic acid, and others; all belonging to one of several gene networks. A total of 157 genes were expressed at lower levels in these MMPC (median 0.61, 0.91-0.08). These genes were involved in RB1-E2F, Interferon alpha, ERK, PI3K, AKT, Insulin, p38, NFkB, MLL, TNF, and VEGFA-related signaling pathways. With respect to molecular subgroups and risk, all MMPC from the un-supported group had low-risk disease with 3 of these belonging to the hyperdiploid (HY) group and 1 to the MS subgroup. In contrast, among the 11 supported MMPC only 6 had low risk with 4 of these belonging to the LB group. Theses MMPC frequently exhibited GEP indicative of chromosome 13 deletions, which was not found in any of the un-supported group. CONCLUSIONS: Our data suggest that MMPC from patients with phenotypic and possibly molecular and karyotypic characteristics of high risk myeloma interact differently with cells in the bone marrow microenvironment, interactions that may, in part, contribute to disease course. These finding may also help identify patients who are more likely to benefit from MSC therapy.

P63

BORTEZOMIB, DOXORUBICIN AND DEXAMETHASONE COMBINATION IS EFFECTIVE IN PRIMARY CELL LEUKEMIA

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Plasma cell leukemia (PCL) is a rare lymphoproliferative disorder defined by more than 2x109 /L (20%) circulating plasma cells. Primary disease (pPCL) presents as denovo leukemia, whereas secondary PCL (sPCL) arises on top of a pre-existing multiple myeloma (MM). In this presentation a pPCL who was successfully treated with a combination of bortezomib, doxorubisin and dexamethasone will be discussed. 75- year-old male, urologist, presented with progressive fatigue in June 2008. He had Billroth II, abdominal aort anevrism greft repairment operation in the past. Only pallor was found on the physical examination. The peripheral blood counts showed hemoglobin 10.4g/dl; platelets 25x109/l; and white cells count 17.5x109/l. Peripheral blood smear revealed 55% plasma cells. Bone marrow aspirate showed 85% plasma cells and plasmablasts. Flow cytometry of the bone marrow aspirate revealed CD 38 and CD 138 positivity as 85% and 71% respectively. Cytogenetic analysis showed complex anomalies. The biochemical tests were normal except beta 2 microglobulin 14016 ng/mL and uric acid 12.10 mg/dL. Serum protein electrophoresis and immunofixation studies showed no anomaly. Ig D also wasn't detected. No lytic lesions were detected. The diagnosis of pPCL was established. A cycle of VAD commenced. Afterwards PAD bortezomib (1.3 mg/m2, bolus injection, on days 1, 4, 8 and 11, adriamycin 9 mg/m2 on days 1-4; dexamethasone 40 mg on days 1-4, 8-11 and 15-18 during cycle and days 1-4 on subsequent cycles) for a total of 6 x21 day cycles. As he developed grade II peripheral neuropathy and diarea bortezomib dosage tapered to 1.0 mg/m2. After first PAD cycle circulating plasma cells disappeared from peripheral blood. His platelet count and hemoglobin level increased. After this treatment regimen the cellularity of bone marrow decreased and the percentage of plasma cells also decreased to 4% . He is now well in condition. Primary cell leukemia continues to be a highly deadly disease. PAD is an effective combination in patients with pPCL. However, the impact of PAD therapy on the survival and the role of early transplantation and maintenance therapy in PCL should be investigated in large multi-centre studies.

P64

SIX YEARS MYELOMA EXPERIENCE OF A SINGLE CENTER

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Purpose: Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 10% of hematologic malignancies. The median age at on set is 66 years; and only 2% of patients are younger than 60 years at diagnosis. In this presentation the details of the MM patients who are treated by a single center would be summarized. Method: Forty six patients' documents analyzed for this study. Four patients were diagnosed before 2003 when the department of hematology was established. Results: Twenty patients were female, 26 were male. All median age was 65.17 (40-82) years. Twenty three patients are under age 65. Twenty patients died, among which 2 of them died in hours after hospitalization. Mean exitus time was 10 months. Three patients are out of follow up. Twenty patients are still under outpatient control. Their follow up median time is 19 months. Monoclonal proteins of the patients are as follows: IgG kappa 24%, IgG lambda 13%, IgA kappa 11%, IgA lambda11%, IgD 2%, Lambda light chain% 17, Kappa light chain 17% . No electrophoretic study could be done for the 2 patients who were died in hours. B symptoms were observed in 22 patients and 80% of the patients had advanced disease. VAD was the first line treatment for the patients who are under 65. PAD (bortezomib, adriamycin, dexamethasone) was the second treatment option before autologous transplantation. Nine autologous transplant were done. Conclusion: Recently by introduction of novel agents in MM treatment the life exceptancy of these patients is being changed. More effords should be done to get better results in myeloma patients.

P65

ABNORMAL PROTEIN BAND IN MULTIPLE MYELOMA PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Objectives: To evaluate the significance of appearence abnormal protein bands (APB) after hematopoietic stem cell transplantation (HSCT) and impact on treatment response and survival in multiple myeloma (MM) patients. Methods: The records of 53 MM patients, who had undergone HSCT (49 autologous and 4 allogeneic) at the transplantation unit of Gazi University Faculty of Medicine between October 2003 and December 2008, were reviewed retrospectively. The patients were evaluated at diagnosis, before and after HSCT with serum and urine immunofixations, bilateral bone marrow aspiration and biopsy, hemogram, biochemical parameters, CRP, beta-2 microglobulin levels. They were staged according to Durie-Salmon staging and International staging systems (ISS). European Bone Marrow Transplantation Unit citeria were used for identifying the disease response before and after HSCT. Results: Fourteen (26.4%) of 53 patients devoleped APB during post-transplanation period. The median time to appearence of APB after HSCT was 3 (range, 1-24) months and the median duration of the persistence of the APB was 5.5 (range, 1.5-14) months. The abnormal protein band disappeared in 11 patients and one pateient died with a persistent APB, one of the patients was lost to follow up and, one patient was alive with persistent APB at the end point of the study and this patient was in complete remission without the disease original monoclonal band. When APB appeared, 5 (35.7%) of the patients were in complete remission, 2 (14.3%) in partial response, 3 (21.4%) in minimal response, 2 (14.3%) in progressive disease, and 2 (14.3%) in relapse from complete response status. The original monoclonal protein was also present in 9 of the 14 patients. The APB band reappeared after 12th months of the initial presentation and disappeared again after 3 months in one patient. This patient was status post 22 months after AHSCT and remined to be in complete remission. Overall survival probability at the end of the follow up was 77% in patients with APB, and 61.4% in patients without APB (p>0.05). Follow up [767 d (range, 220-2905) vs. 726 days (range, 120-1780) p>0.05] was not different in patients with and without APB. Progression free survival was longer (535 days (range, 180-2905) in patients with, compared to patients without APB however without statistical significance p>0.05). Conclusion: APBs are frequently seen in MM patients after HSCT, not necessarily with a prognostic significance. The presence of an APB other than original M protein might be due to oligoclonal reconstitution and or immune deregulation and does not have an impact on posttransplant overall survival. The appearence of a new APB in the post-transplant setting should not be considered as a parameter of disease activity and needs to be closely followed without therapeutic intervention

