Turkish Society of Hematology

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6th International Congress on Leukemia Lymphoma Myeloma

May 11-13 2017 | Antalya TURKEY

Xanadu Resort Hotel

Proceedings & Abstract Book

6th International Congress on Leukemia – Lymphoma – Myeloma

May 11 – 13, 2017 • Antalya, Turkey

Proceedings & Abstract Book

Turkish Society of Hematology

Organizing Committee

Congress President

Ahmet Muzaffer Demir
Trakya University, School of Medicine, Department of Hematology, Edirne, Turkey

Congress Secretaries

Güner Hayri Özsan
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Chronic Lymphocytic Leukemia	Önder Arslan *Ankara University, Ankara, Turkey*
Myelodysplastic Syndromes	H. Joachim Deeg *Fred Hutchinson Cancer Research Center, Seattle, USA*
Follicular Lymphomas	Burhan Ferhanoğlu *Koc University, Istanbul, Turkey*
Diffuse Large B-Cell Lymphoma	Christian Gisselbrecht *Hôpital SaintLouis, Paris, France*
Acute Lymphoblastic Leukemia	*Moniq den Boer* *(Erasmus University Medical Center, Rotterdam, Netherlands)*
Hodgkin Lymphoma	Muhit Özcan *Ankara University, Ankara, Turkey*
Multiple Myeloma	Evangelos Terpos *University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece*
Acute Myeloid Leukemia	Jacob Rowe *Shaare Zedek Medical Center, Jerusalem, Israel*
Chronic Myeloid Leukemia	Teoman Soysal *Istanbul University, Istanbul, Turkey*
Aggressive Lymphomas	Anna Sureda *Hospital Duran i Reynals, Barcelona, Spain*
BCR/ABL Negative Chronic Myeloproliferative Disorders	Francesca Palandri *University of Bologna, Italy*
Meeting the Challenge of Emerging Pathogens in Patients with Hematological Malignancies: Rational Approaches to Diagnosis, Treatment, and Prevention	Thomas J. Walsh *National Cancer Institute, Bethesda, USA*

Dear Colleagues,

It gives me great honor and pleasure to welcome you to the 6th International Congress on Leukemia-Myeloma-Lymphoma (ICLLM 2017) in Antalya, Turkey. The ICLLM2017 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. ICLLM is being held biannually since 2007. The number of Congress participants is showing a substantial increase. In 2015, we hosted over 500 attendees. In general, majority of the participating specialists are from university hospitals, and researchers not only from all countries of Europe, but also from North Africa, Middle East countries, United States, Middle and South America attend the Congress.

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. There are 13 scientific education sessions, 4 satellite symposia with a total 28 scientific chair and 36 speakers. New diagnosis and treatment strategies of the malignant hematological diseases will be discussed with every aspect besides the standard therapies.

Congress has been accredited by both the European Hematology Association (EHA) and the Turkish Medical Association. On behalf of the Board of the Turkish Society of Hematology and scientific faculty, I would like to welcome you to the 6th International Congress on Leukemia-Myeloma-Lymphoma. I believe that you will enjoy both the scientific and cultural aspects of the program, and that you also take advantage of the pleasure of the nice Antalya spring.

Sincerely

On behalf of President, 6th ICLLM & Turkish Society of Hematology President.

Prof. Dr. Ahmet Muzaffer Demir

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6th International Congress on Leukemia – Lymphoma – Myeloma

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SCIENTIFIC PROGRAMME

Scientific Programme

May 11, 2017, Thursday

TIME	MEETING HALL A	
08:30 – 10:00	**ACUTE MYELOID LEUKEMIA** *Scientific Chairs: Jacob Rowe (Shaare Zedek Medical Center, Jerusalem, Israel), Siret Ratip (Acıbadem Kozyatagi Hospital, Istanbul, Turkey)* • **Novel Agents in AML** *Eytan Stein (Memorial Sloan Kettering Cancer Center, New York, USA)* • **Transplants for AML in First Complete Remission** *Nicolaus Kröeger (University Medical Center Hamburg-Eppendorf, Hamburg, Germany)* • **Importance of MRD in AML** *Jacob Rowe (Shaare Zedek Medical Center, Jerusalem, Israel)*	
10:00 – 10:30	**COFFEE BREAK**	
10:30 – 12:00	**MULTIPLE MYELOMA** *Scientific Chairs: Evangelos Terpos (University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece), Güner Hayri Özsan (Dokuz Eylül University, Izmir, Turkey)* • **Optimal Therapy for Newly Diagnosed Patients Who Are Eligible for Autologous Transplantation** *Evangelos Terpos (University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece)* • **Can MRD Tailor Therapy for Myeloma Patients?** *C. Ola Landgren (Memorial Sloan Kettering Cancer Center, New York, USA)* • **Emerging Problems with the Use of Monoclonal Antibodies in the Everyday Management of Myeloma Patients** *Efstathios Kastritis (National and Kapodistrian University of Athens School of Medicine, Athens, Greece)*	
12:00 – 13:15	**LUNCH**	**POSTER DISCUSSION**

13:15 – 14:15	AMGEN **SATELLITE SYMPOSIUM** *Scientific Chair: Ali Zahit Bolaman (Adnan Menderes University, Aydın, Turkey)* **New Era in the Treatment of Relapsed / Refractory Multiple Myeloma** *Evangelos Terpos (University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece)*
14:15 – 14:30	**BREAK**
14:30 – 16:00	**DIFFUSE LARGE B-CELL LYMPHOMA** *Scientific Chairs: Christian Gisselbrecht (Hospital Saint Louis, Paris, France), Levent Ündar (Akdeniz University, Antalya, Turkey)* • **Update on Pathology with New WHO Classification** *Thierry Molina (Necker University Hospital, Paris, France)* • **Relapse DLBCL Where Are We With ASCT?** *Christian Gisselbrecht (Hospital Saint Louis, Paris, France)*
16:00 – 16:30	**COFFEE BREAK**
16:30 – 17:30	**BCR/ABL NEGATIVE CHRONIC MYELOPROLIFERATIVE DISORDERS** *Scientific Chairs: Francesca Palandri (University of Bologna, Italy), Fahir Özkalemkaş (Uludag University, Bursa, Turkey)* **Philadelphia – Negative Chronic Myeloproliferative Neoplasms: Diagnostic Criteria and Personalized Therapy in 2017** *Francesca Palandri (University of Bologna, Italy)*
18:00 – 19:30	**OPENING CEREMONY (Foyer Area)**

Scientific Programme

May 12, 2017, Friday

TIME	MEETING HALL A
09:00 – 10:00	**ACUTE LYMPHOBLASTIC LEUKEMIA** *Monique den Boer (Erasmus University Medical Center, Rotterdam, The Netherlands), Hale Ören (Dokuz Eylül University, Izmir, Turkey)* • **New Prognostic and Predictive Markers for ALL** *Monique den Boer (Erasmus University Medical Center, Rotterdam, The Netherlands)* • **Treatment of Young Adult ALL** *İnci Alacacıoğlu (Dokuz Eylül University, İzmir, Turkey)*
10:00 – 10:30	**COFFEE BREAK**
10:30 – 11:30	Bristol-Myers Squibb **SATELLITE SYMPOSIUM** *Scientific Chairs: Mustafa Çetin (Erciyes University, Kayseri, Turkey), Mustafa Nuri Yenerel (İstanbul University, İstanbul, Turkey)* **The Impact of Dasatinib on Clinical Management and Pathobiology of CML** *İbrahim C. Haznedaroğlu (Hacettepe University, Ankara, Turkey)*
11:30 – 11:45	**BREAK**
11:45 – 13:15	**HODGKIN LYMPHOMA** *Scientific Chairs: Peter Borchmann (Klinik I für Innere Medizin, Cologne, Germany), Muhit Özcan (Ankara University, Ankara, Turkey)* • **First Line Therapy of Early Stage cHL: Should We Go for PET Adapted Treatment Strategies?** *Veronika Bachanova (University of Minnesota, Minnesota, USA)* • **First Line Therapy of Advanced Stage cHL: Pros and Cons for Different Treatment Strategies** *Peter Borchmann (Klinik I für Innere Medizin, Cologne, Germany)* • **Relapsed cHL and Perspectives: Will Immunotherapy Replace Chemotherapy?** *Michael Crump (Princess Margaret Cancer Center, University Health Network, Toronto, Canada)*

13:15 – 14:30	**LUNCH**	**POSTER DISCUSSION**
14:30 – 16:00	**MEETING THE CHALLENGE OF EMERGING PATHOGENS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: ADVANCES IN DIAGNOSIS, TREATMENT, AND PREVENTION** *Scientific Chairs: Thomas J Walsh (Weill Cornell Medicine of Cornell University, New York, USA), Ali Zahit Bolaman (Adnan Menderes University, Aydın, Turkey)* • **Multidrug Resistant Bacterial Infections in Patients with Hematological Malignancies New Compounds for Emerging Pathogens** *Thomas J Walsh (Weill Cornell Medicine of Cornell University, New York, USA)* • **Invasive Fungal Infections in Patients with Hematological Malignancies: Emergence of Resistant Pathogens and New Antifungal Therapies** *Maria N. Gamaletsou (St James's University Hospital, Leeds Teaching Hospitals, Leeds, United Kingdom)* • **Viral Infections in Patients with Hematological Malignancies: Rapid Molecular Diagnosis and Antiviral Strategies** *Nikolaos V. Sipsas (National and Kapodistrian University of Athens, Athens, Greece)*	
16:00 – 16:30	**COFFEE BREAK**	
16:30 – 17:30	**MYELODYSPLASTIC SYNDROMES** *Scientific Chairs: H. Joachim Deeg (Fred Hutchinson Cancer Research Center, Seattle, USA), Zafer Gülbaş (Anadolu Medical Center, Kocaeli, Turkey)* • **Focus on Medical Management of Patients with MDS** *Ibrahim Yakoub Agha (Regional University Hospital, Lille, France)* • **Focus on Transplantation for MDS** *H. Joachim Deeg (Seattle Cancer Care Alliance, Seattle, USA)*	

Scientific Programme

May 13, 2017, Saturday

TIME	MEETING HALL A	MEET THE EXPERT HALL
07:00 – 08:15		GILEAD **SATELLITE SYMPOSIUM** • **Changing Epidemiology of Invasive Mycoses** *Sevgi Beşışık (İstanbul University, İstanbul, Turkey)* • **Antifungal Treatment Algorithms: From Theory to Practice** *Thomas J. Walsh (Weill Cornell Medicine of Cornell University, New York, USA)*
08:30 – 10:00	**FOLLICULAR LYMPHOMA** *Scientific Chairs: Massimo Federico (Università degli Studi di Modena e Reggio Emilia, Modena, Italy), Burhan Ferhanoğlu (Koç University, Istanbul, Turkey)* • **First Line Therapy for Follicular Lymphoma** *Elif Birtaş Ateşoğlu (Kocaeli University, Izmit, Turkey)* • **Are We Ready for a Chemofree Approach for Treating Patients with Advanced Follicular Lymphoma?** *Armando Lopez Guillermo (Hospital Clinic of Barcelona, Barcelona, Spain)* • **Maintenance Therapy: All Fit in One?** *Massimo Federico (Università degli Studi di Modena e Reggio Emilia, Modena, Italy)*	
10:00 – 10:30	**COFFEE BREAK**	
10:30 – 11:30	Celgene **SATELLITE SYMPOSIUM** *Scientific Chair: Yıldız Aydın (İstanbul University, İstanbul, Turkey)* **NEW HOPE for RRMM Patients: FOCUS on Efficacy & Safety of IMNOVID** *Meral Beksaç (Ankara University, Ankara, Turkey)*	
11:30 – 11:45	**BREAK**	

11:45 – 13:15	**CHRONIC MYELOID LEUKEMIA** *Scientific Chairs: Hanan Hamed (Ain Shams University, Cairo, Egypt), Teoman Soysal (Istanbul University, Istanbul, Turkey)* • **WHO 2016 Diagnostic Criteria of CML; What is Old, What is New?** *Hanan Hamed (Ain Shams University, Cairo, Egypt)* • **Current Molecular Monitoring of CML** *Akif Selim Yavuz (Istanbul University, Istanbul, Turkey)* • **Current Clinical Management of CML** *İbrahim C. Haznedaroğlu (Hacettepe University, Ankara, Turkey)*	
13:15 – 14:30	**LUNCH**	**POSTER DISCUSSION**
14:30 – 16:00	**CHRONIC LYMPHOCYTIC LEUKEMIA** *Scientific Chairs: Oliver Karanfilski (University Clinic for Hematology, Skopje, Macedonia), Önder Arslan (Ankara University, Ankara, Turkey)* • **Prognostic Factors in Newly Diagnosed CLL** *Oliver Karanfilski (University Clinic for Hematology, Skopje, Macedonia)* • **First-Line Therapy for CLL as of 2017** *Fatih Demirkan (Dokuz Eylül University, Izmir, Turkey)* • **Relapse/Refractory CLL Treatment** *Ioannis Kotsianidis (University Hospital of Alexandroupolis, Alexandroupoli, Greece)*	
16:00 – 16:30	**COFFEE BREAK**	
16:30 – 17:30	**AGGRESSIVE LYMPHOMAS** *Scientific Chairs: Anna Sureda (Hospital Duran i Reynals, Barcelona, Spain), İnci Alacacıoğlu (Dokuz Eylül University, Izmir, Turkey)* • **The Role of Allogeneic Stem Cell Transplantation in the Treatment of Aggressive Lymphomas** Anna Sureda (Hospital Duran i Reynals, Barcelona, Spain) • **What is New in the Treatment of Peripheral T Cell Lymphomas?** *Norbert Schmitz (Asklepios Klinik St. George, Hamburg, Germany)*	

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Proceedings

Eytan M. Stein

Eytan M. Stein, MD is an Assistant Professor on the Leukemia Service at Memorial Sloan Kettering Cancer Center. He received his MD from the Feinberg School of Medicine at Northwestern University in Chicago where he was elected to the Alpha Omega Alpha Medical Honor Society and was awarded a Howard Hughes Medical Student Fellowship. He went on to complete his residency in Internal Medicine at Northwestern Memorial Hospital and his fellowship in Hematology and Medical Oncology at Memorial Sloan Kettering Cancer Center in New York City. His clinical practice focuses on the treatment of acute and chronic leukemias, myelodysplastic syndromes and myeloproliferative neoplasms. His research interests include developing early phase clinical trials of compounds that target the genetic and epigenetic basis of myeloid malignancies. In this respect, he has led clinical trials of the IDH1/2 inhibitors Ivosidenib and Enasidenib, the DOT1L inhibitor EPZ-5676 and the antibody-drug conjugate Vadastuximab Talirine (SGN-CD33A) as well as many other studies.

Nicolaus Kröger

University Medical Center Hamburg-Eppendorf Hamburg, Germany

Dr. Nicolaus Kröger is Professor of Medicine and Medical Director of the Department of Stem Cell Transplantation at the University Medical Center Hamburg-Eppendorf, Germany. Following the completion of his medical degree, he visited the MD Anderson Hospital, Houston, USA. Prof. Kröger is board certified in Hematology-Oncology and Internal Medicine.

From 2006 to 2012 he served as chairman of the MDS subcommittee of the European Group for Blood and Marrow Transplantation (EBMT), and since 2012 he is the chairman of the Chronic Malignancies Working Party and board member of EBMT, and since 2014 also the chairman of the Scientific Council of EBMT.

In 2015, he was elected as chairman of the German Stem Cell Working Group (DAG-KBT). Prof. Kröger is also member of several editorial boards such as Blood, Haematologica and Bone Marrow Transplantation. Since 2016 he is also member of the Scientific Program Committee and the Editorial Board of the European Hematology Association (EHA) and member of the Scientific Committee of the European School for Hematology (ESH). Additional memberships include societies such as the American Society of Hematology (ASH), European Hematology Association (EHA), European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) , the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) and the International Myeloma Working Group (IMWG).

He has received several awards for his work to date including the prestigious EBMT van Bekkum Award in 2015.

Prof Kröger has co-organized several international meetings such as the “1st and 2nd NCI Workshop on Biology, Prevention and Treatment of Relapse after Stem Cell Transplantation” in Bethesda/USA 2009 and 2012, “Controversies in Stem Cell Transplantation and Cellular Therapies (COSTEM)” in Berlin/Germany 2011, 2013 and 2015 and “Modern Trends in Human Leukemia” in Wilsede/Germany 2014 and 2016.

His research interest is on stem cell biology and stem cell transplantation, the detection and treatment of minimal residual disease by adoptive immunotherapy or novel drugs, the impact of NK-cell allo-reactivity, optimizing outcome with HLA-mismatched donor, and prevention and treatment of chronic graft-versus- host disease.

Prof. Kröger has published extensively in his area of expertise and has contributed to more than 450 publications in peer-reviewed journals such as NEJM, Lancet, JCO, JNCI, PNAS, Blood and Leukemia.

Stem Cell Transplantation for AML in 1. CR

Nicolaus Kröger

Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf Martinistraße 52, 20246 Hamburg

Allogeneic stem cell transplantation is the most effective postremission therapy for patients with Acute Myeloid Leukemia (AML). However, due to the high morbidity and also mortality associated with allogeneic stem cell transplantation, this procedure is clearly indicated for patients with poor and very poor risk AML, while for intermediate risk patients patient-related factors such as comorbidities and age as well as donor availability has to be taken into account. However results of using alternative donor such as mismatched unrelated, cord blood and more recently haploidentical donor has been improved substantially and the issue of the optimal donor is currently a matter of debate. Especially the results of haploidentical stem cell transplantation by using cyclophophamide posttransplant as GvHD prophylaxis has shown very encouraging outcome. AML patients with favorable risk receive in general chemotherapy as consolidation, although more recent studies have shown a very favorable outcome after allogeneic stem cell transplantation. The role of the intensity of the conditioning regimen is still not solved. Randomized studies resulted in inconsistent results. The transplant community is prefering reduced intensity regimens in older patients or those with comorbidities. Autologous stem cell transplantation is considered to be a reasonable alternative for patients with favorable risk and without minimal residual disease. Due to better management of infectious complication, toxicity as well as graft-versus host disease the non-relapse mortality has substantially decreased in the last years. The major treatment failure after allogeneic stem cell transplantation is now relapse and current clinical studies are focusing on prevention of relapse by monitoring minimal residual disease and using posttransplant cellular or drug approaches.

Jacob M. Rowe, M.D., F.A.C.P.

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Present Position

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Emeritus Professor Professor of Hemato-oncology, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

Adjunct Professor of Medicine, Department of Medicine, Northwestern University, Chicago, IL

Education

1972	B.Sc. in Pharmacology (First Class Honors), University of London, London, UK
1975	M.B., B.S. in Clinical Medicine, University of London, London, UK
1975-1976	House Physician, University College Hospital, London, UK
1976-1977	House Surgeon, Chaim Sheba Medical Center, Tel Hashomer, Israel
1977-1978	Resident, Hadassah University Hospital, Jerusalem, Israel
1978-1981	Hematology/Oncology Fellow, University of Rochester School of Medicine & Dentistry, Rochester, NY
	1980-1981 Chief Medical Resident and Oncology Fellow, St Mary's Hospital, University of Rochester, Rochester, NY

Professional Hospital and Administrative Appointments

1981-1983	Director of Internal Medicine Residency Program, St. Mary's Hospital, University of Rochester, Rochester, NY
1981-1996	Attending Physician/Admitting Privileges, Strong Memorial Hospital, Rochester, NY
1989-1991	Founding Medical Director, Bone Marrow Transplant Program, University of Rochester
1989-1996	Director of Clinical Services, Hematology Unit, Strong Memorial Hospital
1992-1996	Director, Medicine Treatment Center, Department of Medicine Strong Memorial Hospital
1993-1996	Acting Medical Director, Bone Marrow Transplant Program, Strong Memorial Hospital, University of Rochester Medical Center
1994-2011	Chief, Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, Haifa, Israel
2006-2009	Vice Dean for Clinical Appointments, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
2009-2011	Chairman Helsinki Committee for Investigation of Human Subjects, Technion, Institute of Technology, Haifa, Israel
2011-pres	Chief, Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel
	Licensure New York State Permanent Medical Licensure No. 139041 Britain 1976 Israel Medical Association, No 27567

Professional Board Certification (ABIM)

1980	Internal Medicine
1982	Hematology

Over 376 abstracts presented at major national or international meetings. Over 450 publications. Multiple research activities nationally and internationally. Editor of multiple international journals. Membership in multiple national and international academic professional organizations. Recipient of multiple national and international honors.