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BILATERAL ORBITAL INVOLVEMENT IN A PATIENT WITH MULTIPLE MYELOMA

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OBJECTIVES: Plasmacytomas have been found in lymph nodes, skin, liver, spleen, upper respiratory tract, oropharynx and occasionally kidneys and meninges in the course of multiple myeloma1. Orbital and eye muscle involvement is very rare in multiple myeloma and occupies approximately 1% of all orbital tumors2. Here we represent an extremely rare case of bilateral orbital muscle involvement in a patient with multiple myeloma. CASE REPORT: A 47-year-old woman was diagnosed to have Immunoglobulin G kappa multiple myeloma in February-2008. She received 6 cycles of VAD (Vincristine, Adriablastina and Prednisolone) chemotherapy between February/2008- July/2008 and complete remission was obtained. On October 2008 she complained of redness, pain, chemosis and exophtalmus on her right eye. Cranial computed tomography scan revealed a 25x15x30 mm contrast-enhancing lesion in the right orbita, near ocular globe causing proptosis. An excisional orbital biopsy from rectus muscle of right orbita revealed "a neoplastic lenfoplasmocytic infiltration with kappa light chain monoclonality". Her symptoms improved spontaneously without any treatment in two months, however appeared in her left eye. An orbital contrasted magnetic resonance imaging revealed "a 24x22x15 mm contrast enhancing mass which is not exactly demarcated from superior levator palpebra and superior rectus muscle in left orbita". Moreover, "12x8 mm contrast-enhancing mass inferomedially to superior rectus muscle and 7 mm space-occupying mass anterosuperior to right bulbus oculi in right orbita" was also seen. On her eye examination visual acuity was normal in right eye whereas 1.7 ph in left eye with proptosis. The patient was consulted to Radiation Oncology Department and radiotherapy to left orbita is planned. CONCLUSION: This report represents a very unusual case of multiple myeloma with plasmocytoma involving both orbital eye muscles. Although it is very rare, extramedullary plasmacytomas should be kept in mind in the differential diagnosis of orbital masses.

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EFFICACY OF BORTEZOMIB IN A PATIENT WITH PLASMA CELL LEUKEMIA AND RELAPSE AT CENTRAL NERVOUS SYSTEM

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Plasma cell myeloma (PCL) is an aggressive variant of multiple myeloma. The median survival of most patients with PCL is 6-8 months.

Case: A 69 year old female presented with complaints of lumbar pain, dyspnea, fatique, easy bruising for 10 days. On physical examination, there was pallor, purpuric spots and hepatomegaly. Blood count revealed anemia (Hb 7.6 g/dl), leukocytosis (leukocyte 68x 10 9/l with 73% plasma cells) and thrombocytopenia (platelet 15x 10 9/l). Clinical diagnosis was primary PCL with IgG lambda paraproteinemia. Serum beta 2 microglobulin

level was 7.5 mg/dl, LDH level was 1006 IU/l. Cytogenetical analysis was normal. After two courses of VAD (Vincristine, adriamycine, dexamethasone) therapy, partial remission was obtained. Second therapy regimen was PAD (bortezomib, adriamycine, dexamethasone). The patient was on clinical and laboratory remission after two courses PAD. Maintenance treatment of oral cyclophosphamide 50 mg /day was started after total 4 courses of PAD. Six months later patient presented with confusion, headache, vomiting, visual disturbances, lethargy and convulsions. We detected isolated leptomeningeal myelomatosis. Bone marrow was in complete remission. Time from primary PCL to leptomeningeal involvement was 10 months. Systemic chemotherapy (bortezomib, dexamethasone) combined with intrathecal chemotherapy (cytarabine, methothreaxate and steroid) was given to the patient and fallowed by cranial radiotherapy. Cranial radiotherapy was effective but the symptoms restarted after cranial radiotherapy. Pancytopenia was occurred. Bone marrow relapse was detected. The patient died from sepsis and recurrent primary PCL 15 months after the initial diagnosis. In conclusion, bortezomib appears to be an effective drug for remission induction of primary PCL. Leptomeningeal myelomatosis can occur even in the presence of systemic complete remission in these patients. Cranial radiotherapy is the most effective treatment for leptomeningeal involvement. The efficacy of bortezomib for leptomeningeal myelomatosis is unknown. The patients with primary PCL should be treated profilactically for leptomeningeal myelomatosis when complete remission obtained.

P68

PX-171-004, AN OPEN-LABEL, MULTICENTER PHASE II STUDY OF CARFILZOMIB (CFZ) IN RELAPSED MYELOMA: AN UPDATE OF EFFICACY AND TOLERABILITY

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Background: Carfilzomib (CFZ) is a structurally and mechanistically novel proteasome inhibitor with single-agent activity against hematologic malignancies, including bortezomib (BTZ) -relapsed myeloma (MM). CFZ is highly selective and in preclinical studies, CFZ lacks the off-target activities of BTZ. This specificity may contribute to its favorable tolerability. PX-171-004 is an ongoing Phase II study to evaluate the safety and efficacy of CFZ in MM patients (pts) with relapsed disease after 1-3 prior therapies. We previously reported an Overall Response Rate (ORR) of 35.5% for all pts, with 90% of initial responses occurring within the first 2 treatment cycles and time to best response achieved within 4 cycles (ASH 2008). Here we present updated data on the first 31 pts. Methods: CFZ 20 mg/m2 was administered Days 1, 2, 8, 9, 15 and 16 in a 28-day cycle, for a maximum of 12 cycles. Dexamethasone 4 mg po was administered prior to each dose in Cycle 1. The primary endpoint was ORR [Partial Response (PR) + Very Good Partial Response (VGPR) + Complete Response (CR)]. Secondary endpoints included safety. Results: 31 pts were enrolled, including 14 (45%) BTZ-naïve pts and 17 (55%) pts whose prior therapies included BTZ (BTZ-exposed). of the BTZ-exposed cohort, 15 (88%) also failed stem cell transplantation and 16 (94%) relapsed following at least one IMID-containing regimen. Eight BTZ-naïve pts (ORR 57%) achieved >PR (1 CR, 2 VGPR, 5 PR) and three BTZ-exposed pts (ORR 18%) had a PR. To date, pts have received an average of 6.6 treatment cycles; 20 pts (65%) received >4 cycles. Nine pts (29% ; 4 BTZ-naïve and 5 BTZ-exposed) completed 12 full cycles without evidence of disease progression. Eleven pts (35%) were discontinued due to progressive disease. Ten pts (32%) discontinued treatment prior to completion of 12 cycles due to AEs. These AEs included rash (1 pt), multi-organ failure (1 pt), tumor lysis syndrome (1 pt), edema/dyspnea (1 pt), congestive heart failure (1 pt) and Grade 1 elevated creatinine/Grade 2 hypertension (1 pt). One pt was withdrawn due to hyperthyroidism, considered unrelated to CFZ. One pt (3%) who entered the study with Grade 1 peripheral neuropathy (PN) attributed to thalidomide, was discontinued for Grade 3 PN despite resolution to Grade 1 prior to receiving her final CFZ dose. Three pts discontinued during their final treatment cycle (Cycle 12): two pts due to AEs (abdominal pain and pneumonia) and one pt withdrew consent. Conclusions: These preliminary results demonstrate that CFZ monotherapy is highly active and well tolerated. Almost one-third of pts in this relapsed population completed 12 treatment cycles (i. e. 1 year) without evidence of tumor progression. Importantly, the rate of peripheral neuropathy necessitating treatment discontinuation remains significantly lower than the rate reported for BTZ. These data support the continuing evaluation of CFZ as a promising new agent in relapsed MM.