Importance of MRD in AML

Jacob M. Rowe

Shaare Zedek Medical Center, Jerusalem Rambam Healthcare Campus and Technion, Israel Institute of Technology, Haifa, Israel

The definition of complete remission or relapse in major clinical trials (5% leukemic blasts) has not changed in over 40 years. The introduction of MRD-sensitive measuring techniques has established that the term "complete" for remission achieved with induction is too ambitious.

"Minimal" residual disease, or preferably "measurable" residual disease, represents the best definition of depth of remission as the quality of remission predicts for short- and long-term response. MRD is a post-treatment condition (induction, consolidation or transplant), referring to the presence of residual leukemia cells that ordinarily are not detected by standard morphologic criteria, but are not eradicated by treatment. With current sensitive techniques, one may detect one in 10,000 or 100,000 (10^{-4} or 10^{-5}) cells. It is important to emphasize at this point that a negative MRD assessment, at any time point, does not define cure; rather, it is an important prognostic indicator at a specific time-point that may impact the decision for subsequent therapy. Similarly, a positive MRD assessment does not preclude a long-term response to current therapy.

Relapses may occur from primitive leukemia-initiating cells, not measured by standard MRD methodology. In addition, leukemic phenotype often shift from diagnosis to relapse and differentiation, or clonal hematopoiesis, and may result in false positive MRD.

The challenge of MRD in AML is obtaining uniform specificity of any test and its wide-spread applicability. Interpreting within, and across, studies is often fraught with hazards. Furthermore, the optimal time-points for reasonable predictability have yet to be defined.

MRD testing has been proven to be accurately predictive in chronic myeloid leukemia (CML) and in acute promyelocytic leukemia (APL). Definitive time-points have now been established and a uniform methodology has been developed. In pediatric acute lymphoblastic leukemia (ALL), it has been incorporated into standard protocols as a prognostic marker impacting therapy; in adult ALL the prevailing direction is very similar (Brüggeman M., Gökbuget N, Kneba M. Acute lymphoblastic leukemia: monitoring minimal residual disease as a therapeutic principle. Semin Oncol. 2012 Feb;39(1):47-57).

In AML, multi-parameter flow cytometry (MFC) detects cell populations with a unique anti-antigen-expression pattern that are usually not present in normal or regenerating bone marrow or peripheral blood. MRD based on MFC is widely applicable with a sensitivity in 1 in 10,000 cells and with a rapid turn-around, usually within 24 hours. There are, however, unique problems with this method of MRD assessment. First, not all leukemia cells have an abnormal phenotype that can be detected. The difficulty of distinguishing between monoblasts and normal monocytes is well-known. Second, the phenotype may change over time, related to clonal evolution or changes in the cell cycle. Most importantly, sample quality and quantity are crucial for precise assessment, and much expertise and experience is needed in the analysis and interpretation of the data from such studies. The best data have been reported where central laboratories perform the tests. In an important German study (Köhnket T, Sauter D, Ringel K, *et al.* Early assessment of minimal residual disease in AML by flow cytometry during aplasia identifies patients at increased risk of relapse. Leukemia 2015 Feb;29(2):377-86), MRD was measured during aplasia in AML. Day 16-18 of induction therapy was used, and a 0.15% cutoff by flow cytometry was considered as MRD positive. Importantly, the post-remission therapy was determined by usual prognostic factors (cytogenetics, WBC and mutations), but was not affected by results of the MRD. The study showed that MRD during aplasia was predictive of an ultimate relapse-free and overall survival across almost all prognostic groups.

MRD using MFC has also been shown to be predictive before myeloblative allogeneic stem cell transplantation for AML. The group in Seattle in the USA studied almost 300 adult patients in CR1 or CR2 using MRD that was measured by ten color FLC

(Zhou Y, Othus M, Araki D, *et al.* Pre- and post-transplant quantification of measurable ('minimal') residual disease via multiparameter flow cytometry in adult acute myeloid leukemia. Leukemia 2016 Jul;30(7):1456-64). This study showed that any degree of MRD positivity pre-transplant was highly predictive of the post-transplant outcome, irrespective of the MRD status immediately post-transplant. Interestingly, and somewhat surprisingly, these data were similar for CR1 and CR2.

Quantitative real-time polymerase chain reaction (PCR) is another highly sensitive technique to monitor MRD in some patients with AML with a sensitivity of around 10^{-5}. In an important recent work from Britain, evaluating the NCRI AML-17 study, NPM1 mutations were evaluated using RT-qPCR. This study took advantage of the fact that these mutations are present in one third of patients with AML and in one half of patients with cytogenetically normal AML. Centralized molecular screening was performed; specimens were collected at various time points following diagnosis, recovery from each cycle, and then at every three months. Importantly, clinicians were not informed of the MRD status. In an analysis of almost 350 patients, MRD positivity was highly predictive of increasing relapse rate when measured after two cycles of chemotherapy (Ivey A, Hills R, Simpson M, *et al.* Assessment of minimal residual disease in standard-risk AML. N Engl J Med 2016; 374:422-433).

Use of RT-qPCR has also been shown to be reliably predictive for runt-related transcription factor AML (RUNX1/RUNX1T). In an analysis of almost 300 patients the MRC AML-15 study, 163 patients with t(8:21) 115 with inv16 measured by fusion transcripts. Once again, any reduction in detection of transcripts led to a significant improvement in the relapse rate (Liu Yin JA, O'Brien M, Hills R, *et al.* Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood 2012 120:2826-2835).

Taken together, these data strongly suggest that MRD in AML, like ALL, is likely in time to supersede many of the previously establish prognostic factors. MRD testing provides a sensitive tool for monitoring of disease activity and response. However, the sensitivity and specificity of any MRD testing technique, should be carefully considered prior to its implementation. No generic approach is applicable to all patients with AML. In core-binding leukemia, and in patients where an MPM1 mutation is present along with a normal karyotype, the use of MRD monitoring is supported by recent clinical data. Multi-parameter flow cytometry is a promising tool in monitoring AML, although it is technically challenging and requires well-trained laboratory staff.

In studies of AML, the prognostic implication of MRD measuring have the greater significance if performed following chemotherapy and prior to allogeneic transplantation. It is likely, within a few years, to be incorporated into routine clinical practice.

Evangelos Terpos

Evangelos Terpos, MD, PhD is an Associate Professor of Hematology in the Department of Clinical Therapeutics in the University of Athens, School of Medicine, Athens, Greece. He has also been appointed as Honorary Senior Lecturer in the Department of Haematology, Faculty of Medicine Imperial College London, UK.

His main research interest is the biology of plasma cell dyscrasias and especially the biology of bone disease in multiple myeloma (MM). In more than 380 papers in peer-reviewed journals, Dr Terpos has reported the significant role of RANKL and osteoprotegerin axis, CCL-3 (MIP-1α), Wnt and TGF-beta signalling in myeloma bone disease and myeloma cell growth. He has studied the predictive value of markers of bone remodelling and osteoclast function in myeloma progression and patients' survival. He has evaluated the effect of bisphosphonates and different anti-myeloma therapies including ASCT, IMiDs- and bortezomib-based regimens on bone metabolism. He has studied the biology and prevalence of osteonecrosis of the jaw in myeloma patients who receive bisphosphonates. Dr Terpos also works on the role of modern imaging (including whole-body low-dose CT and MRI) for MM, of angiogenesis in MM and Waldenstrom's Macroglobulinemia, and of renal impairment in MM. In the clinical research era, Dr Terpos participates in several important clinical trials with novel agents (pomalidomide, carfilzomib, ixazomib, daratumumab, elotuzumab, isatuximab, panobinostat, etc) in the field of multiple myeloma.

Dr Terpos is co-chairing the Bone Subgroup of the International Myeloma Working Group and the Guideline Subgroup of the European Myeloma Network. Dr Terpos has given lectures at ASH, ASCO & EHA meetings, International Myeloma Workshops, International Meetings on Cancer-Induced Bone Disease and in several national meetings. He is reviewer of scientific papers in more than 50 medical journals and has reviewed abstracts for ASH, EHA & EBMT meetings. He is a member of the editorial board of *Haematologica*.

Dr Evangelos Terpos can be reached via e-mail at eterpos@med.uoa.gr and e.terpos@imperial.ac.uk

Optimal Therapy for Newly Diagnosed Patients Who Are Eligible for Autologous Transplantation

Evangelos Terpos

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Therapy options for newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplantation (ASCT) focus on disrupting myeloma cell-bone marrow stroma interactions, enhancing the immune system response, and specific targeting of myeloma clonal cells attempting to deepen the response rates and increase the rates of minimal residual disease (MRD) negativity.

Proteasome inhibitors (PI) have become an integral part of induction therapy regimens for MM. The combination of the first generation PI, bortezomib with thalidomide and dexamethasone (VTD) was approved by the European Commission in 2013 as induction regimen before ASCT. The recommendation to use a bortezomib-based regimen is based on the results randomized trials, which have been summarized in two meta-analyses and which confirmed the superiority of bortezomib-based regimens over conventional regimens. Sonneveld et al (J Clin Oncol 2012;30:2946-55) showed that bortezomib-based induction (PAD) was significantly superior versus non-bortezomib-based induction (VAD) in terms of post-transplantation CR+nCR rates (38% vs 24%, P<0.001), median PFS (35.9 vs 28.6 months, P<0.001) and 3-year OS rates (79.7% vs 74.7%, P=0.04). In a very recent study of the Southwest Oncology Group (SWOG) and the National Clinical Trial Network (NCTN), Durie et al (Lancet 2017;389:519-527) reported the results of a randomized study which compared the combination of bortezomib with lenalidomide and dexamethasone (VRd; n=264) versus Rd (n=261). Median PFS was significantly improved in the VRd group (43 months vs 30 months in the Rd group; stratified HR 0.712, 96% CI 0.56-0.906; one-sided p value 0.0018). The median overall survival was also significantly improved in the VRd group (75 months vs 64 months in the Rd group, HR 0.709, 95% CI 0.524-0.959; two-sided p value 0.025). The rates of overall response were 82% (176/216) in the VRd group and 72% (153/214) in the Rd group, and 16% (34/216) and 8% (18/214) of patients who were assessable for response in these respective groups had a CR or better. This study has established VRd as the standard of care induction regimen in the USA. VRd was also used as induction regimen in another recent study by the IFM (Attal et al; N Engl J Med 2017;376:1311-1320). The aim of this study was to test if ASCT is needed in the era of novel agents. Almost 700 MM patients were randomized VRd and then consolidation therapy with either five additional cycles of VRd (350 patients) or high-dose melphalan plus ASCT followed by two additional cycles of VRd(350 patients). Patients in both groups received maintenance therapy with lenalidomide for 1 year. Median PFS was significantly longer in the group that underwent transplantation than in the group that received VRd alone (50 months vs. 36 months; adjusted hazard ratio for disease progression or death, 0.65; p<0.001). This benefit was observed across all patient subgroups, including those stratified according to International Staging System (ISS) stage and cytogenetic risk.

Despite a lack of regulatory approval, the use of post-transplant therapy, in particular consolidation, defined as a short distinct course of treatment, is increasing across Europe in routine practice, with VTD or VRd being the predominant regimens used. Bortezomib has also been investigated in the maintenance setting, resulting in significant improvements in PFS; however, in these trials bortezomib was also used during induction therapy. Hence, it is as yet not clear which part of bortezomib exposure contributed to the results. However, to-date bortezomib maintenance is recommended at least for del17p patients. Subcutaneous dosing of bortezomib in MM has been demonstrated to be as active as intravenous dosing with a better toxicity profile in NDMM.

The second generation PI, carfilzomib, has also been tested in NDMM but has not been approved yet for this indication. The combination of carfilzomib, lenalidomide and dexamethasone (KRD) followed by lenalidomide maintenance provides high rates of deep remission and minimal residual disease (MRD) negativity. KRD regimen as induction regimen is now tested in phase 3 studies. The combination of KRD with clarithromycinin NDMM was also reported to be safe and active with ORR of 91.7% and very good partial response (VGPR) of

~55.6%, which included a majority of patients with high-risk cytogenetics. As an induction therapy, carfilzomib with cyclophosphamide and dexamethasone (KCD) in transplant eligible NDMM was well tolerated with response rates of 87% and VGPR of ~48% after 4-6 cycles. The novel PI ixazomib, used in an oral regimen with lenalidomide, has been reported to provide response rates of 23-33% in young patients with NDMM. Following induction with ixazomib/lenalidomide/dexamethasone, maintenance of up to 1.5 years with ixazomib alone improved response rates with a median duration of response of 26.5 months in NDMM patients not undergoing ASCT. Clinical studies assessing single agent ixazomib maintenance after ASCT and in combination with lenalidomide after ASCT are ongoing.

Maintenance therapy with immunomodulatory drugs (IMiDs) has been also investigated in a number of trials in the post-ASCT setting. Of note, none of the available agents is approved for use in maintenance. With thalidomide, the treatment duration is limited by toxicity concerns, in particular peripheral neuropathy (PN), however, if tolerated it can be considered. Interestingly, in patients with adverse risk cytogenetics, thalidomide maintenance was shown to result in shorter OS and should therefore not be used in the presence of these characteristics.

Lenalidomide maintenance has been investigated in three randomized trials, all of which demonstrated a PFS benefit with the agent, while OS was improved in two of the studies. A recent meta-analysis based on the above studies confirmed the superiority of lenalidomide maintenance versus placebo with a 2.5 years of median overall survival advantage for patients who receive lenalidomide maintenance till progression after a median follow-up of 7 years. However, patients with high-risk cytogenetics and ISS-3 seem no to have survival advantage by lenalidomide maintenance.

In summary, induction regimen with a bortezomib-based triplet (VTD or VRd) is the standard of care for newly diagnosed MM patients who are eligible for ASCT. Consolidation with 2 cycles of the same induction regimen seems to be beneficial, while maintenance with lenalidomide improves survival for all patients except of those with high-risk cytogenetic features and ISS. For this subgroup of patients, a tandem second ASCT followed by bortezomib maintenance is possibly the best approach to-date. Finally, novel PIs in combination with IMiDs and monoclonal antibodies, such as daratumumab may be the future in the management of myeloma patients who are eligible for ASCT.

Ola Landgren

Dr. Landgren is Professor of Medicine and Chief Attending Physician of the Myeloma Service at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, NY. Dr. Landgren is one of the world leaders in the field of early treatment strategies and molecular- and cell-based monitoring of minimal residual disease (MRD) detection in multiple myeloma and its precursor states. He leads a translational research program at MSKCC designed to discover new treatment paradigms integrating modern therapy and novel MRD assays. Dr. Landgren has designed and led the definitive study showing that all multiple myeloma patients are preceded by a precursor stage. As part of his ongoing research program, he is studying molecular mechanisms underlying the trajectory from precursor to full-blown multiple myeloma with the goal to develop of treatment strategies aiming to delay, prevent, and ultimately define a cure for multiple myeloma.

Dr. Landgren has published over 250 peer-reviewed publications and he is a frequently invited speaker at national and international hematology conferences. He serves on several research committees and editorial boards for scientific journals.

Can MRD Tailor Therapy for Myeloma Patients?

C. Ola Landgren, MD, PhD

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At the beginning of this century, multiple myeloma had an average overall survival of about 3 years. Around that time, in the U.S., three drugs (bortezomib, lenalidomide, and thalidomide) were introduced for the treatment of multiple myeloma and, in 2012, carfilzomib received accelerated approved by the U.S. Food and Drug Administration (FDA). Driven by access to better drugs, younger patients had a median overall survival of >10 years by 2014. The FDA approved 14 new drugs for the treatment of cancer in 2015; four of these were approved for the treatment of myeloma (panobinostat, daratumumab, elotuzumab, and ixazomib). In 2015, 2016 and 2017; expanded label indications were approved by the FDA for lenalidomide and carfilzomib, respectively. The recent increase in approved, highly effective combination therapies for patients with multiple myeloma has opened the door to redefining the goals of therapy.

In 2015-2017, several novel combination therapies evaluated in randomized clinical trials have been published in high-impact journals. The past 6 months, an emerging pattern from these clinical trials of data show that patients who achieve minimal residual disease (MRD) negativity 10^{-5} or 10^{-6} have similar progression-free survival (PFS) and overall survival (OS) patterns – independent of treatment arm. So far, none of the randomized clinical trials have had MRD negativity as the primary end-point, why these observations currently are part of the secondary end-points. Given the consistent data patterns showing that MRD is a surrogate end-point for prolonged PFS and OS, it seems reasonable to conjecture that there soon will be studies using MRD negativity as the primary end-point.

Beyond clinical trials, based on the emerging patterns of MRD negativity being correlated with better clinical outcomes, a few leading academic myeloma centers have already started to integrate MRD testing in routine clinical care. For several years, patients reaching a complete response after high-dose melphalan/autologous stem cell transplant are offered maintenance with lenalidomide; while patients with residual disease (such as very good partial response; VGPR) commonly are recommended to receive additional combination therapy before they go to maintenance with lenalidomide. It seems reasonable to propose that MRD negativity soon will be integrated in clinical decision making in a similar fashion. Major barriers for MRD testing becoming part of standard of care on a broader scale today include the lack of availability for reliable MRD assays. This is presumed to change in the near future as new molecular MRD assays are far along with regards to clinical development.

This presentation will address all the above aspects of MRD testing and clinical care. It will review and discuss available data from the literature. Also the presentation will review and discuss future directions of emerging technologies to measure MRD status in the bone marrow and peripheral blood.

Emerging Problems with the Use of Monoclonal Antibodies in the Everyday Management of Myeloma Patients

Efstathios Kastritis

Monoclonal antibodies have emerged as a new exciting treatment option for patients with myeloma with unique mechanisms of action. In the past two years two different monoclonal antibodies, elotuzumab and daratumumab, were approved for the treatment of patients with myeloma, and have been incorporated in the treatment algorithm of the disease. Elotuzumab is a humanized IgG_1κ) monoclonal antibody that targets and binds the extracellular domain of SLAMF7, which is expressed on both myeloma and NK cells, and has a dual mechanism of action: an antibody-dependent cellular cytotoxicity (ADCC) in myeloma cells and activation of NK cells. Elotuzumab alone has minimal activity in myeloma but based on the results of the large phase 3 study ELOQUENT-2, the combination of elotuzumab with lenalidomide and dexamethasone has been approved for the treatment of patients with relapsed or refractory MM after at least one line of therapy. Daratumumab is a human anti-CD38 IgG_1(κ) antibody that binds to the CD38 antigen of myeloma cells. The main antimyeloma effect of daratumumab is attributed to its prominent antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities; however, other mechanisms may also be important. The clinical activity of daratumumab, as a monotherapy, has been shown in phase I and phase II studies, and has been approved as single agent for patients with relapsed and refractory MM; in addition daratumumab has also shown unprecedented activity in combination with lenalidomide, bortezomib and pomalidomide.

The most common adverse reaction associated with the use of these monoclonal antibodies includes infusion related reactions. Infusion-related reactions (IRRs) were observed in 10% of the elotuzumab-treated patients in the ELOQUENT-2 study, but most were grade 1 and 2, with 70% of the IRRS occurring during the first infusion, while very few (2 patients, 1%) discontinued treatment because of IRRs. Similarly, for daratumumab, IRRs is the most common adverse reaction, with fever, cough, nausea, dizziness, and bronchospasm. These are more common than with elotuzumab, tend to be associated with upper respiratory tract symptoms and may be observed in up to 48% of patients during the first infusion of daratumumab. However, no patients discontinued treatment with daratumumab in the GEN501 and SIRIOUS studies because of IRRs, since in most cases these were mild (grade 1 or 2), in >90% of the cases occurred only in the first infusion and were not repeated in subsequent infusions. With appropriate preventive measures the IRRs frequency and severity may be reduced substantially. Premedication with steroids, which can be started a couple of days before the first infusion, anti-H1 medication and for some patients who will receive daratumumab, montelukast, a leukotriene receptor antagonist, may be very effective. Initial infusion rates should be slow, titrating slowly to higher infusion rates. In subsequent infusions the doses of steroids and H1 antagonists may be reduced or stopped and infusion rates may be higher. Treatment with extra corticosteroids and antihistamines is usually sufficient to manage IRRs, while the infusion can be restarted at a lower infusion rate when IRR symptoms have resolved.

Lymphocytopenia, is common with the elotuzumab, lenalidomide and dexamethasone combination, had no major clinical impact, however, increased rates of herpes zoster infection were observed, thus, prophylaxis for VZV reactivation should be considered. Neutropenia was more common with daratumumab plus lenalidomide and dexamethasone but there was no increased risk of infections in the POLLUX and CASTOR studies.

Both elotuzumab and daratumumab may interfere with immunofixation (IFE) and serum protein electrophoresis (SPEP) assays and therefore may be detected on SPEP in the early gamma region as a persistent IgG-kappa band, which may lead to underestimation of CR rates in patients with IgG-kappa myeloma. A daratumumab-specific IFE reflex assay (DIRA) has been developed to identify daratumumab interference, and a similar method is under development for elotuzumab.

A unique effect of daratumumab (and of other anti-CD38 antibodies) that can cause significant problems is the interference of daratumumab with indirect Coombs testing and blood typing. CD38 is weakly expressed on red cells and daratumumab binds to CD38 on reagent RBCs, causing panreactivity in vitro. Plasma samples from daratumumab-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches; however, daratumumab does not interfere with ABO/RhD typing or with immediate-spin crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol), and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by daratumumab are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. Treatment of RBCs with dithiotreitol (DTT) to denature CD38 so that daratumumab does not bind RBCs may solve the problem. A preventive strategy also includes detailed phenotyping prior to the first infusion of daratumumab. Unlike CD38 monoclonal antibodies, elotuzumab does not interfere with blood compatibility tests because SLAMF7 is not expressed on red blood cells.

Thierry Jo Molina

Thierry Jo Molina, 54 year-old, M.D., PhD., is full Professor of Pathology, Classe Exceptionnelle,Université Paris Descartes, Sorbonne Paris Cité. He has been the Chief of Department of Biology, Pharmacy, Pathology, Hôtel-Dieu, AP-HP, Paris 2008-2010, the Head of the Department of Pathology of Hôtel-Dieu de Paris (2008-2013) and is the current Head of the Department of Pathology of Hôpital Necker-Enfants Malades, AP-HP, Paris since 2013. He has been President of the French Society for Pathology (SFP) (2012-2014) and Member of the Executive Committee of the European Association for Haematopathology (2004-2008). He is a member of the Administrative Council of the LYSA (Lymphoma Study Association) group. He is member of the Editorial Board of Annals of Haematology and reviewer of numerous leading journals in Haematology and Pathology. Dr Molina's research group focuses mainly on the pathology of diffuse large B-cell lymphoma and on the role of NF-kB alternative pathway (RelB) in pathology. He has been PI on many research projects and is author of 140 peer-reviewed publications.

Diffuse Large B-cell Lymphoma, DLBCL: Update on Pathology with the New 2016 Revised WHO Classification

Thierry Jo Molina

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The revised 2016 WHO classification is taking into account the huge amount of molecular data produced within the last 8 years both at a genomic and transcript level to decipher distinct oncogenic pathways that may respond differentially to classical or targeted therapy.

The Cell Of Origin classification based on transcriptome (Germinal center B-cell like, GCB; Activated B-cell like, ABC,; Unclassifiable, UNC) is now recognized linked to different oncogenic pathways activated and potentially specific therapy linked, that should still be demonstrated in ongoing prospective trials. New methods such as RT-MLPA or Nanostring based on a restricted RNA signature from paraffin embedded tissue are validated as highly concordant with the transcriptomic assay and reproducible between laboratories. These methods are currently been implemented within the majority of lymphoma diagnostic laboratories. Immunohistochemical methods such as the one using the Hans algorithm does not recognize the UNC subtype, has reproducibility issues, but has in some laboratories a good correlation with the transcriptome. The future might be a combination of both IHC and targeted RNA signature.

A major change in the new WHO classification is the removal of the entity named "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma, BCLU". Although Gene expression profiling and CGH array recognized an intermediate pattern between Burkitt and DLBCL, criteria to diagnose this entity was too vague and not reproducible between pathologists. Therefore, due to the numerous data showing that *MYC* translocation in DLBCL might be a prognostic factor and that double hit (*MYC* and *BCL2* translocations or *MYC* and *BCL6* translocations) or triple Hit (MYC and BCL2 AND BCL6) DLBCL patients have a worse survival in most but not all series, it was decided to isolate High grade B-cell lymphoma with MYC and BCL2 and/ or BCL6 rearrangements as a single category and to comment the morphology (DLBCL, intermediate between Burkitt and DLBCL, blastoid) . Cases that fulfill the criteria of follicular lymphoma or lymphoblastic lymphoma should be excluded. In addition, cases that appear cytologically blastoid or intermediate but that lack *MYC* and *BCL2* and/ or *BCL6* rearrangements, should be classified as high grade B-cell lymphoma, NOS after exclusion of mantle cell or lymphoblastic lymphoma. This change clearly asks the question not solved of how we should FISH our DLBCL as no absolute criteria (MYC protein expression, Ki67 stain) allow to specifically guide the occurrence of a MYC translocation although we should acknowledge that the great majority of cases are of GCB phenotype.

An other different topic is being addressed in the revised WHO concerning not an entity or a separate category but a prognostic factor inside the DLBCL NOS considering Double expressor (DE) phenotype (MYC protein ≥40%, and BCL2>50%). However, they are not as aggressive as the "High grade B-cell lymphoma with *MYC* and *BCL2* and/ or *BCL6* rearrangements "and not all studies are concordant related to their prognostic value. The DE phenotype comprises roughly between 20-35% of DLBCL series, are more often devoid of double Hit, and are most often of ABC subtype.

In this review we will also present new LYSA (Lymphoma Study Association) results addressing this topic as well as addressing other changes in the classification focusing on EBV DLBCL, EBV+ mucocutaneous ulcer, large B-cell lymphoma with *IRF4* rearrangement, HHV8 positive DLBCL NOS.

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1969 - 1975	:	Resident in hematology.
1971	:	Molecular biology certificate- University of Sciences Paris VII
1975	:	Doctor of Medecine - Creteil University -
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1979	:	Oncology Certificate-Saint Louis-Paris VII University
1981 - 1993	:	Professor Second Class-Saint Louis-Lariboisière Paris VII University
1993 - 2010	:	Full Professor - Hematology Saint Louis - Paris VII –
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Laboratory Work

1973 - 1975	:	Visiting Associate National Institute of Health. Bethesda - Maryland.
1975 - 1996	:	INSERM - Creteil - Saint Louis
1979	:	Pharmacology department Saint Louis - Paris -

Hospital position

University Hospital Saint Louis - Paris -

1979 - 1985	:	Chief Oncology Unit.
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1997- 2009	:	Head Dpt Hemato-Oncology – Hôpital Saint Louis
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Academic position:

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- University teaching for graduate or post-graduate, medical students in Hematology, Seminars - Oncology - Hematology for post-Doctorat students, Director of thesis.

Chairman multicentric study

- Groupe d'Etude des Lymphomes de l'Adulte - GELA : President. Until 2002
- Non Hodgkin's lymphoma : National Protocol LNH87 - LNH93 – LNH98 closed
- Non Hodgkin's lymphoma-HIV protocol study. Closed
- Autologous stem cell transplantation in breast cancer : Société Française de Greffe de Moelle.

Chair : international study CORAL relapse lymphoma,
Several data monitoring committees (DMC)

Society

Member: American Society of Hematology, American Society of Clinical Oncology, American Society of Cancer Research, Société Française d'Hématologie, International Society of Hematology, , EBMT, EHA. LYSA

Editorial Board

Progress in hematology, hematology and cell therapy, CNIMH, leukemia lymphoma, Hematologia, Clinical Lymphoma, Journal of Clinical Oncology, Brazilian Journal of Hematology and Hemotherapy

Expert

Drug Agency (AFSSAPS) since foundation 1999. Present: expert several committees ANSM (renewal). EMA member SAG O since 2010 to present
Several cancer research associations

Main Topics of Interest

- Autologous bone marrow transplantation.
- Non Hodgkin's and Hodgkin lymphoma.
- Pharmacology of antineoplastic agents.
- Publications : See PubMed (300)

Relapse/refractory diffuse large B cell lymphoma. Where are we with autologous transplantation?

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Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Although 5-year survival rates in the first-line setting range from 60% to 70%, up to 50% of patients become refractory to or relapse after treatment. The rate of relapses will depend on prognostic factors and the international prognostic score remains the best predictor. However, with the evolution of the biology we have to consider the different subtypes of DLBCL, GCB and Non GCB, as well as numerous biological markers which can provide target for new treatments.

Salvage chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) is the standard of treatment for chemosensitive relapses in diffuse large B-cell lymphoma (DLBCL). The addition of rituximab to chemotherapy has improved the response rate and failure-free survival following first-line treatment and relapses. Finding the best salvage treatment is still an unmet need as chemosensitivity is required before transplantation and only 50% are in fact eligible for ASCT. The intergroup CORAL trial set the limits for this standard of treatment after first comparing two salvage regimens: rituximab, ifosfamide, etoposide, and carboplatin (R-ICE); and rituximab, dexamethasone aracytine and cisplatin (R-DHAP). Responding patients received BEAM and ASCT and were randomized between observation and rituximab maintenance for one year. The response rates in the R-ICE (63.5%) and R-DHAP (62.8 %) groups and the overall survival (OS) rates (47% vs. 51%; p=.5) did not differ between groups. The three-year EFS was affected by the following factors: prior treatment with rituximab, early relapse (<12 months), and secondary IPI 2-3. For patients with 2 factors, the response rate was 46% with a 5-month median PFS. Moreover, patients with an ABC subtype or GCB with MYC translocation responded poorly to treatment. Subsequently, two other large randomized studies with gemcitabine or ofatumumab based regimens could not demonstrate and advantage over the standard R-DHAP. At the end of the day, over 70% of patients will not benefit from standard salvage therapy, and continued progress is needed.

Analyses of large-scale outcome data from patients with refractory DLBCL are limited. One group of concern are the patients with stable or progressive disease after first line treatment, first salvage or relapsing after ASCT. The international, multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study retrospectively evaluated outcomes in patients with refractory DLBCL, defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤12 months of autologous stem cell transplantation. Pooled data of 636 patients from 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic) were analyzed. For patients with refractory DLBCL, the objective response rate was 26% (complete response, 7%) to the next line of therapy and the median overall survival was 6.3 months. Crossing over salvage regimens can still provide response in patients with a better median survival of 14 months especially if a consolidation with stem cell transplantation could have been performed.

Studies evaluating immunotherapy post-transplantation with the addition of rituximab, lenalidomide or immune check point inhibitor are ongoing. Clearly, from CORAL data, Rituximab post transplant could not reduce the 40% rate of relapse. Allo-transplantation is reappraised with reduced intensity conditioning regimen, better donor availability, MUD or haplo donor. Promising results have been reported also with CAR T cell technologies in DLBCL which warrant further clinical studies. A better biological understanding of these refractory patients and new approaches are warranted with new drugs, especially for the patients non-eligible to transplant.

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Philadelphia-Negative Chronic Myeloproliferative Neoplasms: Diagnostic Criteria and Personalized Therapy in 2017

Francesca Palandri

The 2016 World Health Organization (WHO) classification for Philadelphia-negative myeloproliferative neoplasms (MPNs) has modified diagnostic criteria for polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) by the integration of clinical/laboratory data, marrow histology, and molecular mutations. PV diagnosis is based on reduced hemoglobin (Hb) level threshold, now established at 16.5 g/dL for men and 16 g/dL for women. This reduction was induced by the identification of MPN patients with PV-consistent bone marrow histology but with an Hb level lower than indicated in the 2008 WHO criteria. Prefibrotic/early PMF was recognized as distinct entity that is distinguishable from ET on the basis of marrow histology and that has a higher tendency to progress into overt myelofibrosis or acute leukemia, with overall poorer prognosis. Finally, all mutually exclusive MPN driver mutations (*JAK2*, *CALR*, and *MPL*) have been included as major diagnostic criteria in ET and PMF; in "triple negative" cases, subclonal molecular mutations (eg, in *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, and *SF3B1*) may confirm clonality.

The treatment of MF is guided by the burden of disease, including managing cytopenias, reducing splenomegaly, and alleviating systemic symptoms. Treatment algorithm is also based on the risk category, according to the IPSS and DIPSS scores. Ruxolitinib is the first JAK1/2 inhibitor commercially available for the treatment of MF. The registrative COMFORT studies showed that ruxolitinib ameliorates splenomegaly and symptoms in around 50% of patients, regardless of their mutational status, but its use is limited by hematological toxicity. Several clinical needs still remain unmet, specifically the following: (1) reverting anemia and thrombocytopenia, (2) treating refractory splenomegaly, (3) reducing marrow fibrosis and mutation load, and (4) preventing or at least delaying progression to acute leukemia. To reduce hematological toxicity and to improve efficacy, several trials are investigating the combination of RUX with other agents (danazol, erythropoiesis-stimulating agents, pomalidomide, azacytidin, etc). Additionally, other JAK2-inhibitors are under clinical investigations (particularly, pacritinib is in a more advanced phase of clinical use). Beyond JAK-inhibitors, other agents with different mechanisms of action are being investigated in clinical trials, particularly telomerase inhibitors (imetelstat), transforming growth factor beta inhibitors (sotatercept) and second mitochondria-derived activator of caspases (SMAC) mimetics (LCL-161). Immunomodulating agents (eg: thalidomide) may be useful in patients with anemia.

The current treatment recommendations for patients with PV rely on the assessment of thrombotic risks. The primary objective of treatment is to reduce the hematocrit and associated blood viscosity to minimize the risk of thrombosis without increasing the probability of a disease progression into secondary myelofibrosis or acute leukemia. Phlebotomies to maintain hematocrit below 45% and antiplatelet agent are the basis of PV therapy. In high-risk patients (age >60 yr and/or previous thrombotic events) hydroxyurea should be recommended. In clinical trials, also interferon-alpha has been used with clinical benefit. In case of intolerance or resistance to hydroxyurea, ruxolitinib has been recently approved as second-line therapy.

Monique den Boer

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"Molecular markers and drugable targets in pediatric acute leukemia."

Main topics that are being studied are: 'dissecting genetic abnormalities', 'finding causes of cellular drug resistance' (mainly focused on glucocorticoids and L-asparaginase), 'elucidating leukemia – microenvironment interaction', 'exploring actionable targets and targeted drugs' in pediatric acute lymphoblastic leukemia (ALL).

The research group of Monique den Boer aims to find new molecular markers and targets for precision medicines in children with ALL. This translational research program focuses amongst others on the role of genetic abnormalities and deregulated (phospho) proteins in the pathobiology of pediatric B-cell precursor ALL and is directed to find new drugs with high efficacy and specificity.

Monique den Boer discovered a new high-risk type of pediatric ALL, i.e. *BCR-ABL1*-like ALL, by means of genomic studies (Lancet Oncology 2009). In addition, studies on aberrant genes in both *BCR-ABL1*-like and *TEL-AML1*-positive ALL revealed genomic lesions and aberrant signaling pathways (e.g. JAK/STAT, PI3K/AKT, BTK, RAS, autophagy) that may be targeted by specific inhibitors. Resistance to the spearhead drug prednisone was shown to be caused by increased glucose consumption and Ras-pathway mutations, often subclonal, which could be reversed by specific glycolysis and MEK/ERK inhibitors such as trametinib. Deletions in the B-cell differentiation factor Ikaros were shown to be predictive for an inferior outcome of medium-risk patients. This marker has been implemented in the risk assignment of patients treated with the ongoing DCOG ALL11 protocol.

Another topic of her research addresses the interaction between leukemic cells and the bone marrow microenvironment. Recently, this resulted into the discovery of a pro-survival communication mechanism induced by tunneling nanotubes, which were shown to increase the viability of leukemic cells and to reduce the sensitivity of leukemic cells to chemotherapeutic drugs.

Her group is highly experienced in *ex vivo* testing of patients' leukemic cells to (new) drugs in co-culture with patients' derived mesenchymal cells, including the effect on intercellular communication (tunneling nanotubes). She also studies the potential synergistic or antagonistic effect of new precision medicines in combination with conventional drugs, since this gives a rationale how to combine these new drugs with yet established chemotherapy. New precision medicines which have been tested are for example dasatinib (BCR-ABL1 and Src kinases), bosutinib (BCR-ABL1 and Src kinases), ibrutinib (BTK), barasertib (aurorakinase B), trametinib (MEK/ERK), sorafenib (BRAF), momelotinib (JAK2) and ruxolitinib (JAK2). In addition, patient-derived ALL xenografts are being generated, especially of high-risk and/or rare molecular types of ALL, and used for proof-of-concept studies with new drugs (e.g. ibrutinib in *TCF3-PBX1* positive ALL). Den Boer's mission is to provide solid laboratory evidence that the diagnosis and treatment of ALL can be more tailored and more personalized if directed towards biological targets present on leukemic cells and the nurturing/supportive tissue in the bone marrow. To translate laboratory findings to the clinic, she closely collaborates with the ALL disease and early clinical trial committees of the Dutch Childhood Oncology Group (chaired by Prof.dr. Rob Pieters and Prof.dr. C. Michel Zwaan, respectively), I-BFM family (chair Prof.dr. Andrea Biondi) and the European consortium for Innovative Therapies for Children with Cancer (ITCC, chair: Prof.dr. Gilles Vassal).

Key-publications reflecting the research area covered by Den Boer and her group members:

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New Prognostic and Predictive Markers for Acute Lymphoblastic Leukemia; Hurdles and Opportunities

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Most study groups focusing on the treatment of acute lymphoblastic leukemia (ALL) stratify patients by well-established risk factors into risk-adapted treatment protocols. Despite risk-adapted treatment, the failure rate is still considerable in children (20%) and even very high (50-70%) in adults. Most pediatric study groups notify that their event-free survival curves have reached a plateau in recent years whereas, with a few exceptions, the same drugs are used as decades ago. Meanwhile, the knowledge of the biology of disease has increased enormously by deciphering the human genome, pathways of gene regulation and the development of new and often high-throughput molecular techniques. New (genetic) abnormalities have been identified in leukemic cells that may serve as new diagnostic biomarker and/or as target for new drugs. The hurdle to be taken is to provide functionally proof for the importance of these new lesions in the pathobiology of ALL in order to guide personalized medicine by more optimized risk stratification and targeted drugs.