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DEVELOPMENT OF ACUTE PULMONARY HYPERTENSION AND PULMONARY PARENCHYMAL INFILTRATES AFTER BORTEZOMIB TREATMENT

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BACKGROUND: Bortezomib is a promising agent in all lines of treatment of multiple myeloma (MM) due to its high efficacy and low toxicity profile. The most common side effects are neurological, gastrointestinal and hematological toxicities. Severe pulmonary complications have been reported anecdotally. In this case report, we describe a patient with multiple myeloma who developed acute pulmonary hypertension and parenchymal infiltrates after bortezomib-dexamethasone treatment. MATERIALS AND METHODS: A 57-year-old man admitted to the hospital for a surgical procedure for inguinal hernia. Severe anemia was detected and further assessment led to the diagnosis of stage IIIA MM, IgG

kappa type. IgG level at diagnosis was 8.88 g/dl. Bortezomib (1.3 mg/m2, days 1, 4, 8, 13, every 21 days) and dexamethasone (40 mg, days 1, 4, 8, 13, every 21 days) treatment was initiated. He developed high fever (39 0C), dyspnea, hypotension and hypoxia in the third day of chemotherapy. On physical examination bradycardia, bilateral jugular venous distention, crackles at the bases of the lungs were noted. Radiological evaluation revealed nonspecific pulmonary parenchymal infiltrates and bilateral pleural effusion. Transthorasic echocardiography showed normal left ventricular function, significant dilatation of right heart chambers and pulmonary hypertension with an estimated systolic pulmonary arterial pressure of 70 mm Hg. The perfusion scintigraphy ruled out a pulmonary thromboembolic event. Although empirical antibiotic therapy was initiated, blood and urine cultures were negative and fever subsided rapidly. At the sixth day after admission, control echocardiography revealed that the estimated systolic pulmonary arterial pressure was 40 mm Hg. The development of acute pulmonary hypertension could not be explained with the pulmonary parenchymal infiltrates. The sudden onset of pulmonary hypertension and its rapid decrement without any treatment though to be related to bortezomib. Subsequently, he received 2 cycles of VAD, 1 cycle of thalidomide-dexamethasone. He did not respond to any of these regimens. Therefore, bortezomib treatment was repeated and no pulmonary adverse reactions have occurred. Follow-up echocardiographies revealed pulmonary arterial pressures to be maximally 35 mmHg. RESULTS AND DISCUSSION: Pulmonary toxicity of bortezomib in MM has been reported in only 14 patients so far. In all these patients the clinical findings were parenchymal infiltrates and pleural effusions. Our patient is the first case in the literature presenting with acute pulmonary hypertension following bortezomib. The pathogenesis of the pulmonary toxicity of bortezomib is unclear, but a proinflammatory effect by release of cytokines has been suggested. It has been shown that further exposure to bortezomib can sometimes be fatal in these patients. In our case bortezomib rechallenge did not lead to recurrence of pulmonary toxicity.

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RETROSPECTIVE EVALUATION OF MULTIPLE MYELOMA PATIENTS: SINGLE CENTER EXPERIENCE

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We evaluated 225 multiple myeloma patients who were admitted to our center from 1999 to 2009 retrospectively. The patients were 144 men and 81 women with an age range of 26-96 years old. The types of heavy chains were IgG, A, D/E, M, 162, 39, 3, 1 patients respectively. There were 15 patients with light chain, 5 patients with non secretory myeloma. According to Durie-Salmon staging system 16 patients were accepted as stage I, 86 patients as stage II, 123 patients as stage III. In 46 patients hypercalcemia, in 54 patients renal failure and in 22 patients plazmositom was detected. The B2-microglobulin levels of patients changed between 1.9-83.9 mg/l. We obtained CR+PR in 80 patients with VAD treatment regimen and refered 20 of them to other centers for autolog stem cell transplantation (ASCT). We treated 22 of them with ASCT in our center. In only 13 patients, CR were obtained with MP treatment regimen. In patients whom remission was not obtained with MP and VAD, we used different treatments, such as thalidomide, bortezomib, bortezomib+dexamethasone, cyclophosphamide. In 67 patients ASCT couldn't be applied because of advanced age. During treatment in 10 patients neuropathy, in 4 patient deep venous thrombosis, in 2 patients pulmonary embolism, in 2 patients osteonecrosis of the jaws and 1 patient portal venous thrombosis were found. 70 patients were diagnosed in our center but they attended to different centers for continuing clinical follow-up because of individual and social causes. During follow-up 26 patients were died of refractary disease or reasons those are not related with their own disease.

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CAUDA EQUINA INVOLVEMENT IN MYELOMA

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Multiple myeloma is a clonal plasma cell malignancy and systemic disease. Complications of multipl myeloma include neurologic and bone complications (pathologic fractures, spinal cord compression) and neurologic complications (spinal cord and nerve root compression). In our presented case 51 years old patient admitted to our hospital because of weakness. Laboratory examination: Hb: 9 gr/dL, Hct: 27%, globulin: 3.7 g/dL, serum protein electroforesis monoklonal gammopati, sedimentation 68 mm/h, IgG: 2282 mg/dL, Kappa: 1014 mg/dL. Bone marrow aspiration smears and trephine biopsy was correlated myeloma. The patient diagnosed stage III A IgG Kappa myeloma. Direct radiography was demonsteated vertebral compresion fractures. Magnetic resonance (MR) of the spine showed multipl vertebral compression fractures and marked contrast enhancement of the cauda equina region. Neurological demonstreated sfincter dsyfunction, decreased deep tendon reflexes, frust hemiparesia, reflected cauda equina syndrome. After VAD treatment, MR showed no infiltration. In literatüre there is only one case presenting with cauda equina involvement in myeloma patient.