Aim of this presentation: This presentation addresses the hurdles and opportunities for new risk factors in pediatric ALL. The identification and characterization of a new subtype of B-cell precursor ALL (BCR-ABL1-like ALL) will be used throughout this presentation as example.

In 2009 a new subtype of ALL at high risk of treatment failure was discovered by gene expression profiling. The gene expression signature and clinical outcome of 50-60% of yet-genetically unclassified B-cell precursor (BCP) ALL cases resembled that of BCR-ABL1-positive ALL and therefore these group of patients were named BCR-ABL1-*like* ALL. BCR-ABL1-*like* ALL can be found in ~15% of childhood BCP-ALL cases and 5-years event-free survival estimates are ~50%, similar to the poor prognosis of children with BCR-ABL1-positive ALL. BCR-ABL1-*like* ALL cases are found across all risk stratification arms of contemporary treatment protocols, including standard, medium and high risk arms. BCR-ABL1-*like* ALL is characterized by a high frequency (80%) of lesions in B-cell development genes, including IKZF1, TCF3 (E2A), EBF1, PAX5 and others. The most frequent genomic lesion is found in IKZF1; about 40% of BCR-ABL1 *like* cases have deletions in the B-cell transcription factor IKZF1 compared to 12.5% in BCP-ALL cases negative for BCR-ABL1 translocation or BCR-ABL1-*like* gene signature. Both deletions in IKZF1 and BCR-ABL1-*like* gene signature are independent prognostic factors in children with BCR-ABL1-negative BCP-ALL. BCR-ABL1-*like* cases harbor translocations and gene mutations affecting tyrosine kinase receptor signaling molecules, a.o. EBF1-PDGFRB, JAK2-translocations and mutations in JAK-family genes as well as ABL1-translocations (other than to BCR), and frequently dic(9;20) and iAMP21 genomic lesions are observed. Cells with translocated JAK2, but not those harboring single nucleotide mutations in JAK2, may be sensitive to the JAK-inhibitor ruxolitinib. Cells harboring EBF1-PDGFRB or ABL1-fusions were shown to be sensitive to the dual Src/Abl tyrosine kinase inhibitor dasatinib, both in vitro and in ALL xenograft studies. Case reports recently showed that imatinib and dasatinib may be effective in relapsed/refractory BCP-ALL patients harboring an EBF1-PDGFRB or SNX2-ABL1 fusion, paving the way for more upfront inclusion of these type of inhibitors in future treatment protocols for newly diagnosed ALL. Ongoing research focusses on identifying additional (genetic) lesions in BCR-ABL1-*like* ALL that may serve as diagnostic marker and/or target for therapy. The progress in this research will be presented at the meeting.

Treatment of Young Adult Acute Lymphoblastic Leukemia

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Summary

Acute Lymphoblastic Leukemia is an heterogenous disease. The cure rates of pediatric ALL is over 90%. But adult ALL has cure rates roughly half those seen in children. The main causes are the adverse genetic features of adult ALL and the impaired tolerability of chemoterapy in particularly older patients. However, modest improvements have been seen in outcomes for adolescents and young adults. This may depend on using pediatric-type combination chemotherapy regimens in patients with 40-50 years or younger and also applying best supportive care and better managing the toxicity of the pediatric protocols. Still persistent residual disease is important problem causing poor prognosis. In the following, the treatment of young adult ALL patients will be tried to summarized.

ALL has distinct biologic and prognostic characteristics that make this disease very heterogenous. To understand the biology of the disease, important progress that has caused making distinct prognostication and tailoring specific treatment strategies to specific disease groups, has been made. There are dramatic improvements in outcomes of children with ALL, with cure rates up to 90%. But adolescents and young adults (AYA) have shown a poorer prognosis historically with event-free survival (EFS) of 30-45% (1). The National Cancer Institute has defined the adolescent and young adult group (AYA) as being between ages of 15 and 39 years (2,3). Nowadays, in the treatment of adult ALL, mostly pediatric protocols are preferred because of the high cure rates in pediatrics. Although, pediatric protocols have increased the EFS rates, they could not catch same results with that of pediatric patients. This difference has been mostly attributed to insufficient compliance of adults to intensive treatment protocols used in pediatrics and the greater incidence of adverse cytogenetic subgroups found in adults. Pediatric patients with ALL (<10 years) mostly have hyperdiploidy, TEL/AML translocation or favorable trisomies at presentation. But AYA patients have much more common high risk features than pediatric group such as T- cell phenotype, hypodiploidy, t(9;22), complex karyotype (2,4).

On the other hands, acute lymphoblastic leukemia in young adults is thought to be a special category, because of differences in response to therapy and disease biology. It should not be forgotten that AYA patients are not big children (4).

Continued research in the biology of ALL and developing targeted therapies (monoclonal antibodies and CAR-T cells), will hopefully lead to comperable survival rates in the near future (1).

Treatment of AYA patients

Traditional adult protocols generally include intensive myelosuppressive agents like cytarabine, daunorubicin, cyclophosphamide and they mostly are directed to allogeneic bone marrow transplantation in first remission (3-7). In pediatric protocols, less intense myelosupressive agents (asparaginase, corticosteroids, vincristine) are used in higher doses. There are prolonged post-remission asparaginase and delayed re-induction. They make central nervous system prophylaxis early during induction. Allogeneic bone marrow trasnplantation is restricted to only very high-risk patients (8,9).

In several large retrospective sudies, it was shown that AYA patients have superior outcomes when they are treated with pediatric protocols.

In the retrospective large study of Stock W et al, treatment plans, presenting fetures, complete remission rates (CR) and outcome of 321 adolescents and AYA patients aged between 16-20 years who were treated on trials in either Childern's Cancer Group (CCG) (n=197) or the Cancer and Leukemia Group B (CALGB) (n=124) from 1988 to 2001, were evaluated (5). Two groups were matched in case of sex, ethnicity, immunophenotype and initial WBC count. There were no remarkable differences with respect to karyotypic analysis. But there was age distribution differences between two goups (median age CCG: 16, CALBG: 19, $p<0.001$). Event free survival (EFS) and overall survival (OS) with pediatric CCG protocol (BFM and augmented BFM) was 63% and 67% respectively and 34% and 46% with adult protocols

(n=124) at 7-year follw-up. There was no hematopoietic transplantation in both groups. In CCG group, patients received considerably more treatment with non-myelosuppressive drugs (including glucocorticoids, vincristine and L-asparaginase) and CNS prophylaxis administered earlier and with greater frequency. Patients in CALBG group received lower cumulative dosage of prednisone compared to CCG group and also lower L-asparaginase dosage. In contrast, CALBG patients received higher cumulative doses of myelosuppressive agents. EFS and OS differences between two groups can be dependent on the median age differenecies between two groups. Because they did not found any statistical differencies in case of EFS in CALBG group (16-17 years). In other words, adult protocols might include more free young adults who tend to be less compliant with complex protocols (5).

In another retrospective study, pediatric French FRAILLE-93 and adult LALA-94 trials were compared, to investigate pediatric and adult protocol results in adolescents. At 5-year EFS was 67% vs 41% for FRAILLE-93 and LALA-94 respectively. Again there was median age differencies between two goups (Median age: 15.9 x 17.9, FRAILLE x LALA). There were some differences between two treatment arms. In pediatric protocol, there were more prednisone and asparaginase doses, and also in LALA- protocol, L-asparaginase was not included in induction period (6). In various retrospective studies, ıt was shown that young adults have superior outcomes when they treated with pediatric protocols with survival approaching those of younger children at 5-year EFS of over 70% (1, 10,11).

Based on these retrospective studies, prospective trials using pediatric and pediatric-like regimens had been designed for adults with ALL.

In the multicenter study of DeAngelo et all, adult patients aged 18-50 years were treated with DFCI Pediatric ALL Consortium regimen. 85% of the patients achieved CR, 4-year disease free survival (DFS) for the patients achieving CR was 69%, and 4-year OS was 67%. Toxicity was tolerable and results were improved compared to historical regimens (12).

In GRAALL-2003 study, 225 adult patients (median age,31 yers; 15-60) with Ph (-) ALL were enrolled. Some adult options like allogeneic bone marrow transplantation were retained. They compared results with historical LALA-94 experience (aged 15-55). CR rate, EFS and OS were found to be comparable favorably with LALA-94. They concluded that pediaric-like therapy markedly improves outcome of adult patients at least until the age of 45 years (13).

Based on these retrospective and prospective studies, it is recommended that young adult patients with ALL can be treated with pediatric-like regimens, resulted in marked improvement in EFS from 39% to up to 70%. But further progress still needs to be made.

Asaparaginase in AYA

Major concern in pediatric-like protocols in AYA patients is asparaginase related toxicities. One of them is hepatotoxicity particularly occuring during induction therapy (1,14). Hypersensitivity reactions like systemic allergic reactions, urticeria or anaphylaxis occur in as many as 20% of children and adults. These reactions can be associated with neutolizing antibodies. These antibodies have been shown in 26-71% of patients in various studies (1,15). Pegylated asparaginase was found to be less immunogenic than the native E.coli enzyme. But with the use of these type of asparaginase, this hypersensitiviy reactions can be seen also. To reduce dose-related toxicities while maintaining adequate therapeutic level, many efforts had been made (16). However, there is still a need for validation of treatment approaches based on asparaginase dose adjustment in AYA patints before application in routine clinical practice. Other serous toxicities are pancreatitis, bleeding, thrombosis, asthenias. The pancreatitis was reported as 13% in adults treated with asparaginase in one study (17). Because of the reccurence risk, re-administration of the drug is contraindicated in these patients. High-grade hypertriglyceridemia which is not correlated with the occurence of pancreatitis, is noted about 50% of the patients (1,18). Venous thrombosis is seen (12%) more commonly than bleeding and it is more common in adult patient. But the place of prophylactic anticoagulation is uncertain. Another side effect is hypofibrinogenemia (<100 mg/dl in 48%), and cryoprecipitate replacement therapy can be administered to prevent bleeding,with caution to the risk of thrombosis (18).

Treatment of Ph (+) ALL in AYA patients

Ph (+) ALL occurs in 3% of pediatric patients, 25% of adult patients. It is seen in 5-7% of young adults. Nowadays, TKIs are incorporated into most protocols in combination with

chemotherapy, providing long-term remissions in Ph(+) ALL compared to pre-TKI era. MRC UKALLXII/ECOG2993 ALL trial in pre-TKI era showed that ALL patients with Ph(+) have a 36% OS after undergoing matched unrelated donor allogeneic-HSCT and 40% OS after matched related donor HSCT. Because without allogeneic HSCT, they have only 19% OS with chemotherapy, allogeneic HSCT was offered to all patients in first remission in routine parcatice (19). However, TKIs changed this strategy. In multiple phase II trials, ıt was suggested that patients having negative minimal residual disease (MRD) might not require transplantation in first remission, but still in routine practice transplantation is important offer for eligible patients.

Conclusion

Because of the biological heterogenity of the disease and complexity in therapeutic approach, treatment of AYA patients needs special approach. Current clinical trials should kept in mind whenever possible in these patients. The usage of pediatric-like regimens, monitoring of the disease with MRD assesment and novel therapies can cause improvements in outcomes of AYA patients.

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First Line Therapy of Early Stage cHL: Should We Go for PET Adapted Treatment Strategies

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Early stage classical Hodgkin lymphoma is amongst cancers with the highest cure rate. Current standard treatment combines chemotherapy with radiation therapy using involved field radiation. Given excellent prognosis and relative low level of immediate treatment related toxicities, the issues of long-term treatment effects, secondary neoplasia and late cardiovascular toxicity are of increasing concern in this population. Notably, late events contribute to the overall mortality more than relapsed primary malignancy. Therefore, several clinical investigations were aimed to reduce therapy while achieving excellent tumor control. Functional imaging with [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) performed early in the course of treatment allows modifications either by omitting more therapy or intensifying it. We will review the reproducibility tools used in PET/CT imaging such as Deauville scale and emerging role of quantitative PET parameters. A negative interim PET (iPET) is reached in 75-90% of stage I/II cHL patients treated with 2-3 cycle of standard induction chemotherapy doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). We will review findings from two recent prospective randomized clinical trials in early stage cHL: the EORTC/LYSA/FIL H10 trial and the Randomized Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease [RAPID]) trial. Using the response-adaptive design, these studies examined whether there is an unacceptable increase in the relapse rate among patients with negative iPET findings who are assigned to arm omitting radiotherapy. In non-inferiority design, RAPID trial determined that radiation therapy can be omitted without detriment to overall survival, however at the expense of ~5% increase in rates of recurrence. Results of H10 trial confirmed the superiority of combined modality therapy combining ABVD chemotherapy with involved field radiation even for patients with negative iPET scan in terms of progression-free survival but with no impact on overall survival. These results suggest that early stage cHL patients who relapse after front-line therapy often attain second remission and yield subsequent long-term survival. We will discuss the limitations of both studies such as use of progression-free-survival as an end-point, the non-inferiority margin chosen, the need to a longer follow-up period to determine second cancers, cardiovascular disease. We will highlight the recommendation to apply iPET response adapted strategy while using individualized approach to balance the effective disease control with the risk of overtreatment and the late toxicity.

Peter Borchmann

Peter Borchmann is Assistant Medical Director in the Department of Hematology/Oncology at the University Hospital of Cologne. He is head of the lymphoma program in this department. He is also Co-Chairman of the German Hodgkin Study Group (GHSG) and responsible for development of investigator initiated clinical studies in Hodgkin Lymphoma. His scientific focus within the GHSG is to optimize the treatment of advanced stage HL patients and elderly patients. He is also the leader of the working group “Survivorship” (http://www.ghsg.org).

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Degrees
1984 MD, Dept of Medicine, University of Toronto

Qualifications, Certifications and Licenses
1990 Specialist Certification, Hematology, University of Toronto, Toronto, Ontario, Canada
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EMPLOYMENT
Current Appointments
2009 Jul - present Professor, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
2001 Jul - present Courtesy privileges, Mount Sinai Hospital, Toronto, Ontario, Canada
1998 Nov - present Active Staff, Department of Medical Oncology & Hematology, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada

PREVIOUS APPOINTMENTS
Hospital
2007 May - 2009 Jun Deputy Head and Director of Clinical Services, Division of Medical Oncology and Hematology, University Health Network/Mount Sinai Hospital, Toronto, Ontario, Canada

2000 Nov - 2016 Oct Lymphoma Site Leader, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

1999 Aug - 2013 Aug Director, Autologous Bone Marrow Transplantation Service, Princess Margaret Hospital, Toronto, Ontario, Canada

1992 Jun - 1998 Nov Active Staff, Division of Hematology-Oncology, Department of Medicine, The Toronto Hospital, Toronto, Ontario, Canada

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1999 Jul - 2009 Jun Associate Professor, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

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PROFESSIONAL AFFILIATIONS AND ACTIVITIES
Professional Associations
Member, American Society of Clinical Oncology
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Member, Canadian Association of Medical Oncology
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RESEARCH FUNDING
Peer-reviewed Grants
2013 Mar - present Collaborator. Randomized controlled trial of the efficacy of pre-emptive tenofovir to prevent hepatitis B reactivation in patients who are anti-HBc antibody positive receiving curative intent rituximab-based chemotherapy for non-Hodgkin's lymphoma. Canadian Institutes of Health Research. 302516. PI: Feld, Jordan. Collaborator(s): Chan K, Hicks L, Crump M. 143,445 CAD. [Grants]

2014 - 2019 **Co-Investigator**. NCIC-CTG Clinical Trials. Canadian Collaborating Clinical Trials Network (NCTN). National Institutes of Health/National Cancer Institute (NIH/NCI). CA180863. PI: Dancey, J. Collaborator(s): Seymour L; Shepherd L; Parulekar W; O'Callaghan C; Hay A; Tu D; Ding K; Chen B; Richardson H; Mason W; Gelmon K; Whelan T; Jonker D; Chi K; Fleshner N; Hirte H; Fung Kee Fung M; **Crump M**; Couban S; Goss G; Ung Y; Petrella T; Spatz A; Alcindor T; Nielsen T; Wong R; Brundage M; Ringash J; Tsao M; Leighl N; Mittmann N. 15,115,295 CAD. [Clinical Trials]

Relapsed Classical Hodgkin Lymphoma: Will Immunotherapy Replace Chemotherapy?

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In the current era, treatment of limited and advanced stage Hodgkin lymphoma (HL) remains a therapeutic success story. Despite the application of combined modality therapy in stage I-II HL or the use of FDG-PET guided strategies to reduce the need for radiation, 5-10% of patients still experience recurrence. In addition, while treatment intensification with escalated BEACOPP may improve progression-free survival, most comparative studies have not been powered to show an overall survival difference, and up to 10% of patients with advanced-stage HL will not achieve complete remission (CR), and 20%–30% of responding patients subsequently relapse after treatment. Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the treatment of choice in patients with refractory or relapsed HL. (1)

The role of aggressive second-line therapy in HL has been defined by 2 published phase 3 randomized trials.(2,3) The GHSG/EBMT assigned 161 patients with relapsed HL to receive 2 cycles of dexa-BEAM chemotherapy and randomized responding patients to either 2 additional cycles of dexa-BEAM or high-dose therapy and ASCT. Although there was no difference in OS, freedom from treatment failure at 3 years was significantly improved in the ASCT group (55% vs 34%, $P = .02$).**(2)** Neither this trial or the smaller study reported from the British National Lymphoma Investigation(3) included chemorefractory patients, and only cohort and registry data address the benefit of ASCT in these patients. There are limited modern data on the role of ASCT in lymphoma overtly refractory to chemotherapy. Data from our centre show that response rate to second-line or salvage chemotherapy, one of the strongest predictors of outcome post-ASCT, is inferior in patients who have refractory HL (progression during or within 3 months of completion of therapy).(4) In addition, those who experience progression during salvage therapy have a low likelihood of cure even if there is response to second-line salvage such as miniBEAM (5 year PFS 22%).(5) While long-term outcomes of patients who relapse one year or more after primary therapy, or who have a complete response by CT scanning or FDG-PET scanning(6) have excellent outcomes after salvage therapy, these favourable factors are present in the minority of patients referred to transplant, and additional strategies are needed for the majority of patients who experience treatment failure.

Interest in immunologically based therapies to enhance the benefits of salvage therapy and ASCT have been heighted by reported success rate of the anti-CD30 chemo-immunoconjugate brentuximab vedotin, and by biological observations underlying the remarkable activity of immune checkpoint inhibitors (programmed death (PD)-1 antibodies) in Classical HL. Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) consisting of the microtubulin toxin monomethyl auristatin E (MMAE) linked to an anti-CD30 antibody by a dipeptide linker. The single agent response of BV patients with relapsed HL following ASCT was 75%, with progession-free survival of 6 months and with a favourable toxicity profile.(7) One-third of complete responses lasted more than 20 months, and these data led to the approval of BV in the post ASCT relapse setting in many countries. Combination of BV with bendamustine is currently being tested in phase II trials, with encouraging overall and complete response rates, and will be tested pre-transplant in a planned phase III international trial.

Addition of BV as maintenance therapy following ASCT in patients with high risk HL responding to salvage therapy and completing ASCT has also been reported. In the study by Moskowitz et al, patients

with response or stable disease to salvage therapy were stratified by duration of prior response (refractory, early or late relapse (>1 year) and response to salvage to receive BV every 3 weeks for 16 doses or placebo.(8) Progression-free survival by independent review was significantly improved in the 165 patients receiving BV compared with 164 patients in the placebo group (median 42.9 vs 24.1 months, hazard ratio [HR] 0·57, 95% CI 0·40–0·81; p=0·0013). There was no difference in overall survival, but follow-up maybe be too short to capture sufficient events for this endpoint; nonetheless, the reported improvement in outcome with addition of an immunologically targeted treatment in this high-risk patient population is very promising

Evasion of the immune system through expression of inhibitory molecules PD-L1 and PD-L2 has been observed in many solid tumors and lymphomas, including cHL. The majority of cHLs tested have chromosome abnormalities involving 9p24.1, with copy number gain or amplification of the PD-L1 and PD-L2 loci.(9) PD-L1 expression on the surface of Hodgkin Reid Sternberg cells has been shown to be correlated with these genetic alterations, leading to engagement of the PD-1 receptor on T cells and induce PD-1 signaling and T-cell exhaustion by reversible inhibition of T-cell activation and proliferation. The new PD-1 antibodies nivolumab and pembrolizumab have been tested in patients with relapsed cHL, producing high response rates and relatively little toxicity, although full potential of these agents to produce immune-mediated side effects and the durability of responses requires much longer follow-up.(10,11)

Detailed discussion of these therapeutic developments, including a better understanding of the role of the immune system in cHL, and their implications for alternative treatments to ASCT in the relapsed setting, will be the focus of this presentation.

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Thomas J. Walsh

Dr. Walsh serves as Professor of Medicine, Pediatrics, and Microbiology & Immunology at Weill Cornell Medicine of Cornell University and founding Director of the Transplantation-Oncology Infectious Diseases Program, Chief of the Infectious Diseases Translational Research Laboratory, as Adjunct Professor of Medicine of the University of Maryland School of Medicine, Sharp Family Foundation Scholar in Pediatric Infectious Diseases, and Investigator of Emerging Infectious Diseases of the Save Our Sick Kids. Following graduation from the Johns Hopkins University School of Medicine, he completed 10 postdoctoral years of training and served with distinction as the Chief of the Immunocompromised Host Section of the Pediatric Oncology Branch of National Cancer Institute for 23 years. He then was recruited to build the first Transplantation-Oncology Infectious Diseases Program in Weill Cornell Medicine and New York Presbyterian Hospital. Dr. Walsh directs a combined clinical and laboratory research program dedicated to improving the lives and care of immunocompromised children and adults. The objective of the Program's translational research is to develop new strategies for molecular diagnosis, immunopharmacology, pharmacokinetics / pharmacodynamics, treatment, and prevention of life-threatening invasive mycoses and other bacterial, fungal, and viral infections in immunocompromised children and adults. These objectives are achieved through laboratory investigations using parallel *in vitro* systems, and robustly predictive *in vivo* animal model systems, leading to more than 60 phase-I, phase-II, and phase-III clinical trials. The Program's current targeted laboratory investigations and clinical trials in medical mycology include invasive candidiasis, pulmonary aspergillosis, mucormycosis, fusariosis, and phaeohyphomycosis, and in the infections caused by multidrug resistant bacteria, including *Klebsiella* pneumoniae, *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. In addition to patient care and translational research, Dr. Walsh has also mentored from 28 different countries more than 180 students, fellows, and faculty, many of whom are emerging leaders in the field of infections in immunocompromised patients.

Diagnosis and Treatment of Emerging Multidrug Resistant Bacteria in Patients with Hematological Malignancies: New Molecular Methods and Novel Antimicrobial Agents

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The emergence of infectious diseases caused by multidrug-resistant (MDR) bacteria poses a major public health threat to immunocompromised patients, especially those with hematologic malignancies. The causes for this emergence of resistance is multifactorial and includes deficient infection control practices, limited antimicrobial stewardship, the intrinsic ability of bacteria to develop and transmit resistance-conferring mutations, and complicated hosts needing intensive antimicrobial management.

Enterobacteriaceae cause approximately one-fourth of all healthcare-associated infections. These organisms include *Escherichia coli, Klebsiella* spp., and *Enterobacter* spp. During the past decade, there has been a global emergence of carbapenem-resistant Enterobacteriaceae (CRE). These carbapenemases confer resistance to all cephalosporins such as cefepime and ceftazidime, to all extended spectrum penicillins, such as piperacillin-tazobactam, and to all carbapenems, such as meropenem and imipenem.

Klebsiella pneumoniae carbapenemase (KPC) producing bacteria were initially described in hospitals of New York City and Israel. Subsequent reports now described these organisms in multiple cities throughout the developed nations. There are now reports of CRE infection in all 50 states in the United States and more than 30 countries reporting these infections. The Center for Diseases Control and Prevention in 2006-2007 reported that 21% of *Klebsiella pneumoniae* isolates from NYC were carbapenem-resistant. Carbapenem resistance among Enterobacteriaceae in the USA is most commonly caused by KPC. These organisms express the plasmid-based gene bla_{KPC}, which encodes a broad spectrum carbapenemase.

Further adding to this public threat of multidrug resistance has been the emergence of New Delhi Metallo-beta-lactamase-1 (NDM-1) in Enterobacteriaciae as a new antibiotic resistance mechanism in India, Pakistan, Iran, and the United Kingdom. The NDM-1 containing Enterobacteriaciae now also now have the capability of thriving in the community and quickly spreading across countries and continents in relation to accessible, rapid global travel.

Satlin and colleagues at Weill Cornell Medical Center in New York hypothesized that expansion of KPC and other CRE organisms into patients with hematologic malignancies was a serious threat to survival and would have serious implications for empirical antimicrobial therapy. As Enterobacteriaceae are the most common causes of Gram-negative blood stream infections in this patient population, a CRE phenotype would have potentially lethal consequences. All of the recommended empirical antimicrobial agents for the initial management of fever and neutropenia in patients with hematological malignancies have no *in vitro* or *in vivo* activity against CRE. Such patients would be expected to have a high risk of mortality as they would not be receiving effective therapy for 24-48 hours while the CRE was being identified.

These investigators, therefore, studied the emergence of CRE in patients with hematologic malignancies in a large, oncology-hematopoietic stem cell transplant (HSCT) center located in an endemic area (2007-2010) in New York City. Eighteen patients with hematologic malignancies developed bloodstream infections (BSIs) caused by CRE during the study period. Fourteen of these BSIs were caused by *Klebsiella pneumoniae*, three by *Enterobacter cloacae*, and one was polymicrobial. Initial empirical antimicrobial therapy was active in

only two patients (11%). Moreover, a median of 55h elapsed between culture collection and receipt of an active agent. Ten (56%) of the 18 patients died. Nine (69%) of the 13 neutropenic patients also died. Accounting for this strikingly elevated mortality, a median of 4 days elapsed between time of culture collection and death.

Among the CRE isolates that were analyzed for carbapenemase production, β-lactamase genes, and outer membrane porin deletions, carbapenem resistance mechanisms included bla_{KPC} in most cases, while CTX-M-15 production with an absent outer membrane porin protein was found in one isolate. Among the isolates that were further characterized by multilocus sequence typing and pulsed-field gel electrophoresis (PFGE), no isolate had ≥95% homology on PFGE, indicating a heterogeneous, non-outbreak population of isolates. Such a heterogeneous group of CRE BSI isolates suggests that infection control measures alone will not be sufficient to curtail this spread into the population of hematological malignancies.

These findings indicate that CRE infections are emerging in patients with hematological malignancies and are associated with ineffective initial empirical therapy, long delays in administration of active antimicrobials, and high mortality rates. The mortality rate of 69% in neutropenic patients with CRE is consistent with earlier data in the 1960's and 1970's when monotherapy with gentamicin was being used for treatment of febrile neutropenic hosts. The mortality of the CRE bacteremic neutropenic patients were also compatible with earlier studies three decades ago that in the absence of immediate, effective, broad-spectrum, empirical antimicrobial therapy, approximately 50% of neutropenic patients with Gram-negative bacteremia died within 3 days of presentation.

Treatment of *Pseudomonas aeruginosa* infections has driven the recommended empirical antibiotic choices for fever in neutropenic patients with hematologic malignancies. This organism is the third most common cause of Gram-negative bacteremia in this population and *P. aeruginosa* bacteremia is associated with high mortality rates. Early studies conducted before development of empirical antibacterial therapy for fever demonstrated that approximately 50% of neutropenic patients with *P. aeruginosa* bacteremia died within three days and 70% died within seven days. *Pseudomonas aeruginosa* is especially challenging because of its intrinsic resistance to many classes of antibiotics and its ability to develop resistance during therapy through multiple mechanisms. Antimicrobial options for MDR *P. aeruginosa* infections have historically been limited to polymyxins and/or aminoglycosides. Ceftolozane-tazobactam is a new option for treatment of MDR *P. aeruginosa* infections.

In predicting risk of CRE bacteremia in patients with hematological malignancies, prior exposure to carbapenems is not a reliable determinant. Satlin and colleagues demonstrated that the absence of recent carbapenem exposure does not preclude the development of CRE BSI in patients with hematologic malignancies. The majority of CRE BSIs that occurred during neutropenia were not "breakthrough" infections. These infections principally occurred as the initial BSI during neutropenia. Indeed, the most common setting for CRE bacteremia in these patients was the new onset of fever and neutropenia. The two most common possible risk factors in patients with hematological malignancies predicting CRE bacteremia are (1) exposure to a non-oncology unit, such as a surgical unit or an ICU, elsewhere in the hospital that is known to have CRE infection, and (2) previous or ongoing exposure to a fluoroquinolone or cephalosporin.

Given the continued expansion of CRE into the highly vulnerable population of patients with hematological malignancies, new diagnostic, therapeutic, and preventive strategies are critically needed. Surveillance cultures of mucosal surfaces may provide early warning of patients with hematological malignancies who would be colonized with CRE. Among the possible strategies currently being studied for surveillance of mucosal surfaces of high risk patients with hematological malignancies are selective chromophore agar-based media for CRE, rapid PCR systems for the bla_{KPC} gene, and mass spectroscopic systems, such as Matrix Assisted Laser Desorption Ionization Time of Flight (MALD-TOF). Once patients are found to be colonized, they are placed on isolation and specific plans are implemented for including antimicrobial agents active against CRE if they become febrile.

There is a crisis in the development of new antimicrobial agents that threatens the public health of all patients, especially those with hematological malignancies, where infections are treated through well-established algorithms. Although new agents are being developed that show activity against CRE, other multidrug resistant bacteria will continue to emerge with different mechanisms of resistance. There needs to be a global effort directed to improved surveillance, infection control measures, rapid molecular diagnostics, and new antimicrobial agents, in order to better protect our patients with hematological malignancies.

Ceftolozane-tazobactam (CXA-201) has potent antimicrobial activity against strains of multidrug resistant *P. aeruginosa* that express resistance through several mechanisms, including porin mutations, efflux pumps, and beta-lactamase production. Currently licensed for treatment of complicated urinary tract infections and intraabdominal infections, ceftolozane-tazobactam has the potential for targeted therapy against multidrug resistant *P. aeruginosa* in patients with hematological malignancies. Ceftazidime-avibactam (NXL-104) has potent activity in the inhibition of KPC-encoded beta-lactamases, including those associated with NDM-1-resistant Enterobacteriaciae. This compound also serves a critical unmet in need in expanding the antimicrobial armamentarium against multidrug-resistant Gram-negative bacterial infections.

Acinetobacter baumannii, which is frequently panresistant due to multiple integron-resistant regulated genes encoding proteins mediating high level resistance to most classes of antimicrobial agents. The challenges of resistant Gram-positive bacteria, such as MRSA and VRE, also pose additional challenges to patients with hematological malignancies.

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I graduated "Summa Cum Laude" from the Medical School of the National and Kapodistrian University of Athens, Greece. I completed my Internal Medicine training at the Athens University Laikon Hospital and the New York-Presbyterian Hospital, Weill Cornell Medical Center of Cornell University. I was then trained in Infectious Diseases at the Athens University Laikon Hospital. I completed my PhD thesis on candidemia among patients with hematological malignancies at the Athens University Medical School and my Master in Public Health, at the School of Public Health, Athens Greece. I served for two months as a clinical observer at the HIV department of the Chelsea and Westminster Hospital, London under a scholarship of the Hellenic Society of Infectious Diseases, and for one year as Senior Clinical Fellow at the National Aspergillosis Centre, University Hospital of South Manchester. Currently, I am Clinical Research Fellow at the St James University Hospital, Leeds, UK. I am a founding member of the International Osteoarticular Mycoses Study Consortium. I am recipient of 12 awards, grants, and competitive scholarships. I have served as invited speaker in numerous National and International conferences and my teaching portfolio includes lectures in pre- and post-graduate students in both Greece and UK. I have authored or co-authored more than 40 original articles in peer-reviewed medical journals, in the field of Infectious Diseases.

Recent Advances in Risk Assessment and Management of Invasive Fungal Infections in Patients with Hematological Malignancies

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Neutropenia is a key risk factor for the development of invasive fungal infections. Neutropenia may develop as the result of chemotherapy, radiation, bone marrow failure (myelodysplasia and aplastic anemia), and by replacement of hematopoietic cells in the bone marrow by malignant cells. In the classic description of the inverse relation between risk of infection and degree of neutropenia, Bodey *et al.* underscored the role of profound neutropenia (ANC<100) in leukemia patients for increasing the risk for infection. In a classic study of patients receiving treatment for acute leukemia Gerson *et al.* later demonstrated that the risk of invasive aspergillosis is directly related to the duration of neutropenia in patients with acute leukemia. Neutropenia is also a surrogate marker for other risk factors for IFIs. For example, mucositis associated with intensive chemotherapy increases the risk for translocation of *Candida* spp. across the alimentary tract. Lymphocytopenia in hematological malignancies increases the risk for fungal infections associated with impaired cell mediate immunity (CMI). Fludarabine, which is a lymphotoxic compound primarily affecting CD4+ lymphocytes and corticosteroids markedly increases the risk of infection caused by *Pneumocystis jirovecii* and *Cryptococcus neoformans*. In addition to their effects on CMI, corticosteroids markedly alter the distribution, trafficking and functions of neutrophils, monocytes, and lymphocytes. Corticosteroids also impair oxidative function and hyphal damage capacity of neutrophils and impair phagocytosis of macrophages. The risk of infections caused by invasive filamentous fungi, such *Aspergillus* spp. and the *Mucorales,* is significantly increased in these patients receiving a prednisone equivalent of 0.5 mg/kg for longer than 30 days. Among allogeneic HSCT recipients, corticosteroid therapy for GVHD is a major risk factor for invasive aspergillosis and filamentous fungal infections.

Among the humanized immunosuppressive biological agents, alemtuzumab (Campath-1H; anti-CD52 humanized monoclonal antibody that targets normal and most malignant T-lymphocytes) is associated with severe lymphopenia and an increased risk for opportunistic infections, including *Pneumocystis jirovecii* pneumonia. TNF-alpha inhibiting agents, including infliximab, etanercept, and adalimumab, increase the risk for infections caused by intracellular pathogens, such as *Histoplasma capsulatum.*

Candida species are a component of the endogenous microbiome that invade the bloodstream through disruptions in anatomical barriers. The alimentary tract is the principal portal of entry in patients with acute leukemia resulting in candidemia. *Candida albicans* historically was the most common *Candida* species isolated from blood. With the advent of triazole and echinocandin prophylaxis and therapy, there has been a major shift in the causes of candidemia toward non-*albicans Candida* spp. Serum (1→3)-β-D-glucan may reveal the presence of invasive candidiasis before positive blood cultures.

A recent prospective, multicenter study specifically designed to investigate the epidemiology, risk factors, and outcome of candidemia among hospitalized patients with hematological malignancies found that most infections (87.5%) were caused by non-*Candida albicans* species, with *C. parapsilosis*, being most common. Independent risk factors for the development of candidemia were the presence of CVC, hypogammaglobulinemia, and high APACHE II score. Twenty-eight-day crude mortality was 45%. Patients with candidemia had significantly lower survival than those without candidemia. Among patients with candidemia, an elevated APACHE II score was an independent risk factor for death; recovery from neutropenia was independently associated with improved survival.

Recent studies indicate that removal of central vascular catheters in patients with hematological malignancies does not improve outcome. If a multilumen catheter is not immediately removed, antifungal therapy should be administered parenterally through all lumens. As candidemia in neutropenic patients may be complicated by chronic disseminated candidiasis of liver, spleen, and kidney, and eyes, ophthalmologic examination and CT scan of the abdomen is recommended upon recovery from neutropenia. Chronic disseminated candidiasis (hepatosplenic candidiasis) may persist with new episodes of fever following recovery from neutropenia. After the resolution of neutropenia, elevated alkaline phosphatase and development of numerous target lesions in the liver and spleen may develop. An open liver biopsy is advisable but may not be feasible. Antifungal therapy with fluconazole or echinocandin should be initiated with anticipation of treatment for several months until resolution of lesions. The presence of persistent lesions does not preclude further chemotherapy.

As most patients with hematological malignancies are receiving fluconazole prophylaxis, an echinocandin (anidulafungin, caspofungin, or micafungin) is recommended as the initial therapy of invasive candidiasis in neutropenic patients with hematologic malignancies. For non-neutropenic stable patients with uncomplicated candidemia an initial course of echinocandin followed by fluconazole is reasonable if the organism proves to be *C. albicans*. The sino-pulmonary tract is the most common portal of entry of *Aspergillus* spp. and other filamentous fungi. Profound and persistent neutropenia, repeated cycles of prolonged neutropenia, concomitant corticosteroid therapy, and graft *versus* host disease (GVHD) increase the risk of development of invasive sino-pulmonary aspergillosis (ISPA). Other risk factors in HSCT recipients include lymphopenia, GVHD, CMV disease, and respiratory viral infections.

ISPA may initially only manifest as fever. More advanced infection presents with sinus pain or congestion, cough, pleuritic chest pain, and hemoptysis. Invasive pulmonary aspergillosis (IPA) includes nodules, halo sign, bronchopneumonia, lobar consolidation, wedge-shaped segmental pneumonia, and cavitary lesions. CNS aspergillosis may present as focal neurological deficits. Early diagnosis of aspergillosis is important for improved outcome. Recovery of organism from bronchoalveolar lavage, percutaneous needle aspirate, and biopsies, in sino-pulmonary lesions is advised but may have limited sensitivity. Serum galactomannan detected by double sandwich ELISA improves early detection of aspergillosis and complements CT scans. Serial quantitation of galactomannan antigenemia also predicts response to antifungal therapy. Serum (1→3)-β-D-glucan may also detect invasive aspergillosis and other invasive mold infections. PCR-based detection of *Aspergillus* DNA in BAL fluid may be useful for the diagnosis of IPA. *Aspergillus fumigatus* followed by *Aspergillus flavus* are the most common species causing invasive aspergillosis. *Aspergillus terreus* is observed with increasing frequency at several hematological malignancies centers, and is notable for being resistant to amphotericin B. Voriconazole or isavuconazole are the preferred agents for initial therapy of ISPA and disseminated aspergillosis. Isavuconazole has been recently shown in laboratory animal studies and in clinical trials to be comparable to voriconazole in antifungal activity against IPA. Isavuconazole, however, has fewer adverse events, particularly reduced CNS toxicity, cutaneous reactions, and hepatotoxicity. Isavuconazole also demonstrates linear dose-proportional plasma pharmacokinetics with once daily dosing and fewer adverse drug interactions. For patients for whom voriconazole and isavuconazole is contraindicated, liposomal amphotericin B (LAmB) is used instead. Posaconazole is approved for use as prevention of invasive aspergillosis in patients with acute leukemia and in HSCT recipients.