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A RARE OCCURRENCE: MULTIPLE MYELOMA AND PLEURAL ADENOCARCINOMA

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Pulmonary involvement is rare in multiple myeloma (MM). This occurs usually when it is recalcitrant to treatment and progressive and associated with pathological fractures and renal failure. In the course of MM; the most common causes of pulmonary involvement are

pulmonary infections and interstitial diseases. Simultaneous development of other malignant disease seldom occurs. Case presentation: A 73 old female patient administered melphalan and prednisolon with the diagnosis of stage IIIA MM, started to complain of cough, breathlessness and right flank pain three months later. In thorax computed tomography, pleural effusion was observed. The histopathological investigation of both pleural fluid and pleura biopsy yielded results compatible with adenocarcinoma. In repeated analyses, the absence of progress in myeloma or the lack of pleural involvement was corroborated. Patient was lost due to respiratory failure related to the progression of adenocarcinoma. The development of pleural adenocancer soon after the diagnosis of MM was made is a rare concurrence. It should be borne in mind that in myeloma nonhematogenic malignities may also develop as well as infectious disease causing pleural effusions.

MYELOPROFILERATIVE DISORDERS

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MYELOPROLIFERATIVE DISORDERS AT A GLANCE - GAZİ UNIVERSITY EXPERIENCE

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Myeloproliferative disorders (MPD) are clonal stem cell diseases characterized by the expansion of mature forms of granulocyte, erythroid and megakaryocyte precursors in bone marrow. The invention of Janus Kinase (JAK2V617F) mutation in a high percentage of patients with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) has provided new insights into the underlying molecular mechanisms for these disorders. A total of 173 patients[M/F: 93/80; median age 57 (19-84) years] who were diagnosed as bcr abl negative MPDs[PV, ET, PMF and unclassified MPD (uMPD)] at Gazi University Hospital were retrospectively reviewed. The median follow up period of the study cohort was 30,1 (0,4-219) months. Seventy six patients (44%) were diagnosed as PV,30 patients (17.3%) were ET,45 patients (26%) PMF and 22 patients (12.7%) uMPD. A total of 96 patients (55.5%) were evaluated as high risk and 77 patients (44.5%) as low risk. Thrombosis was shown in 9 patients. Five were diagnosed in PV,2 were in ET and 2 in uMPD groups, respectively. Portal vein thrombosis was observed in 5 patients, splenic vein thrombosis in 1, deep venous thrombosis in 1 and pulmonary thromboembolism in 2 patients. The frequency of thrombosis did not differ among the subgroups of MPDs. Two patients experienced thrombosis before the diagnosis of MPD. Thirty two PV patients (42.1%) did not require cytoreductive therapy during follow up,39 patients (51.3%) were treated with hydroxy urea (HU) ± aspirin and 5 patients (6.6%) with interferon. In the ET group,11 patients (36.7%) did not receive cytoreductive therapy, HU±aspirin was used in 16 patients (53.3%) and anagrelide in 3 patients (10%). HU±aspirin was used in 9 uMPD patients (40.9%) and 13 patients (59.1%) did not require cytoreductive therapy in the uMPD group. Thirty seven patients (82,2%) did not receive cytoreductive therapy in PMF group. JAK2V617F mutation status was evaluated in 31 patients. Twenty three (74.2%) positive results [15 PV; 5 ET; 1 PMF; 2 uMPD] were obtained. Splenomegaly was more frequent in JAK2 positive patients who were also more likely to develop bone marrow fibrosis (BMF) without statistical significance (p>0.05). No significant association was found between JAK2 mutation and risk of thrombosis. There was a negative correlation between hemoglobine level and degree of BMF in PV and ET patients [(p=0.043, r=-0.28), (p=0.016, r=-0.50)] and a positive correlation between leukocyte count and splenomegaly in PV patients (p=0.002, r=0.62). As recently pointed out by several studies, anemia is associated with the degree of BMF in MPDs. Whether the presence of JAK2V617F modifies the thrombotic risk in this specific group of patients needs to be confirmed by large prospective studies. Further evaluation is warranted to validate the role and therapeutic benefit of JAK2V617F as a molecular target in MPDs.

	PV	ET	PMF	uMPD
Hb (g/dl) (mean±SD)	17, 5±2, 8	13±2, 2	9, 7±2, 9	13, 2±3, 6
Hct (%) (mean±SD)	57, 3±7, 8	40, 5±5, 5	31, 6±9, 9	43, 8±1, 59
WBC (μL) (mean±SD)	14745±8215, 8	11267±6154, 7	12044, 8±12943, 2	17166, 3±9285, 3
Platelet (μL) (mean±SD)	620770, 3±332871, 9	993069±402600, 4	326945, 2±353791, 4	620714, 3±477885
Bone Marrow Fibrosis (frequency, median grade)	46 %, 1 (0-4)	50 %, 0, 5 (0-2)	-	50 %, 1 (0-3)
Splenomegaly (cm) (mean±SD)	15, 4±3, 5	13, 9±1, 2	19±3, 6	15, 4±1, 4

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THE LEVELS OF COAGULATION FACTORS IN MYELOPROLIFERATIVE DISORDERS

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Background: Thromboembolic and hemorrhagic complications are seen frequently in myeloproliferatif diseases (MPD). Thromboembolic events are the most important cause of mortality in essential thrombocytemia (ET) and polyctytemia vera (PV). This condition may be explained with the functions and counts of platelets, leukocytes, and interactions of receptor and ligand expression of endothelial cells. But studies on coagulation factors is limited in MPD. Aim: To investigate the changes on coagulation pathways in MPD. Materials and Methods: Nineteen patients (12 female, mean age 57±15 years) with MPD and 15 healthy controls (9 female, mean age 56±9 years) were enrolled to the study. Thirteen of the patients had ET, 2 PV, and 2 had agnogenic myeloid metaplasia (AMM). Prothrombin (PT) and activated partial thromboplastin times (APTT), D-dimer, fibrinogen, vWF, activities of factors 2, 5, 7, 8, 9, 10, 11,12, protein-C (PC), protein S (PS), antithrombin-III (AT-III), activated protein-C resistance (APC-R) were examined in patients and controls not receiving myelosupressive, antiplatelet, and anticoagulant treatments. Results of two groups were compared using Mann-Whitney U test. Values of $p<0.05$ were accepted as significant. Results: The levels of D-dimer ($p<0.01$) and fibrinogen ($p<0.01$), the activities of vWf ($p<0.01$), and factor 8 in the patients with MPD were significantly higher than the control group. Moreover the activities of factor 5 ($p<0.01$), factor 9 ($p<0.05$), factor 10 ($p<0.01$), factor 11 ($p<0.001$), and factor 12 ($p<0.001$) and the level of APC-R ($p<0.005$) in the patients with MPD were significantly lower than the control group. But there were no differences for the levels of APTT, PT, PC, PC, AT-III and other coagulation factors between two groups. Conclusion: We detected some changes in coagulation pathways in MPD patients. Especially increase in the level of D-dimer and the activities of coagulation factors such as fibrinogen, vWf, and factor 8 may contribute to the pathogenesis of thromboembolic events. Moreover decrease in the activities of factors 5, 9, 10 and 11 may explain the hemorrhagic complications occurring in the course of all MPD.