Risk factors for mucormycosis among patients with hematological malignancies include prolonged neutropenia, corticosteroids, diabetic mellitus, iron overload, and GVHD. Mucormycosis in patients with hematological malignancies typically manifests as pulmonary, sinus, sino-orbital, rhino-cerebral, or cutaneous disease. Patients with pulmonary mucormycosis may present with cough, hemoptysis, pleuritic pain, and single or multiple pulmonary nodules, which also may demonstrate a reverse halo sign. In rhino-cerebral disease, fever, facial pain and headache are common symptoms.

Isolated primary cutaneous disease may follow minor trauma.

There are three cornerstones of therapy for mucormycosis: lipid formulation of amphotericin B or conventional deoxycholate amphotericin B; early and aggressive surgical debridement; and reversal of immunosuppression, as well as correction of hyperglycemia in diabetic patients. Isavuconazole is an emerging alternative for primary therapy for treatment of mucormycosis. Laboratory animal data and the results of a prospective non-randomized trial for primary treatment of mucormycosis demonstrate favorable activity of isavuconazole. The role of isavuconazole in relation to lipid formulations of amphotericin B remains to be defined through future studies. There is no advantage to combination therapy of isavuconazole and amphotericin B.

Fusarium species in patients with hematological malignancies cause sino-pulmonary and disseminated infection. Prolonged neutropenia is the most common risk factor. The lower respiratory tract is the frequent portal of entry. Fungemia with positive blood cultures occurs in approximately one-half of cases during neutropenia. Multiple hematogenously disseminated cutaneous lesions are common and usually reveal the organism in biopsy. *Fusarium* species, which include *Fusarium solani* species complex and *Fusarium oxysporum* species complex, have variable *in vitro* susceptibility to amphotericin B and to voriconazole. Initial therapy consists of both amphotericin B and voriconazole for spectrum (not synergy) while awaiting susceptibility results. Although interpretive breakpoints have not been established, readings of >4μg/ml usually signify lack of response ("resistance") to the antifungal agent. Survival from disseminated fusariosis is critically dependent on resolution of neutropenia. Granulocyte transfusions have been life-saving in selected patients until recovery from neutropenia.

Other infections for which patients with hematological malignancies are vulnerable include those caused by *Scedosporium* spp., dematiaceous moulds, *Cryptococcus* spp., *Pneumocystis*, *Trichosporon* spp., *Malassezia* spp. and e*ndemic* dimorphic fungi, including *Histoplasma capsulatum, Coccidioides* spp*., Blastomyces dermatitidis,* and *Talaromyces marneffei.*

Nikolaos V. Sypsas

Dr. *Nikolaos V. Sipsas, MD, PhD (Zurich), FIDSA* received his medical degree from the National and Kapodistrian University of Athens in Greece. He did his post-doctoral thesis, in History of Medicine at the Medical School of the Zurich University in Switzerland, and in Infectious Diseases at the Athens University Medical School, Greece. Then he was trained in Internal Medicine at the Athens Naval Hospital and the Athens University Laikon Hospital. He was subsequently trained as a research fellow in Infectious Diseases at Massachusetts General Hospital in Boston. He is currently attending physician at the Department of Medicine, head of the Infectious Disease Unit at the Laikon General Hospital, in Athens, Greece and Associate Professor at the Athens University Medical School. He served as guest researcher at the MD Anderson Medical Center, Houston, Texas for 3 months and as invited speaker in numerous National and International conferences, hospitals and universities. His research interest include infections in the Immunocompromised host, (mycoses in patients with hematological malignancies, neutropenic patient, autoimmune rheumatic disease patients); HIV infection: markers of immune activation, cytotoxic T-cell responses, autoimmune phenomena, anemia, and metabolic complications; Zoonoses: work on brucella infections, especially spondylodiskitis, leishmaniasis in immunocompromised patients, Q-fever; CNS infections: endocrine complications of meningitis, treatment of cryptococcal meningitis; Nutrition and hospital-acquired infections; Animal models for experimental osteomyelitis; and Bacterial infections due to multi-drug resistant pathogens. He is a reviewer in >20 peer-reviewed journals in Infectious Diseases and Internal Medicine and he has authored more than 95 peer-reviewed papers and 4 chapters in textbooks.

Viral Infections in Patients with Hematological Malignancies: Rapid Molecular Diagnosis and Antiviral Strategies

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Infections are an important complication of hematological malignancies, especially after chemotherapy or during hematopoietic stem cell transplantation (HSCT) procedures and contribute significantly to morbidity and mortality. Besides the risk of developing bacterial and fungal infections, there is a substantial risk of primary viral infection and reactivation.

Respiratory viruses can cause severe pneumonia after chemotherapy and/or HSCT, with high morbidity and mortality. Historically, their clinical significance in patients with hematological malignancies has been underestimated, but nowadays they are increasingly recognized as common causes of upper respiratory infection (URI), lower respiratory tract infection (LRTI), and are frequently associated with bacterial or fungal co-infections. Common respiratory viruses affecting patients with hematological malignancies include respiratory syncytial virus (RSV), influenza and parainfluenza viruses, adenoviruses, rhinoviruses, and coronaviruses. More recently, newly identified viruses such as human metapneumoviruses (HMPV), new strains of coronaviruses, and bocavirus have also been detected in symptomatic HSCT recipients. Respiratory viruses can be acquired in the community or during hospitalization. With regard to diagnosis, prompt and accurate identification of the respiratory viral pathogen is of paramount importance for the management of infection, because it allows for timely implementation of virus-specific infection control measures, the initiation of appropriate antiviral therapy, and for potential modifications of immunosuppressive therapy or rescheduling of HSCT. Proper collection of specimens is critically important for accurate identification of viruses in clinical samples. Different diagnostic methods have been used, including several biomarkers, but during recent years, the use of multiplex PCR technique is becoming the standard of care, it may detect multiple respiratory viruses from a single, readily obtained specimen. Management of respiratory viral infections has been controversial. Apart from influenza infections for which neuramidase inhibitors have been shown to be effective, there are no established treatments. There is a paucity of well-designed, randomized, controlled, clinical studies for the treatment of respiratory viral infections among patients with hematological malignancies. There are only a few studies, mostly retrospective and from single centers, and "expert opinions" that guide physicians on the therapy of these serious and sometimes fatal infections in patients with hematological malignancies and/or HSCT.

Heavy immunosuppression of patients with hematological malignancies can lead to reactivation of latent viruses, including herpes viruses (varicella-zoster virus [VZV], herpes simplex virus [HSV], human herpes virus 6 [HHV-6], Epstein Barr virus [EBV] cytomegalovirus [CMV]), polyomaviruses, and adenovirus. These systemic viral infections occur usually in HSCT recipients, after conditioning or later, due to the administration of immunesuppressive agents. New antiviral agents, such as Letermovir, new antiviral vaccines and new immunotherapies have been introduced in the clinical practice or they are at an advanced stage of development, and increase the armamentarium against these deadly infections.

Finally, viral hepatitis B and C are emerging as an important issue, especially in patients undergoing HSCT.

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Professor Ibrahim Yakoub-Agha, completed his four-year residency in Medical Biology at the Brest University Hospital (1986-1990) and his two-year Clinical Hematology fellowship at the University of Paris VI (1990-1992). He also obtained a University Diploma of Oncology at the University of Paris XI/Institut Gustave Roussy (1995). Additionally, he completed two years of fellowship in Allogeneic Stem Cell Transplantation at the Saint-Louis University Hospital in Paris (1996-1998). He accomplished his PhD degree at the Lille University Hospital where he is appointed as a Professor of Hematology and head of Hematopoietic Stem Cell Transplantation Unit since 2008.

He has published several scientific articles related to the field of allogeneic Stem Cell Transplantation especially in patients with Myelodysplastic Syndrome.

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Myelodysplastic Syndromes: Nontransplant Approaches

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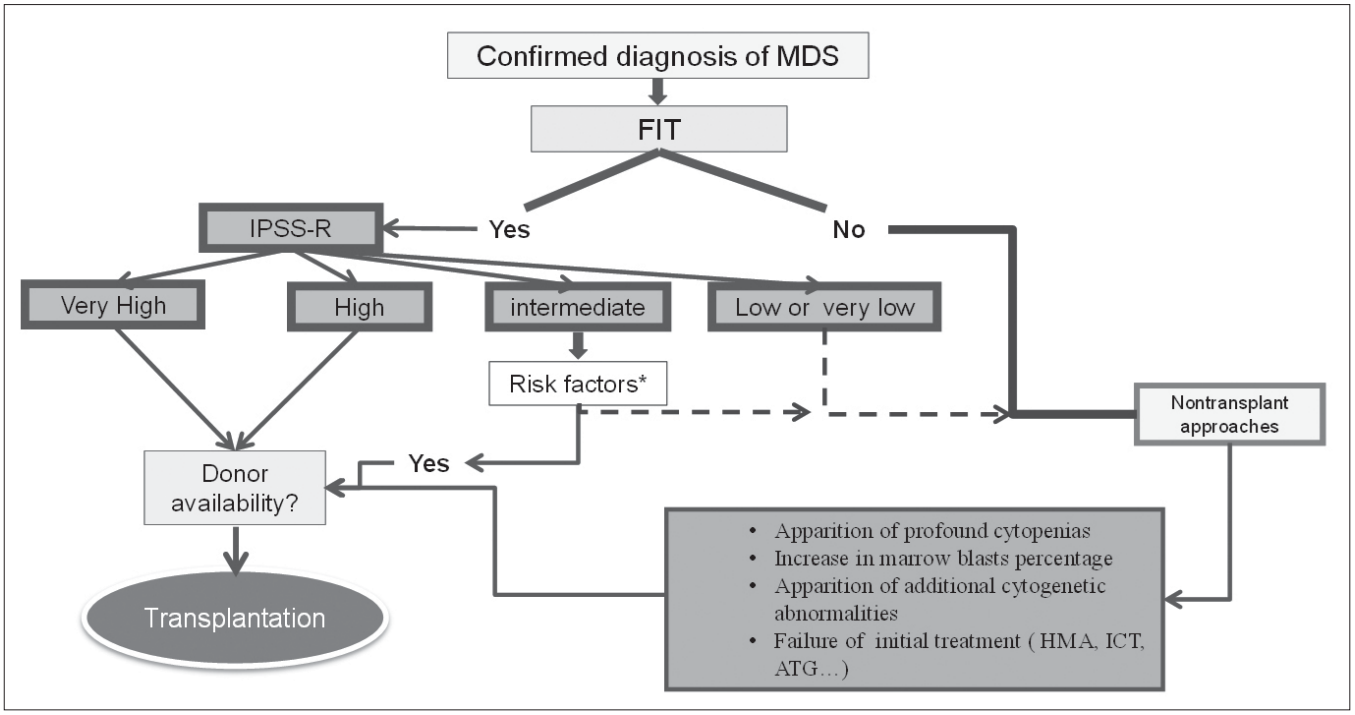
Myelodysplastic syndromes (MDS) are heterogeneous disorders that range from conditions with a near-normal life expectancy to forms approaching acute myeloid leukemia (AML). A risk-adapted treatment strategy is mandatory, and the definition of individual risk requires the use of prognostic systems. In 1997, the International Prognostic Scoring System (IPSS) has been developed and become a benchmark for clinical trials and decision-making. Nonetheless, a not negligible heterogeneity was observed in IPSS subgroups, in particular in patients classified in low and intermediate-1 risk categories. Recently, the International Working Group for Prognosis in MDS revised the IPSS. On the basis of a large data set that allowed the prognostic value of even less frequent cytogenetic abnormalities to be estimated, five cytogenetic risk groups were determined representing the basis for the revised IPSS (IPSS-R), together with refined categories for bone marrow blasts and peripheral blood cytopenias. IPSS-R improved the capability to capture prognostic information in untreated MDS as well as in patients receiving disease-modifying treatments.

Despite improved understanding of the molecular pathogenesis of myelodysplastic syndromes (MDS), currently available therapeutic agents lead to prolongation of life and no cure. Therefore, allogeneic stem cell transplantation (allo-SCT), is still considered as a conventional therapeutic option until the age of 65–70 in eligible patients. Its efficacy, however, is considerably limited by morbidity and mortality, resulting in a long-term survival rate of about 30%.

Decision making flow chart:

Disease risks according to IPSS-R and presence of comorbidity according to the HCT Comorbidity Index (HCT-CI) are currently recognized as relevant clinical variables for allo-SCT eligibility.



*** nontransplant strategies are offered to patients with intermediate except those with risk factors (i.**e. profound cytopenias, poor risk cytogenetic, marrow blasts ≥ 5% and/or severe myelofibrosis) (12)

Nontransplant approaches

Patients how are not candidate for allo-SCT are affected primarily by cytopenias-related symptoms as well as progression to acute myeloid leukemia in higher risk patients. Severe thrombocytopenia, although less common in lower-risk MDS, is associated with increased risk of bleeding. For anemic patients, the principal aim of treatment is to improve anemia and decrease red blood cell transfusions. While lenalidomide is effective in del(5q) patients, for transfusion-dependent patients with lower-risk MDS without chromosome 5q deletion [non-del(5q) MDS], there are limited effective treatments. Erythropoiesis-stimulating agents (ESAs) are generally first-line therapy, yielding frequent responses with a median duration of 18-24 months. Immunosuppressive therapy is restricted to select patients. New strategies for ESA-refractory or relapsed patients include lenalidomide, alone or in combination with ESAs; oral azacitidine; and new molecules such as the activin receptor type II ligand traps luspatercept and sotatercept. In thrombocytopenic patients, thrombopoietin receptor agonists are under evaluation. While trials to evaluate these treatment strategies are underway, efforts are needed to optimize therapies through better patient selection and response prediction as well as integrating molecular and genetic data into clinical practice. At the 6th international Congress on Leukemia Lymphoma Myeloma, the issues of current nontransplant treatment approaches for MDS will be addressed. Promising directions for future research will be also be discussed.

H. Joachim Deeg

Dr. Deeg is a Professor of Medicine at the University of Washington, Seattle, and a Full Member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center, Seattle, WA

He earned his medical degree from the University of Bonn, Germany, completed his internal medicine training and was Chief Medical Resident at the University of Rochester School of Medicine, Rochester, N.Y. He did his Hematology/Oncology fellowship under E.D.Thomas and R. Storb at the University of Washington, Seattle, where he then joined the faculty.

Dr Deeg has worked and published extensively on clinical and pre-clinical models of transplantation, on conditioning regimens, GVHD, the pathophysiology and therapy of marrow failure, in particular aplastic anemia and the myelodysplastic syndromes, late complications of cancer therapy and related questions. Recent studies have focused on molecular aspects of the pathophysiology of the myelodysplastic syndromes as well as ethical aspects of treatment decisions. He has published more than 800 scientific papers and several books.

Dr Deeg has been the mentor to many graduate students and more than 40 post-doctoral fellows, guiding them on their laboratory-based or clinical careers into academia or industry positions.

He is the recipient of the Alexander von Humboldt Research Award, he presented the Till and McCullough Lecture at the 11th Biennial CBMTG Conference (2008) in Montreal, and was recognized with the "Leadership in Science 2008" award by the Aplastic Anemia and MDS International Foundation. He has served or continues to serve on various NMDP and ASBMT committees and is currently the Director for Laboratory Sciences of the ASBMT. He has served on numerous editorial boards, including *Blood, Transplantation, Leukemia* and *Biology of Blood and Marrow Transplantation* among others.

Hematopoietic Cell Transplantation for MDS: Where do we Stand?

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Why not transplant all patients with MDS?

Allogeneic hematopoietic cell transplantation (HCT) is curative for as many as 50%- 70% of patients, dependent upon the risk categorization at the time of transplantation. There is considerable progress over the past decade. Why, then, do we not transplant *all patients* with MDS?

Firstly, patients with low-risk MDS, defined by the revised International Prognostic Scoring System (IPSS-R), the WPSS (see below) or other criteria, may have life expectancies of a decade or more with minimal support or even without therapy.

Secondly, HCT is associated with several risks including treatment-related toxicity and mortality, and the development of graft-versus-host disease (GVHD). Further, despite success in many patients, the post-HCT relapse incidence may be as high as 30% or even 40%.

In general, the emphasis in allogeneic HCT has shifted from high-intensity conditioning regimens (HIR),

aimed at maximum tumor cell kill, to low or reduced intensity conditioning (RIC), relying on immune effects mediated by donor cells (graft versus tumor [GVT] effects) to eradicate the disease. So far, separation of GVHD from GVT effects in human patients has been difficult. However, the use of post-HCT cyclophosphamide or the incorporation of ATG in the conditioning regimens has reduced the incidence of GVHD, without necessarily increasing the incidence of relapse.

Disease stage and transplantation

Patients with lower risk MDS (no high risk cytogenetics or mutations, low myeloblast count) tend to have a more indolent, albeit still progressive course. In fact, the presence of severe neutropenia or thrombocytopenia or red blood cell transfusion dependence may be indications for HCT, particularly in younger individuals even with a low IPSS-R score since none of the available non-HCT therapies have been shown to be curative . Whether chelation therapy of iron overload improves outcome after HCT, has yet to be determined.

The decision to proceed to HCT is easier in patients with advanced/high risk disease as their prognosis is poor. Patients with MDSEB-1 or MDSEB-2 patients in WPSS or IPSS-R categories intermediate , high and very high risk should definitely be considered for HCT .

Patients with therapy-related MDS should also be offered transplantation. In fact, once adjusted for the patient's karyotype, the probability of transplant success is similar to that in patients with de novo MDS.

Timing of transplantation

Optimal timing of HCT for MDS has remained controversial. The probability of post-HCTrelapse increases progressively with increased IPSS-R or WPSS scores, the major determining parameters being cytogenetics and myeloblast count. Patients with very high, high and probably intermediate risk by IPSS-R who have HLA-identical sibling donors and are prepared for HCT with HIC regimens are likely to benefit from early HCT, while patients with low or very low risk may have a longer life expectancy if HCT is delayed until evidence of disease progression.

The conditioning regimen

The ideal regimen should be non-toxic and prevent relapse in all patients. The severity of toxicity correlates with conditioning intensity. RIC regimens are associated with minimal toxicity, but carry also a higher risk of relapse than HIC regimens.

A major advantage of RIC is the possibility of applying HCT to older patients, who would not tolerate high dose therapy. Currently, patients more than 60 or 65 years of age and patients of younger age with significant comorbid conditions are typically offered allogeneic HCT using RIC regimens. A higher relapse incidence is counterbalanced by lower non-relapse mortality (NRM). However, a Clinical Trials Network-sponsored phase III trial comparing

toxicity and efficacy of HIC and RIC regimens, has shown higher relapse rates and reduced treatment-related mortality with RIC, and this was associated with an inferior survival probability, although the difference was not statistically significant.

Post-HCT relapse has remained a challenge, particularly in patients with high risk diseaseEncouraging results have been reported recently with regimens including treosulfan, Fludarabine and 2 Gy of TBI, resulting in a probability with high risk cytogenetics that was not different from that observed in patients with low risk disease.

Outlook

With the increasing understanding of the role of somatic DNA mutations, in particular the impact of TP53, RAS, DNMT2A or JAK mutations it will be important to incorporate those findings into the design of new trials. Furthermore, GVHD remains a problem, and novel prophylactic and therapeutic strategies are needed.

Firstline Therapy for Follicular Lymphoma

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Epidemiology

Follicular lymphoma(FL) is the second commonest of all lymphomas after Diffuse Large B-cell Lymphoma and the most common type of "indolent" lymphoma.It constitutes 70% of indolent lymphomas.

The median age at diagnosis is 64 years.