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LIFE EXPACTATION AND INTENSITY OF CANCER IN BRIEF- AND FAMILY HISTORIES OF THE PATIENTS WITH MYELOPROLIFERATIVE DISEASES

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Background: Thrombosis and bleeding are the most important prognostic factors in myeloproliferative diseases (MPD). But there is not a prognostic factor for predicting survival at diagnosis. The determination of the intensity of the cancer incidence in brief- and family histories of patients may help to make a comment on the nature of the MPD. Aim: In this study, we investigated the effects of the concomitant diseases on survival and cancer intensity in brief- and family histories of the patients with MPD. Materials and Methods: Thirty-five (19 female, mean age 59 ±11 years) patients with MPD were enrolled to the study. The diagnosis of the patients were essential thrombocythemia in 19, polycythemia vera in six and primary myelofibrosis in six, and chronic myelocytic leukemia in four. By using Charlson's concomitant disease index, concomitant disease weight incidence, concomitant state-age relationship, and probability of 10 years survey were investigated. Results: In brief history of the patients, only one (3%) patient had skin cancer. However there were some cancers in family history of 9 patients (26%). These were hematological malignancies in four patients (2 acute myelocytic leukemia and 2 non-Hodgkin's lymphoma) and solid tumors in five patients (2 breast, 2 colon cancer, one skin and lung cancers). Mean Charlson's concomitant disease weight index was 1.4±1.5 (0-6), concomitant state-age relationship was 3.2±2 (0-8), and probability of 10 years survey was 63±35% (0-98%). Conclusion: Although our study group is small, Charlson's concomitant disease index may be used for the determining of life expectancy in MPD. Moreover cancer cluster in family history of these patients was notable.

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A COMMON JAK2 HAPLOTYPE CONFERS SUSCEPTIBILITY TO JAK2-V617F POSITIVE MYELOPROLIFERATIVE NEOPLASMS

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OBJECTIVES: Myeloproliferative neoplasms (MPN) are a heterogeneous group of chronic disorders characterized by clonal hematopoiesis. A somatic gain-of-function mutation in the JAK2 gene (JAK2-V617F) has been identified in about 50% of patients with MPN. Other rare oncogenic mutations and cytogenetic aberrations have also been implicated in the MPN pathogenesis. Individual genetic variation of JAK2 has been shown to associate with distinct MPN entities and to play role in phenotypic diversity. In a series of investigations on the relation between JAK2-V617F and other chromosomal aberrations, we identified a patient harboring JAK2-V617F in two distinct progenitor clones. Subsequent assessment of the JAK2 allele that acquired the mutation revealed that JAK2-V617F preferentially occurs on one of the two common JAK2 haplotypes. Therefore this sequence variant of the JAK2 gene confers susceptibility to JAK2-V617F positive MPN. METHODS: Peripheral blood mononuclear cells were plated in clonogenic methylcellulose media. DNA from colony-forming units was isolated for PCR genotyping of chromosome 13q and 20q deletions. The JAK2-V617F mutational status was determined by quantitative allele-specific PCR. Multiple occurrence of JAK2-V617F was assessed with V617F-specific PCR amplification and subsequent Taqman genotyping of the product for rs12343867 to determine the JAK2 allele that acquired the mutation. Genotyping of 8 single nucleotide polymorphisms (SNPs) in the JAK2 locus for haplotype determination was carried out using Taqman SNP genotyping assays. RESULTS: We

detected a frequency of 2.8% of multiple JAK2-V617F acquisitions in 109 MPN patients tested. We observed an unequal distribution of the JAK2-V617F mutation between the two JAK2 alleles defined by an intron 14 polymorphism (chi-square=60.38, P=7.8x10-15). Patients heterozygous or homozygous for the C variant of rs12343867 were more likely to acquire JAK2-V617F than patients homozygous for the T variant (P=5.69x10-6; OR 2.36, 95% CI 1.37-4.06 and 5.73, 2.75-11.92, respectively). Genotyping of 8 SNPs in the JAK2 locus in 333 MPN patients and 99 controls revealed a common JAK2 haplotype that preferentially acquires V617F and confers susceptibility to JAK2-V617F positive MPN (haplotype-specific chi-square=19.17, P=1.19x10-5). CONCLUSION: Our results indicate that the JAK2-V617F mutation can occur multiple times in the same patient in independent acquisition events. Furthermore, our investigations revealed that JAK2-V617F preferentially occurs on one of the two common JAK2 haplotypes. Therefore, patients harboring one specific variation of the JAK2 gene sequence are at higher risk to acquire the JAK2-V617F mutation. This new concept, that a certain DNA sequence variant sustains susceptibility to somatic mutations gives rise to the more general hypothesis, that cancer associated loci may harbor yet unknown mutations of pathogenetic relevance.

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THE ROLE OF SOLUBLE ENDOTELIAL PROTEIN C RESEPTOR AND NATURAL ANTICAOAGULANTS IN PATIENTS WITH POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA WHICH HAVE HISTORY OF THROMBOEMBOLISM

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The most important complications seen in myeloprolipherative diseases are thromboembolic events. Factors responsible for thrombosis are increase in platelet numbers, activation of leukocytes, circulating leukocyte and platelet aggregates, spontaneous aggregation and activation of platelets, tromboxane A2 production, hiperviscosity and endothelial damage. We planned to investigate levels of soluble endothelial protein C receptor (sEPCR) -a relatively new molecule which causes propensity to thrombotic state and natural anticoagulants in patients with polycythemia vera (PV) and essential thrombocythemia (ET). In addition, we aimed to study whether sEPCR and natural anticoagulant levels were different in patients with history of thromboembolic event from others without. We studied sEPCR, thrombin-antithrombin complex (TAT), prothrombin fragment 1+2 (F1+2), D-dimer and natural anticoagulants (antithrombin (AT), protein C (PC), protein S (PS)) in venous blood samples achieved from 25 patients with PCV and ET followed by our clinic for 5 years and 29 healty volunteers. Patients were 17 female, 8 male and mean age was 66±11. In TAT, D-dimer, F1+2 and sEPCR levels were statistically significant higher than control group (Table1). sEPCR, TAT, F1+2, D-dimer were found higher in patients with ET than patients with PCV (Table-2). In one study which investigated levels of natural anticoagulants in PCV and ET patients, PC, PS and AT levels were found lower than control group, However in our study these parameters were not different from control group. The parameters reflecting coagulation activation such as sEPCR, TAT, F1+2, D-Dimer were higher in PCV and ET patients than control group and this supports that all patients whether have thrombosis history or not have tendency for thromboembolic events. Strong positive correlation with TAT and sEPCR shows that sEPCR can be used as a marker in studies investigating coagulation activation.

	PATIENTS					HEALTHY CONTROLS					
	Mean±SD					Mean±SD					
	Median (Min-Maks)					Median (Min-Maks)					
D-Dimer	F1+2	TAT	AT 3	Prot S	Prot C	SEPCR	D-Dimer	F1+2	TAT	AT 3	Prot S	Prot C	SEPCR	p*
0. 26±0. 18	1192. 64±245. 22	209. 15±102. 28	108. 36±19. 34	82±28. 99	89. 68±30. 33	919. 20±336. 83	0. 23±0. 16	1091. 58±294. 22	199. 03±103. 65	106. 25±19. 80	87. 33±34. 78	84. 67±38. 12	788. 83±184. 90	
0. 21 (0. 05-0. 65)	1239 (298-1530)	223. 59 (4-422, 65)	110 (75-136)	79 (31-134)	96. 0 (9-134)	929 (328-1646)	0. 20 (0. 07-0. 59)	1195. 50 (298-1361)	196. 72 (4-345)	109 (75-134)	88 (31-134)	105 (9-126)	766 (542-1082)	
0. 15±0. 17	543. 41±246. 60	2. 50±5. 09	106. 28±22. 19	94. 14±30. 51	103±23. 15	524. 48±272. 08	0. 28±0. 20	1285. 92±145. 86	218. 50±104. 30	110. 31±19. 50	77. 08±22. 75	94. 31±21. 44	1039. 54±403. 59	
0. 13 (0, 0-0, 84)	616 (101-989)	0, 57 (0, 03-24)	102 (82-183)	97 (24-145)	105 (20-140)	655 (101-848)	0. 21 (0. 05-0. 65)	1250 (1014-1530)	223. 59 (94. 16-422. 65)	110 (76-136)	70 (42-118)	90 (55-34)	1022 (328-1646)	
0. 008	0. 0001	0. 0001	0. 131	0. 112	0. 101	0. 0001	0. 03	0. 0001	0. 0001	0. 285	0. 180	0. 251	0. 0001	

	PCV					ET					
	Mean±SD					Mean±SD					
	Median (Min-Max)					Median (Min-Max)					
D-Dimer	F1+2	TAT	AT 3	Prot S	Prot C	SEPCR	D-Dimer	F1+2	TAT	AT 3	Prot S	Prot C	SEPCR	p*
0. 23±0. 16	1091. 58±294. 22	199. 03±103. 65	106. 25±19. 80	87. 33±34. 78	84. 67±38. 12	788. 83±184. 90								
0. 20 (0. 07-0. 59)	1195. 50 (298-1361)	196. 72 (4-345)	109 (75-134)	88 (31-134)	105 (9-126)	766 (542-1082)								
0. 28±0. 20	1285. 92±145. 86	218. 50±104. 30	110. 31±19. 50	77. 08±22. 75	94. 31±21. 44	1039. 54±403. 59								
0. 21 (0. 05-0. 65)	1250 (1014-1530)	223. 59 (94. 16-422. 65)	110 (76-136)	70 (42-118)	90 (55-34)	1022 (328-1646)								
0. 03	0. 0001	0. 0001	0. 285	0. 180	0. 251	0. 0001								

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FAMILIAL CHRONIC MYELOPROLIFERATIVE DISORDER AND CAROTID STENOSIS

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In a 46 year old male patient who referred with the complaints of burning sensation, bruising and redness in the ends of lower extremities and headache underwent investigations and thrombocyte was found to be 1.5×109/μL, leukocyte 17×103/μL and hematocrite 55% . Mild splenomegaly was estahlished with abdominal ultrasonography and bone marrow biopsy yielded results consistent with chronic myeloproliferative disease, (Essential thrombocytosis -ET). Patient was diagnosed with ET. Upon cytogenetic analysis, Janus Kinase 2 V617F (JAK2) mutation was found to be positive. It was also learned that the mother of our patients has been being treated and followed with the diagnosis of JAK2 positive CMPD-idiopathic myelofibrosis for approximately 6 years. Patient was diagnosed with familial CMPD. In the history, it was learned that he had cerebral thrombosis two years ago and as sequel, he had slight loss of power in upper right extremity. Cytoreductive treatment and theropatic phlebotomus were commenced and thrombocyte, leukocyte and hematocrite levels returned to normal levels. Further investigations were carried out as patient had syncope attacks lasting for 1-3 sec. for the last 1-2 months and a thrombotic stenosis at the length of 2.5 cm which narrowed lumen in right carotid artery by 65% . Results of echocardiography and coronary angiography were normal. Patient was a smoker and he was made to quit smoking by being warned of smoking as a risk factor. Patient has symptomatic carotid artery stenosis and is being followed in neurology and neurosurgery clinics for endarterectomy. In conclusion, patients was followed with the diagnosis of ET and was found to have thrombosis attack and the newly developing sycope like attacks was ascribed to carotid artery stenosis. In CMPD patients in whom trombosis develops, many factors should be considered in etiology and treatment should be planned accordingly.

PALLIATIVE CARE – SUPPORTIVE THERAPY

P79

THE SELF-CARE AGENCY IN CHEMOTHERAPY RECEIVING AND NONRECEIVING PATIENTS

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Background. The number of patients chemotherapy receiving is increasing steadily. The aim of the present study was to evaluate self-care agency and to determine the factors affecting patients chemotherapy receiving (CR) and nonreceiving (CNR). Methods and Materials. This cross-sectional study was based in the Turkish city of İstanbul. The sample comprised 80 patients on maintenance CR and 15 patients on maintenance CNR. Data were collected through a self-report questionnaire and the Exercise of Self-Care Agency Scale, which was developed by Kearney and Fleischer. Results. The maximum score in the Kearney and Fleischer scale is 140, which indicates the highest degree of self care. The overall self-care agency mean score of the participants in this study was 113±18.33 (range, 48-137). No significant difference was found between the CR and CNR groups. Variables such as sex, health perception, no complications during chemotherapy therapy, and maintaining a suitable diet were significantly related to self-care agency. Male patients had a higher overall self-care agency mean score than did women. Patients who maintained a suitable diet, whose did not have complications during chemotherapy therapy, who perceived their health as good; and whose families were not affected negatively by chemotherapy had higher overall self-care agency mean scores than the others. Conclusions. The overall self-care agency means score of the chemotherapy receiving and nonreceiving patients was found to be moderate in level. Compliance programs may help patients and families cope with chemotherapy-related problems. Patients should be given support in handling self-care capabilities.