FL is derived from germinal center (GC) B cells. Approximately 85% of patients with FL have t(14;18) which occurs early in B-cell development and results in the overexpression of the BCL-2 protein .Dysregulation of BCL2 expression alone is not sufficient to induce lymphomagenesis, but it provides a survival advantage. FL is histologically classified into grades depending on the number of centroblasts per high-power field(hpf). Grade I with 0 to 5 centroblasts/hpf , Grade II with 6 to 15 centroblasts/hpf, Grade III with more than 15 centroblasts/hpf. Grade III has been subdivided into grade IIIa, in which centrocytes are present, and grade IIIb, in which there are sheets of centroblasts. Most patients are classified as low grade (75% grade 1 to 2), 20% as grade 3a, and only 5% as grade 3b.Patients with FL grades 1 to 3a have OS of approximately 12 years without a plateau.Patients with grade 3b disease behave similarly to DLBCL and has the possibility of cure and 5-year OS of 43%.FL cells are CD19(+), CD20(+), CD10(+), BCL-6(+), CD5(-) and CD23(-).

Prognostic factors

Prognostic scores

The Follicular Lymphoma International Prognostic Index (FLIPI) is based on 5 simple independent risk factors (hemoglobin < 12 g/dL, serum LDH levels above the upper limit of normal, Ann Arbor stage III–IV, more than four nodal sites, age > 60 years). The FLIPI score was developed from retrospective analysis and uses overall survival (OS) as its end point. Patients are divided into three risk groups, low risk (FLIPI 0–1) with 10-year OS of 71%, intermediate risk (FLIPI 2) with 10-year OS of 51% and high risk (FLIPI 3–5) with 10-year OS of 36%.

FLIPI2 prognostic index was developed in a study in which data were collected prospectively and rituximab was used in the treatment of 60% of patients. FLIPI-2, identified age .>60 years, elevated β2-microglobulin, hemoglobin <12 g/dL, bone marrow involvement, and lymph node diameter >6 cm as independent risk factors for progression-free survival. Patients with a FLIPI2 score of 0 are low risk and have a 3-year PFS of 91%, score 1–2 is intermediate risk with a 3-year PFS of 69% and score 3–5 is high risk with a 3-year PFS of 51%.

A recent clinicogenetic risk model that integrates the mutational status of 7 genes (EZH2, ARID1A, MEF2B, EP300, FOX01, CREBBP, and CARD11) with the FLIPI termed m7-FLIPI is established. m7-FLIPI identifies a high-risk group of patients (22% of the cohort) with a 5-year failure-free survival of 25%. The 5-year failure-free survival of the high-risk cohort identified by FLIPI alone was 46%. This indicates the superiority of the m7-FLIPI for identifying a high-risk population.

Response to therapy

A pooled analysis of data from 3 prospective multicenter studies in high-tumor-burden FL revealed that PET-negative status after firstline therapy is predictive of improved PFS and OS.

Although PFS is a standard study end point for first-line FL therapy studies, advances in treatment and the indolent nature of FL makes it diffucult to assess the PFS as median PFS now approaches 6 to 8 years in FL. So the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) investigators performed a meta-analysis of 13 randomized trials of first-line treatment in FL and included more than 3000 patients treated with a variety of regimens. They have found that CR rate at 30 months was able to predict PFS and proposed this as a possible end point for clinical trials in FL.

Early disease progression

Relapse within 2 years of first-line treatment of FL occurs in as many as 20% of patients, independent of maintenance rituximab. Early relapse

after firstline chemoimmunotherapy is an extremely powerful prognostic indicator of outcome in FL and should be used to stratify risk at the time of relapse.

Minimal residual disease

Minimal residual disease detected by polymerase chain reaction amplification of the t(14;18) translocation after first-line therapy is highly sensitive and has prognostic importance.

Tumor microenvironment

Gene expression profiling studies have demonstrated that there are 2 distinct gene signatures that predicts survival: immune-response 1 and immune-response 2. Immune response 1 is associated with favorable outcomes and includes expression of genes enriched from T cells. Immune response 2 is associated with less favorable outcomes and includes expression of genes expressed by macrophages and follicular dendritic cells. These unique gene signatures are based on molecular features from nonneoplastic tumor-infiltrating cells rather than malignant FL cells.

Treatment

Early stage follicular lymphoma

Early-stage FL means stage I and contiguous stage II. Early-stage FL represents 10–20% of all new FL diagnosis. It is important to identify this group because the prognosis, treatment intent and the treatment modalities employed are different from advanced-stage disease.Follicular lymphoma is a radiosensitive lymphoma.There are several studies suggesting that radiotherapy may achieve long-term disease free survival and possibly cure. Involved field radiotherapy 24 Gy in 12 fractions is the preferred treatment with a potentially curative potential. 4 Gy in 2 fractions can merely be palliative. Studies evaluating chemotherapy plus radiation have demonstrated improved PFS without an obvious effect on OS. A study showed that stage I and II patients who received no initial therapy were free of any therapy at a median of 6 years, and 85% of patients were alive at 10 years. So in selected cases, watchful waiting or rituximab monotherapy may be considered to avoid the side-effects of radiation.

Advanced stage follicular lymphoma

The majority of patients have advanced stage disease at diagnosis.The frontline treatment of advanced stage FL depends on several factors: The presence or absence of symptoms, the tumor burden, the patient's age, the comorbidities and the goals of therapy. GELF criteria are commonly used to assess tumor burden. For high-tumor-burden FL, GELF criteria include at least 1 of the following: 3 distinct nodal sites, each ≥3 cm; single nodal site ≥7 cm; symptomatic splenomegaly; organ compression; pleural effusions, ascites; B symptoms or any systemic symptoms; LDH or β2M above the upper limit of normal.

Advanced stage asymptomatic low tumor burden FL

There are several retrospective studies showing no detrimental outcome in patients followed with watch and wait strategy. This 'watch-and-wait' approach was confirmed in a

few prospective randomized studies demonstrating that the application of systemic cytotoxic therapy could be safely delayed until treatment became necessary without any negative impact on patients' outcome. Ardeshna et al conducted a study comparing early use of single-agent rituximab to observation in low-tumor-burden, asymptomatic patients. When compared with observation, rituximab use resulted in an improved time to a new treatment, but no survival benefit could be reported. But this study also revealed that patients having difficulty in adjusting to their diagnosis may experience a quality-of-life benefit from single-agent rituximab.

Advanced stage high tumor burden FL

There are 4 randomized trials showing that the addition of rituximab to conventional chemotherapy improves outcomes in FL, including response rates, PFS, event-free survival, and OS. The optimal chemotherapy backbone to Rituximab has been investigated in several studies. FOLL05 study compared different rituximab containing frontline regimens: R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) vs R-CHOP ((rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) vs R-FM (rituximab, fludarabine, and mitoxantrone) in the up-front setting. Both R-CHOP and R- FM had the same antilymphoma profile and were both superior to R-CVP in terms of TTF and PFS.But R-FM had higher hematological toxicity and was associated with higher number of second malignancies. A phase 3 trial from the Study group indolent Lymphoma (StiL) compared BR (bendamustine-rituximab) to R-CHOP in high-tumor-burden indolent NHL and mantle cell lymphoma.

The overall response rates were similar in the BR vs R-CHOP groups (92.7% vs 91.3%, respectively), but the complete response rate was significantly higher in the BR group (39.8%) compared with the R-CHOP group (30.0%) (p=0,03). When only the FL patients were considered, the median PFS was significantly longer after BR compared with R-CHOP (median PFS, not reached vs 40.9 months, p=0,007). However, OS did not differ between the groups. There was less hematologic toxicity in the BR group .In the SAKK trial , previously untreated or relapsed/refractory FL patients received 4 weekly doses of single agent rituximab and patients with responding or stable disease at week 12 were randomized to no further treatment or prolonged rituximab maintenance every 2 months for 4 doses. Forty-five percent of chemotherapy naive and responding patients receiving prolonged treatment were still alive without disease progression at 8 years. Moreover, 35% of responders to rituximab induction were free of progression after 8 years. So Rıtuximab monotherapy can be a choice depending on the patients age and comorbidities.

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Are we Ready for a Chemofree Approach for Treating Patients with Advanced Follicular Lymphoma?

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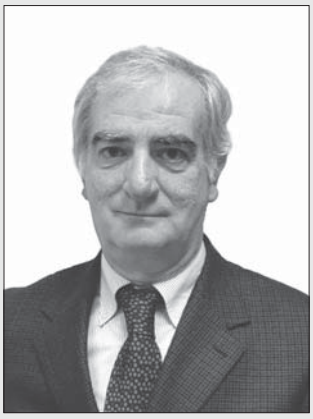
Follicular lymphoma (FL) is the second more frequent type in Western countries and the paradigm of indolent lymphoma. Although FLs characteristically respond well to first-line immunochemotherapy, typically manifest repeated relapses with the need for recurrent therapeutic interventions, and with disease-free intervals becoming progressively shorter. It is well known the toxicity associated to chemotherapy, particularly in patients with advanced age and frequent co-morbidities that need treatment several times. Adverse events chemotherapy-related include early toxicity, infectious complications and secondary malignancies. During the last decade, the knowledge on the deregulated pathways and the immune responses against the tumor in FL has extraordinarily improved. Furthermore, major therapeutic advances have been reached in the development of novel targeted therapies, completely different from standard chemotherapy, that have shown notably efficacy against lymphoma. Thus, for the first time, the possibility of "chemo free" active treatment has become a near-future reality. We will review different "chemo free" approaches in FL, including single monoclonal antibodies (new anti-CD20 and antibodies against other surface antigens), active immunotherapy such as vaccines, immunomodulators agents, alone or in combination, and other targeted therapies, such as inhibitors of key molecules of the B-cell receptor pathway. We will point out pros and cons, particularly regarding new toxicities ("chemo free" does not mean "toxicity free") and anti-tumor efficacy.



Massimo Federico

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Professor Federico is board-certified in hematology and internal medicine, and Professor of Medical Oncology at the University of Modena and Reggio Emilia, Modena, Italy, as well as President of the Angela Serra Association for Cancer Research. In the years 2011-2013 he has been the President of the Fondazione Italiana Linfomi (FIL). From 2013-2016 chaired the Advisory Bard of the Lymphoma Hub a global online platform whose vision is to provide up-to-date, practical, clinical advice to community hem-oncologists, hematologists and oncologists seeking treatment and management options for Lymphoma and CLL (Lymphomahub.com). He is at present president of the AIBE (Associazione Italo Brasiliana di Ematologia).

Professor Federico is Professor of Medical Oncology at the University of Modena and Reggio Emilia, Modena, Italy, and Advisor of the Lymphoma Unit at Modena Cancer Center. Professor Federico has been the president of Gruppo Italiano Studio Linfomi (GISL) and thereafter of Fondazione Italiana Linfomi (FIL) being at present in the Board of Directors. He is curently President of the AIBE (Associazione Italo Brasiliana di Ematologia), and Chairman of the Lymphomahub, a global online platform whose vision is to provide up-to-date, practical, clinical advice to community hem-oncologists, hematologists and oncologists seeking treatment and management options for Lymphoma and CLL.

He is the author or co-author of more than 400 peer-reviewed publications. Professor Federico has designed and conducted several phase II and III clinical trials in different subtypes of Hodgkin and non Hodgkin's lymphoma. Moreover, has widely investigated the role of prognostic factors in different lymphomas, including Hodgkin, Follicular, and Peripheral T Cell Lymphomas.

He is currently leading the T Cell Project and the Aristotle study, a large international project on the risk of transformation in Follicular Lymphoma in the immunotherapy era.

Maintenance Therapy in Follicular Lymphoma: All Fit in One?

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Follicular lymphoma (FL) is one of the most common subtypes of lymphoma in Western countries and accounts for 10-20% of all newly diagnosed non-Hodgkin's lymphomas. The median age at presentation ranges from 55 to 60 years, and the incidence increases with age.

Biologically, the neoplastic clone of the great majority (up to 80%) of FL patients bears the t(14;18) translocation in which the bcl-2 proto-oncogene on chromosome 18 is translocated to the immunoglobulin heavy chain (IgH) region on chromosome 14, thus creating a hybrid bcl-2/IgH gene. The translocation causes an over expression of the bcl-2 protein , which inhibits apoptosis of lymphoid cancer cells. The research of the hybrid bcl-2/IgH gene generated by the translocation could be used for confirming the diagnosis of FL, but for evaluating the quality of response to treatment as well. Despite enhancement in treatment for this disease, leading to substantial improvements in survival, FL is often managed as an incurable disease. However, over time a substantial and growing fraction of patients are achieving long-term disease-free survival from appropriate treatment approaches. The advent of the anti CD20 monoclonal antibody Rituximab (R) has dramatically changed the approach to this disease, and R with chemotherapy is at present considered the standard of care for patients diagnosed with FL. Estimates of median survival for patients with FL who receive R as part of their initial therapy, and respond to it, are approaching 15-20 years. Twenty-five years ago the median survival of patients with FL was 5 to 10 years. This means that a significant proportion of people with FL are not likely to die from the lymphoma.

The use of maintenance strategies after the first treatment in FL has been considered over a long time. The use of interferon was first evaluated, showing benefits in terms of duration of remission and survival; however the safety profile of the drug and the low manageability of treatment has led most physicians to abandon this treatment option. The availability of R as an effective and low toxic single agent has suggested to explore the possibility to use it not only to improve efficacy of chemotherapy in first line therapy, but also to delay progression after initial treatment. At the beginning, maintenance with R has been mostly considered after relapse, or in case of refractoriness to treatment. More recently, the results of the PRIMA trial provide robust data on the use of maintenance after first line therapy. The study included 1217 patients with previously untreated follicular lymphoma requiring systemic therapy. Patients received initial therapy on a non-randomized basis, by choosing among one of three chemoimmunotherapy induction regimens used in routine practice: R-CHOP, R-CVP and R-FCM, that were adopted in 74%, 22% and 4% respectively. After induction therapy 1019 patients achieving a complete or partial response were randomly assigned to receive 2 years of R maintenance therapy (375 mg/m2 every two months) or observation. The primary endpoint was progression-free survival (PFS). With a median follow-up of 36 months, PFS was 74.9% in the R maintenance group and 57.6% in the observation group (218 progressed; hazard ratio [HR] 0.55, 95% CI 0.44–0.68, p<0•0001). The results of a meta-analysis including nine trials and 2586 FL patients receiving rituximab maintenance showed both an improved overall and progression free survival if compared with those who were not administered maintenance (pooled HR of death = 0.72, 95% CI = 0.57-0.91). PRIMA trial clearly showed that rituximab maintenance in patients achieving a response to initial chemoimmunotherapy results in an improved outcome in terms of prolonged PFS and made a step forward in the management of patients with FL.

One important question that can be raised is if this approach is really needed for all patients with FL or if some of them could benefit from a risk adapted maintenance strategy, intensifying treatment in those recognized at higher risk of recurrence. Both PET/CT and MRD analyses have demonstrated a promising role in this context, being patients resulting PET or MRD negative at the end of induction therapy at lower risk of recurrence.

Actually, as we were convinced that the same maintenance therapy didn't fit in all patients, as

Fondazione Italina Linfomi (FIL), we launched a national based large phase III trial (ClinicalTrials.gov Identifier: NCT02063685) testing whether a FDG-PET and MRD response-based maintenance therapy could permit to single out groups of patients at different risk of progression and to consequently modulate maintenance therapy. In our experimental approach patients at low risk defined by post induction PET and MDR negativity, are only observed: among them 4 weekly doses of R are prescribed in case of MDR positivity. Patients at high risk (PET post induction positive), receive intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by R maintenance therapy for 2 years.

So far, more than 700 patients have been enrolled in four years, with the study enrollement likely to be completed within the end of this year, when 770 evaluable patients will be accrued. We hope the study will be positive, thus offering the opportunity to better tailor maintenance therapy in patients responding to first line chemoimmunotherapy.

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WHO 2016 Diagnostic Criteria of CML; What is Old, What is New?

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that is characterized by the Philadelphia (Ph) chromosome and driven by its product, the BCR-ABL1 tyrosine kinase [1].

The 2016 revision of the WHO Classification of Tumours of the Hematopoietic and Lymphoid Tissues1 was recently previewed in two articles published in Blood almost a year ago.

The classification now shows more abundant evidence of the impact of genetic markers on diagnosis and disease management [2].

Most cases of CML in chronic phase can be diagnosed from peripheral blood (PB) findings combined with detection of t (9; 22)(q34.1;q11.2) or, more specifically,BCR-ABL1 by molecular genetic techniques. However, a bone marrow (BM) aspirateis essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease [3, 4].

In the era of tyrosine-kinase inhibitor (TKI) therapy, newly diagnosed patients may have a nearly normal lifespan, but regular monitoring for BCR-ABL1 burden and for evidence of genetic evolution and development of resistance to TKI therapy is essential to detect disease progression [5, 6].

The criteria for AP in the revised WHO classification include hematologic, morphologic, and cytogenetic parameters which are supplemented by additional parameters usually attributed to genetic evolution, [7] and manifested by evidence of resistance to TKIs. These latter "response to TKI therapy" criteria for AP are considered as "provisional" until further supported by additional data.

Diagnosis of blast phase (BP) still requires either at least 20% blasts in the blood or BM or the presence of an extra-medullary accumulation of blasts. However, because the onset of lymphoid BP may be quite sudden, the detection of any bona fide lymphoblasts in the blood or marrow should raise concern for a possible impending lymphoid BP, and prompt additional laboratory and genetic studies to exclude this possibility [8].

For those patients with BCR-ABL1-negative myeloid leukemia characterized by high levels of neutrophils or neutrophil precursors, our understandings of the molecular basis of the disease and treatment strategies have lagged far behind. One such BCR-ABL1-negative myeloid leukemia is chronic neutrophilic leukemia (CNL), a rare disease entity that was officially recognized as part of the World Health Organization (WHO) classification of tumors in 2001 [9].

Chronic neutrophilic leukemia (CNL) now includes specific mention of CSF3R T618I or other activating CSF3R mutation as a major diagnostic criterion. Diagnosis is still permitted in the absence of this mutation if neutrophilia is present for three months with no identifiable cause or if another clonal finding is identified [2].

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Current Clinical Management of Chronic Myeloid Leukemia

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1. Introduction

Chronic myeloid leukemia (CML) is a slowly progressive clonal malignant disease characterized by myeloid neoplastic expansion with heterogeneous clinical manifestations. CML could be functionally cured by the tyrosine kinase inhibitor (TKI) drugs.[1] Standardized therapeutic approach may be useful in the *de novo* or TKI-responsive patient with CML since TKIs could successfully modulate the disease course.[2] However, treatment schedule should be personalized in the CML patient with progressive disease despite the administrations of more than one TKI (multi-TKI).[1] Disease progression under TKI is a 'difficult-to-treat' situation with the available drugs in CML.[3]

The aim of this paper is to outline the perspectives for the drug therapy choices in the CML patient with progressive disease course of CML in the current TKI era.

2. CML disease status and challenges after multi-TKI failure

Clinical key decision making for the choice of TKI drug depends upon the best available evidence obtained from randomized clinical trials (RCT), physician experience, and particularly individual characteristics of the patient and his/her disease. The integrative approach among the drug (efficacy, safety, tolerability, toxicity, and pharmacoeconomy of the TKI), the patient (CML disease risk, age, co-morbidities, molecular BCR-ABL dynamics, compliance, life style, adherence, drug off-target risk profile), and the status of physician/clinics (TKI availability, TKI reimbursability, drug/ disease experience of physician, CML monitoring techniques, the cooperation between CML specialized centre and the home physicians) is the 'real-World' management of CML.[1] Most of those critical parameters are negatively affected in the 'handicapped' CML patient with progressive disease course after sequential multi-TKI regimen.