Table I. Chemotherapy-related characteristics of the study patients.

Variable n (%)	
chemotherapy type	
Receiving	80 (83. 7 %)
Nonreceiving	15 (16. 3 %)
chemotherapy duration	
<1 year	13 (14. 1 %)
1-3 years	36 (39. 1 %)
4-6 years	28 (30. 4 %)
7 years	15 (16. 3 %)
health perception	
good	72 (78. 3 %)
moderate	16 (17. 4 %)
bad	4 (4. 3 %)
disease compliance	
yes	88 (95. 7 %)
no	4 (4. 3 %)
maintenance of suitable diet	
yes	65 (70. 7 %)
no	27 (29. 3 %)
attention to drug therapy	
yes	88 (95. 7 %)
no	4 (4. 3 %)
attention to daily fluid intake	
yes	71 (77. 2 %)
no	21 (22. 8 %)
additional chronic health problems	
yes	51 (55. 4 %)
no	41 (44. 6 %)
problems during chemotherapy	
yes	48 (52. 2 %)
no	44 (47. 8 %)
chemotherapy -related problems	
Lack of appetite	39 (42. 4 %)
other (e. g., baldness)	7 (7. 6 %)
effect of chemotherapy therapy on family life	
yes	46 (50 %)
no	46 (50 %)

STEM CELL TRANSPLANTATION

P80

DONOR LYMPHOCYTE INFUSION FOR LEUKEMIA RELAPSE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION: AN ATTEMPT TO LIGHT THE LAST BEACON

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Leukemia relapse is the major cause of treatment failure after allogeneic hematopoietic stem cell transplantation (HSCT) and presents a serious therapeutic challenge. Adoptive immunotherapy with donor lymphocyte infusion (DLI) has proven to be effective in chronic myeloid leukemia, however patients with high tumor burden show far lower responses to DLI. Twenty three acute leukemia patients (15 (% 65.2) acute myeloblastic leukemia (AML), 8 (34.8%) acute lymphoblastic leukemia (ALL) ; Male/Female: 13/10; median age: 28 (18-64)) who received DLI ± induction chemotherapy for posttransplant leukemia relapse were retrospectively reviewed. Median follow up of the cohort was 106 (28-718) days. The overall response rate of DLI was 60.9% for the whole group, 66.7% for AML and 50% for ALL. The probability of disease free survival was 15.2% for AML and 50% for ALL (p>0.05). A total of 15 patients (65.2%) developed acute graft versus host disease (GVHD) at median 16 (2-100) days after DLI. Response rates were significantly higher in patients with post DLI GVHD (80% vs 25% ; p=0.01). This significance was confirmed on logistic regression analysis (p=0.01; OR: 12.0). The probability of overall survival (OS) was 16.5% for AML and 37.5% for ALL (p>0.05). Remarkably, the probability of OS was significantly higher in patients who respond to DLI (p=0.04). Allogeneic HSCT is the only treatment option with curative potential for many adult patients with acute leukemia. Besides eradicating the leukemic cells with intensive conditioning chemo/radiotherapy, adoptive transfer of antitumoral donor immunity also plays role in obtaining leukemia free survival. Increased relapse rates in syngeneic HSCTs and patients without GVHD suggest that alloreactive donor T cells might play an essential role in graft versus leukemia responses. Further studies are warranted to validate the survival benefit of DLI in leukemia relapse after allogeneic HSCT.

P81

ELEVATED FERRITIN LEVELS ARE ASSOCIATED WITH INCREASED FREQUENCY OF HEPATOSPLENIC CANDIDIASIS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES WHO ARE CANDIDATES FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Invasive fungal infections have emerged as an important causes of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. Hepatosplenic candidiasis (HSC) has been recognized a distinct form of invazive candidiasis in patients with acute leukemia since the 1980s. HSC is form of dissemined fungal infections with main involvement of the liver, spleen and occasionally the kidneys. This infection represents a rather distinct clinicopathologic entity with predominant involvement of the liver and spleen by candidal microabscesses. Patients and Methods: We investigated the role of iron overload (IO) in patients who were candidates for HSCT. The charts of 245 patients (M/F: 161/84; median age: 34 (16-71) who were evaluated pre HSCT between 2003 and 2008 at Gazi University Hospital were retrospectively reviewed. Results: Hepatosplenic candidiasis was demonstrated in 6 (2.2%) patients. Hepatosplenic candidiasis was more common in patients who received two or more chemotherapy regimens before HSCT, without statistical significance (p>0.05). The patients who developed HSC were found to have worse pretransplant performance status according to WHO and Karnofsky scale respectively (p=0.001, p=0.007). Pretransplant ferritin levels were found to be significantly higher in patients with HSC (p=0.008). Pretransplant acute phase reactants including erythrocyte sedimentation rate (p=0.025) and C reactive protein (p=0.007) were significantly higher, albumin level was lower (p=0.022) in patients with HSC while when compared to patients without HSC. Discussion: Iron overload has been suggested as a risk factor for HSC in patients with hematologic malignancies including haemochromatosis and thalassaemia. The association between invasive fungal infections, such as invasive aspergillosis and mucormycosis, and iron overload has also been documented in HSCT recipients. Iron does play a role in the function of phagocytes, as well as T and B cells, leading to an increased risk of fungal infections. As iron is essential for the growth of C. albicans, IO greatly exacerbates the course and progress of disseminated C. albicans infections. In vitro proliferation of Candida organisms correlates positively with transferrin saturation and negatively with non transferrin bound iron (NTBI). Remarkably, oxidative stress may cause IO related tissue damage and tendency to systemic fungal infections. Further clinical efforts should focus on the adverse impact of IO on fungal infections in HSCT recipients.

P82

EVALUATION OF CELLAVISION DM96™ IN MALIGNANT HEMATOLOGICAL DISORDERS

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Introduction: The bone marrow (BM) aspirate smear examination is a critical parameter in the diagnosis and management of malignant hematological disorders. A correct and rapid BM evaluation is necessary to follow-up with the appropriate laboratory tests, specifically immunophenotyping. Cella Vision DM96™ is an automated image analysis system that presents images of blood cells and suggests cell classification for white blood cells. The system preclassifies the following WBC classes: Band neutrophils, segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes, promyelocytes, myelocytes, metamyelocytes, blast cells, plasma cells on peripheral blood smears. In this study, we evaluated the DM96™ in the enumeration of BM aspirate smear and the clinical performance of DM96™ in the diagnosis and management of malignant hematological disorders. Method: BM aspirate smears of 62 patients with malignant hematological disorders from various types, were examined by the DM96™. Slides were prepared with SP-100 SYSMEX and also counted on the Sysmex XE-2100. Manuel microscopic analysis were performed by clinical hematologist. The reclassified results from the DM96™ for all cell classes were compared with manual microscopic / flow cytometric results. Results: DM 96™ succesfully analysed 62 patients bone marrow aspirate smears with the diagnoses of normal BM (16), acute lymphoblastic leukemia (10), acute myeloid leukemia (18), B-cell chronic lymphoproliferative disorders (13), and myelodisplastic syndrome (5). The correlation coeefficients between results from DM96™ after reclassification of cells and the results obtained by manuel microscopic analysis were 0.99 (blast cells), 0.70 (band neutrophils), 0.90 (segmented neutrophils), 0.90 (lymphocytes), 0.77 (monocytes), 0.74 (myelocytes), 0.70 (metamyelocyte), 0.65 (promyelocyte) and 0.51 (eosinophil). The lowest correlations were observed for eosinophils and promyelocytes. Correlation coefficient between the percentage of blast cells detected by DM96™ and flow cytometry analysis was 0,96. Conclusion: In this study, we demostrated that the results obtained from DM96™ correlated well to those obtained by manual microscopic analysis and flow cytometric analysis of all bone marrow smears with different haematological disorders. Although the DM 96™ is designed for the peripheral blood differantial count, we suggest its use in bone marrow aspirate smears, and also the system is very useful tool for correct and rapid hematological evaluation in diagnosis of malignant hematological disorders.

P83

LAMIVUDIN PROPHYLAXIS IN HBSAg POSITIVE STEM CELL RECIPIENTS

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Viral hepatitis is one of the major causes of liver dysfunction. Prevalence of hepatitis B virus (HBV) infection increased compared with the general population worldwide and has become a significant concern in patients with hematological malignancies receiving chemotherapy. HBV reactivation in patients undergoing chemotherapy is associated with a high mortality rate. Thus, identification of patients with hematological malignancies who are at risk for viral hepatitis is very important. HBV reactivation may necessitate interruption of chemotherapy. We have 8 allogeneic 4 autologous hematopoietic stem cell transplant patients who were HBaAg positive recieved chemotherapy under lamivudin prophylaxis. 4 patients with AML, 1 patient with CML, 1 patient with AML, 1 patient with NHL and one patient with aplastic anemia underwent allogeneic stem cell transplantation. 2 patients with multiple myeloma, 1 patient with NHL and one patient with AML underwent autologous stem cell transplantation. Liver function tests of these patients were in normal limits and HBV DNA levels were under 10.000 copies/ml before and during the transplantation. No acute flares of hepatitis B was seen after transplantation in the first 100 days. Lamivudine prophylaxis during chemotherapy is effective in reducing the rate of HBV reactivation in patients with immune suppression. HBsAg positivity is not a obstacle for giving chemotherapy or hematopoietic stem cell transplantation. It is recommended to screen for HBV infection in all patients with hematological malignancies. HBsAg positive or HBV DNA positive patients should be started on lamivudine treatment before chemotherapy.

MISCELLANEOUS

P84

THE ROLE OF BODY MASS INDEX AND OTHER BODY COMPOSITION PARAMETERS IN EARLY POSTTRANSPLANT COMPLICATIONS IN PATIENTS WHO UNDERWENT ALLOGENEIC STEM CELL TRANSPLANTATION WITH THE CONDITIONING REGIMEN BUSULPHAN- CYCLOPHOSPHAMIDE

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Background: Both underweight and overweight patients were reported to be under increased risk of transplant related mortality. The aim of this study was to determine whether body mass index (BMI) and other body composition parameters [lean body mass (LBM), body fat mass (BFM), body fat ratio (BFR)] are related to early post-transplantation NCI toxicity and mortality in patients who underwent allogeneic haematopoietic stem

cell transplantation (AHSCT) with the conditioning regimen busulphan- cyclophosphamide (Bu- Cy). Patients and Methods: We retrospectively evaluated the records of 71 patients [46 male, 25 female; median age 29 years (range 17- 55)] who had undergone AHSCT with the conditioning regimen Bu- Cy between September 2003-January 2009. Primary diagnosis were; acute myeloid leukemia in 44 patients (62%), acute lymphoblastic leukemia in 12 patients (16.9%), chronic myeloid leukemia in 7 patients (9.9%) and myelodisplastic syndrome in 8 patients (11.3%)]. Adjusted body weight [ideal body weight + 0. 25 (actual body weight- ideal body weight)] was used in overweight patients to calculate adjusted chemotherapy doses. BMI was defined as; underweight: < 18.5 kg/m2, normal: 18.5-24.9 kg/m2, overweight: 25.0-29.9 kg/m2, and obese: ≥ 30.0 kg/m2. LBM for men was defined as low < 16. 6 kg/m2 and normal > 16. 7 kg/m2. For women it was defined as low < 14. 5 kg/m2 and normal > 14. 6 kg/m2. Results: BMI was classified as underweight in 4 patients (5. 6%), normal in 39 patients (54. 9%), overweight in 17 patients (23. 9%) and obese in 11 patients (15. 5%). LBM was classified as low in 9 patients (12. 7%), and normal in 62 patients (87. 3%). BMI was found to be negatively correlated with the NCI grade of mucositis (r=-0.291, p=0.014), cardiotoxicity (r=-0.330, p=0.005), nausea (r=-0.317, p=0.007) and hyperglycemia (r=- 0.243, p=0.041). Both BMI and LBW were negatively correlated with the number of erythrocyte transfusions (r=-0.290, p= 0.014), and r=-0.241, p=0.043 respectively). The grade of febril neutropenia was positively correlated with LBM (r=0.257, p=0.031). BFM and BFR were negatively correlated with the day of neutrophil engraftment (r=-0.276, p=0.027 and r=-0.303, p=0.015 respectively) and the NCI grade of mucositis (r=-0.329, p=0.005 and r=-0.440, p=0.000 respectively). In Cox regression analysis BMI and other parameters of body composition did not show any effect on early post-transplant mortality (p> 0. 05). Discussion: In our study, obese patients did not experience unfavorable outcome for the grade of NCI toxicity, transfusion requirement, and early post-transplant mortality. Dose adjustment according to ideal body weight might have decreased the risk of the degree of NCI toxicity of chemotherapeutic agents. Higher incidence of NCI toxicities in patients with low BMI might be a result of poor nutritional status and/ or aggressive disease status. Our results show that, obesity alone should not be predicted as a contraindication in the transplant setting.

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