Disease duration is important in the pathobiology of CML. Time is matter in CML. As a function of time, Ph*(+) neoplastic hematopoiesis dominates normal blood cell production. Meanwhile; self-renewal of leukemic CML stem cells, genomic instability, impaired DNA repair mechanisms, proliferation/ anti-apoptosis of Ph*(+) neoplastic progenitors, clonal selection, and the acquisition of additional mutagenic events complicate the biology of CML as well as the clinical manifestations. Moreover, TKI-induced, increased oxidative stress and altered mutational phenotype further complete the disease course. Terminal stage of this malignant neoplastic development is the accelerated phase (AP)/ blastic crisis (BC) of CML. Progressed late chronic phase (CP) uncontrolled under TKI is also a very risky situation prone to AP/BC CML. The terrible end of CML makes 'prevention of disease progression' is the ultimate aim of TKI treatment. Thus, early and rapid reduction of BCR-ABL with acceptable TKI control is a major goal of CML therapy. However, that goal had already failed in the CML patient with progressive disease after the intake of sequential multi-TKI regimens.[2]

3. How to proceed to manage CML disease after multi-TKI failure?

European LeukemiaNet (ELN) recommendations indicated the way of management in the *de novo* or TKI-responsive CML patient based on the data obtained from numerous RCTs.[2] However, the level of research solid evidence is low (at most Phase II trial data) for the decision making about the choice of drugs in the CML patient resistant to previous multi-TKI drugs. Official ELN recommendation for third-line CML treatment (failure of and/or intolerance to 2 TKIs) in CP-phase is "*..Anyone of the remaining TKIs; allogeneic hematopoietic stem cell transplantation (alloSCT) recommended in all eligible patients (HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT)*" quite similar to the suggestions in the AP/BC phase-CML "*..Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible for alloSCT*" .[2]

Several clinical scenarios (and drug suggestions accordingly) can be generated to describe the 'third-line CML' from the ELN recommendations;

- The CML patient with failure of imatinib and dasatinib (candidate for nilotinib, bosutinib, ponatinib; then alloSCT)
- The CML patient with failure of imatinib and nilotinib (candidate for dasatinib, bosutinib, ponatinib; then alloSCT)
- The CML patient with failure of nilotinib and dasatinib (candidate for bosutinib, ponatinib; then alloSCT)

Table 1. Strengths and limitations of the drugs for the 'third-line' management of chronic myeloid leukemia (CML)

Drug	Pharmacobiology	Patient population	Efficacy data	Safety, tolerability, toxicity	Clinical challenges
Ponatinib	Pan-BCR-ABL kinase inhibitor	• Multi-TKI (imatinib, nilotinib, dasatinib) resistant CML patient • T315I mutation • AP/BC-CML	Major cytogenetic response (MCyR) within the first 12 months in over half of patients with CP- CML and major hematological responses within the first 6 months in at least 50 % of adults with AP- CML and 34 % of patients with BC-CML or Ph*+ ALL after a median follow-up duration of 15, 16 and 6 months, respectively.[7]	The analyses about the 24 months follow up safety data of the PACE trial disclosed non-serious and serious arterial and venous adverse events combined occurred in about 20% of ponatinib-treated patients (Cardiovascular events 6.2%; Cerebrovascular events 4.0%; Peripheral vascular events 3.6%; venous occlusion 2.9%)[8]	• Problems of availability and reimbursability[9] • Cost[9] • Thrombotic cardiovascular and cerebrovascular adverse effects[8]
Bosutinib	3rd generation dual SRC/ ABL TKI	Multi-TKI (imatinib, nilotinib, dasatinib) resistant CML patient	MCyR was attained by 32% of patients; CCyR was attained by 24%, including in one of 3 patients treated with 3 prior TKIs. CHR was achieved/ maintained in 73% of patients.[10]	Gastrointestinal adverse effects (diarrhea [86%], nausea [46%], vomiting [37%]). Grade 3/4 myelosuppression [41%]. Alanine aminotransferase elevation [17%][11]	• Problems of availability and reimbursability[9] • Cost[9] • Gastrointestinal co-morbidity[2,3]
Omacetaxine mepussecinate	Induction of apoptosis, non-TKI antiproliferative effect	• Multi-TKI (imatinib, nilotinib, dasatinib) resistant CML patient • T315I mutation	Forty-six patients were enrolled: all had received imatinib, 83% had received dasatinib, and 57% nilotinib. A median 4.5 cycles of omacetaxine were administered (range, 1–36). CHR was achieved or maintained in 31 patients (67%); median response duration was 7.0 months. Ten patients (22%) achieved MCyR, including 2 (4%) CCyR. Median progression-free survival was 7.0 months [95% confidence interval (CI), 5.9–8.9 months], and overall survival was 30.1 months.[12]	Grade 3/4 hematologic toxicity included thrombocytopenia (54%), neutropenia (48%), and anemia (33%). Nonhematologic adverse events were predominantly grade 1/2 and included diarrhea (44%), nausea (30%), fatigue (24%), pyrexia (20%), headache (20%), and asthenia (20%).[12]	• Problems of availability and reimbursability[9] • Cost[9]
Nilotinib	2nd generation BCR-ABL inhibitor	'Remaining TKI' after the failure of imatinib and dasatinib	CHR and MCyR rates in CP were 79% and 43%, respectively. Of 17 evaluable patients with CML-AP, 5 (29%) had a confirmed hematological response and 2 (12%) a MCyR. At 18 months 59% of patients were progression-free.[13]	Rash (28% CP, 19% AP), nausea (15% CP, 10% AP), pruritus (15% CP, 10% AP), headache (13% CP, 5% AP) and fatigue (10% CP, 10% AP). neutropenia (23% CP, 33% AP) thrombocytopenia (28% CP, 19% AP). hyperphosphatemia (13% CP, 24% AP), elevated total bilirubin levels (8% CP, 14% AP), elevated lipase levels (25% CP, 10% AP), hypokalemia (5% CP, 10% AP), hyperglycemia (13% CP, 5% AP), hypermagnesemia (11% CP, 11% AP) [13]	• Cost[9] • Pancreatic and metabolic co-morbidity[2,3]
Dasatinib	2nd generation BCR-ABL and SRC inhibitor	'Remaining TKI' after the failure of imatinib and nilotinib	Among the 14 patients treated with dasatinib as second-line treatment, 8 patients were in CP (57%), 3 in AP (21%), and 3 in BP (21%). The best response to dasatinib included 2 CCyR (14%), 1 PCyR (7%), 5 mCyR (36%), 4 CHR (29%), and 2 NR (14%).[14]	7 patients (21%) discontinued treatment because of toxicity despite an acceptable response, including 2 patients who discontinued because of pleural effusion, and 1 each for gastrointestinal bleeding, neutropenia, renal failure, atrial fibrillation, and myalgias.[14]	• Cost9 • Lung co-morbidity2,3

- The CML patient with failure of nilotinib and bosutinib (candidate for dasatinib, ponatinib; then alloSCT)
- The CML patient with failure of dasatinib and bosutinib (candidate for nilotinib, ponatinib; then alloSCT)

The timing of alloSCT has changed to third- or fourth-line CML after failure of the second-generation TKIs.[2,4] The definition of transplant eligibility is never absolute since it is based on the balance between the disease risk of CML and the mortality/ morbidity risk of alloSCT.[3]

Mutational analyses shall be performed in all of the CML cases with multi-TKI failure during the drug treatment decision. BCR-ABL1 kinase domain point mutations are detectable in about 50% of patients with treatment failure and progression. The mutations detected during the TKI therapy may be resulted in drug switches based on the nature of the mutation. Dasatinib and nilotinib retain activity against most of the mutations that confer resistance to imatinib. Likewise, distinct mutations exhibit decreased sensitivity to dasatinib versus nilotinib.[5] T315I, Y253K, E255K, E255V, F359V, F359C, are the mutations poorly sensitive to nilotinib; whereas T315I, T315A, F317L, F317C, V299L are the mutations poorly sensitive to dasatinib. T315I is a unique mutation making the CML patient irresponsive to all available TKIs but ponatinib, non-TKI drug omacetaxine mepussecinate and allografting.[2,6]

4. Difficulties in the treatment of CML after multi-TKI failure

The most challenging situations in the patients CML are failure to all available TKIs and cannot be transplanted, or relapsing after allografting particularly to the advanced phases. Those patients need effective and safer treatment options. Therefore, patient-centered clinical decision is absolutely necessary in this difficult situation. [3] Table 1 summarizes the current status of 'third-line management of CML' with the available drugs.

5. Perspectives for the treatment of progressing CML disease after multi-TKI failure

Current standard practice is allografting for all of the CML cases with multi-TKI failure based on the availability of the donor and EBMT transplant risk scores. Before the alloSCT procedure, all of those patients should be treated with the best available 'remaining' TKI in order to reach best promising response/ remission land (complete hematological response (CHR), complete cytogenetic response (CCyR), stable molecular response (MR)). The drugs of bosutinib, ponatinib, dasatinib, nilotinib, and omacetaxine mepussecinate shall be used for this aim. During the CP-CML phase of multi-TKI failure, 2nd generation TKIs (nilotinib or dasatinib) are used if they remained. Bosutinib and ponatinib (3rd generation TKIs) can be administered in triple-TKI failed (Imatinib and nilotinib and dasatinib) patients. The presence of T315I mutation at any phase requires ponatinib or omacetaxine mepussecinate therapy before allografting. Combinations of TKI and interferon (IFN) or PEG-IFN are used in the everyday clinical practice for the unresponsive cases to TKI alone but limited data is available for the combination approach. During the AP/BC -CML phase of multi-TKI failure, the most powerful TKI available (ponatinib or dasatinib if remained) together with multi-agent chemotherapy should be given before alloSCT. The clinical picture is darker for the transplant-ineligible CML patients with multi-TKI failure or post-transplant relapsed patients. TKI (bosutinib, ponatinib, dasatinib, nilotinib) and non-TKI (omacetaxine mepussecinate, IFN or PEG-IFN; including their combinations with TKI) drugs should be used based on the same principles in those 'handicapped' CML patients as summarized above. Monitoring of CML disease and drug off-target risks (particularly vascular thrombotic events) are vital. Expected hematological, cytogenetic, and molecular responses to those drugs during the monitoring of CML are variable based on the disease phase, mutational status, resistance profile, age, co-morbidities, molecular BCR-ABL dynamics, compliance, life style, adherence, and drug off-target risk profile.

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Level in national or international classification	1980: Level 5A and 5B (ISCED 1997) 2000: Level 6 (ISCED 1997)
Personal skills and competences	
Mother tongue(s)	Macedonian
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Self-assessment		Understanding		Speaking		Writing				
European level (*)		Listening		Reading		Spoken interaction			Spoken production	
English Language	C2	Proficient user	C2	Proficient user	C2	Proficient user	C2	Proficient user	C2	Proficient user
German Language	A2	Basic user	A2	Basic user	A2	Basic user	A2	Basic user	A1	Basic user
(*) Common European Framework of Reference for Languages										

Social skills and competences	good communication skills on a collegiate level, on a doctor-patient level, as well as on a teacher-student level, acquired through practice and necessary for everyday work adaptable to various surroundings and different social and cultural environments, shown by living in foreign countries (USA, Japan) for longer periods, and through frequent travels abroad
Organisational skills and competences	manifested solid level of organizational and managerial capacity, reflected through several head positions at the Clinic, including director President of the Organizing Committee of the 1st Congress of the Macedonian Hematology Association and the 7th Balkan Day of Hematology, Skopje, Macedonia, Oct 4-7 2012 organizing meetings of the MHA on a regular quarterly basis during 2011-2015 mandate appointed and elected to positions relevant for organization of education co-investigator in international projects
Technical skills and competences	not professional, but still developed to a fairly high level, utilized on a daily level
Computer skills and competences	continuously utilizing PC for everyday work, as well as at home, for more than 20 years, using all components of Microsoft Office and Internet Explorer on a daily basis, Adobe, Corel, Statistica and other programs on a "need to" basis, all for professional as well as for personal needs
Artistic skills and competences	Attended music school for 6 years, during elementary and high school education, acquiring both theoretical knowledge and playing the piano
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Annexes	Publication list attached separately (if requested)

Prognostic Factors in Newly Diagnosed CLL

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Humanity can take pride in the speed with which inventions, discoveries and developments occur in the contemporary era. What took decades in the past, now takes hours, or even minutes. In the same manner in which progress is visible in technology, informatics and other fields, advances can be clearly made apparent in medicine as well.

Defining a disease has been brought down to details, and all the technical developments, together with the immense knowledge in our hands, serve as an infinite potential in order to better characterize distinct medical conditions.

Nevertheless, in spite of the precision in characterization of an entity, in spite of the explained mechanisms regarding the initiation and nature of a disease, and in spite of being able to define those characteristics down to the level of a single molecule, even the members of the medical community remain often dazzled by how the same problem can have so many different faces. In two different patients the same disorder can have a significantly different beginning and appearance, a very diverse evolution, as well an absolutely ambiguous outcome, even when it is treated in the same manner.

Therefore, we still employ a whole lot of efforts in meticulous characterization of a disorder, in order to define common grounds and points of variation. The result should be better understanding and defining procedures and methods for controlling, containing and ultimately eliminating the disease.

In that process we look for characteristics that could direct us towards choosing the optimal course of action, which in view of prior relevant evidence, supports our preference and allows us to foresee the most favorable outcome for that particular patient. Such long-term experience and the derived evidence, in conjunction with elaborate repeated analyses, form the basis for construction of prognostic scores and systems.

The prerequisite for a justifiable system is the identification, and subsequent validation of individual prognostic factors. Two terms are used. The term *prognostic* would relate mostly to life expectancy, while the term *predictive* would anticipate a potential harmful evolution of a disease. The sole purpose of defining these factors is to make responsible and proper management decisions, interfere with the grave and life threatening course of the disease, counteract effectively and secure a gratifying future for the patient. All of these tasks are rendered even more difficult when there is a malignant disease at stake, one of them being chronic lymphocytic leukemia.

Although depicted as not very aggressive, it still remains a hematological disease where complete remission is the least frequently used definition for outcome. Progress in technology enabled us to understand that below the surface of a single disease lies astonishing diversity and variations, making definition of common grounds in CLL a very demanding and challenging task.

Risk factors could imply aggressive disease manifestations, rapid evolution, need for urgent treatment, poor response to therapy, possibility of relapse, low life expectancy and other aspects in a patient.

Risk factors could be classified in three areas: a) patient characteristics, in general, at the time of disease onset and personal history, b) disease characteristics in terms of both quantity and quality, on several levels, i.e. physical appearance on examination and using visualization techniques, biochemistry, biology, genetics, molecular level, genomics, proteomics, etc., and c) availability of various treatment options, in particular regarding targeted therapy.

Patient characteristics should be assessed in detail, with regard to performance status, comorbidities, medical history, etc. In this segment, quite a few moments have been defined as significant prognostic factors, reflecting the probability of an indolent disease course, possible evolution, treatment intolerance or compromise, achieving a response, its duration and stability, as well as life expectancy in general. Patients age and gender, performance

status and comorbidities have been confirmed to significantly impact treatment possibilities and consequently prognosis in patients with CLL.

The field of disease manifestations is the one with the largest number of factors affecting outcome, as well as the arena for immense research and investigations, directed towards defining the disease risk factors. It is not a surprise that technology has enabled us to go into depth with these characterizations. Also, the variations in disease biology and manifestations are responsible for creating so many different factors, shown to significantly affect the course of disease. A plethora of risk factors have been identified, some reflecting the disease biology, others delineating important biochemical characteristics, both as a possible tumor product, or as a host response consequence. Medicine in the past decades has intensely been driven towards connecting and explaining diseases through genetics, and CLL does not represent an exception in this sense. The genetic prognostic factors are confirmed to influence the necessity and choice of treatment, as well as survival expectations. Furthermore, genetic risk factors are continuously being defined on a deeper, molecular level, and progress in genomics and proteomics are contributing towards very precise definitions for the roots of the instabilities, encompassing deletions, translocations, mutations, polymorphisms, etc. in astonishing quantities.

There is probably no larger field for evaluating treatment options, than it is the case with CLL. Although the oldest treatment approach is still not completely abandoned, research in cellular immunophenotyping, signaling pathways, specific tumor targets, etc., has led to discoveries and developments in the pharmaceutical industry, designed at targeting this entity, measured in two, and maybe soon in three digit quantities. For some, the mode of action is very general, but many new agents, mostly small molecules, bear the attribute of specific interactions and targeted approach. The available treatments are not going to be elaborated in this presentation, since they are portrayed and discusses by designated experts. Treatment options cannot be eliminated form prognostic systems. When a multitude of agents is available, and shown to have effect on the disease, it is clearly understood that a particular treatment option can overcome the prognostic significance of a given risk factor, and thus render it obsolete. When one or two options are available for treating a disease, risk factors may not be affected, but when we have a choice of treatments, evidently being capable of targeting a certain mutation, or a biological product, or a small molecule, or signaling pathway, effective therapy becomes a significant favorable prognostic factor. Contrary to this, some "old" prognostic factors cannot retain their validity across the variety of treatment classes. Others cannot obtain the general, or system significance character, since they have not been evaluated against the older treatment options, or manifest importance only in subgroups, or selected groups of patients.

Risk factors can be attributed with individual significance. Nevertheless, such can rarely remain with prognostic significance across all variants of the disease, among all age subgroups, among both genders, and disregarding different disease characteristics. Therefore, there is a strong tendency to validate the risk factors, identifying them as affecting the prognosis in all, or eventually in most of the patients, and in a multivariate environment, attributing such factors as steady influence over a variety of possible manifestations or evolutions. Such essential risk factors can then be incorporated in a prognostic system, scale, or score, which, in return enables both retrospective, as well as prospective analysis of patient populations.

Prognostic models in CLL have the setback of continuously being revised, upgraded, changed, and probably improved, and therefore making it difficult for them to remain "in power" for longer periods of time. This is mainly due to the fact that in the ocean of available treatment options, it is almost impossible to design, evaluate and validate trial results within a critical patient population size, especially with comparable characteristics, regarding both patients and disease. Also, progress has introduced new methods for identification of risk factors, but diversity in methodology results in different cutoff points for some risk factors, depriving them of general validity.

Although maybe not the most frightening hematological disorder, CLL continues to attract research interest, innovation in treatment and professional clinical interest, engaging knowledge, skills, potential and expertise with the aim of successfully controlling and managing this disease. Identifying factors that convey favorable or poor prognosis will certainly and significantly contribute towards eventually stamping this lymphoproliferation as another successful story in hematological oncology in the very near future.

Ioannis Kotsianidis

Current position: Professor of Hematology, Head of the Hematology department of the University Hospital of Alexandroupolis. Dragana, Alexandroupolis, 68100, Greece. E-mail: ikotsian@med.duth.gr

Education: Ioannis Kotsianidis obtained his medical degree at the Aristotelian University of Thessaloniki in 1993 and his PhD degree in Hematology at Democritus University of Thrace in 2003. From 2003 to 2005 he has worked as a clinical research fellow at the Hammersmith Hospital, Imperial College London.

Employment: Prof. I. Kotsianidis has longstanding clinical and scientific experience in Hematology and Immunology. More specifically:

2003-2005, Clinical Research Fellow, Department of Hematology, Faculty of Medicine –ICSTM, Hammersmith Hospital, London UK; **2005-2009**, Lecturer of Hematology, Democritus University of Thrace, Alexandroupolis, Greece; **2009-2013**, Assistant Professor of Hematology Democritus University of Thrace, Alexandroupolis, Greece; **2013-2016,** Associate Professor of Hematology Democritus University of Thrace, Alexandroupolis, Greece; **Since 2016** Professor of Hematology Democritus University of Thrace, Alexandroupolis, Greece; Head of the Hematology department, University Hospital of Alexandroupolis., Alexandroupolis, Greece.

Publications: Prof. I. Kotsianidis has published **61** original papers. His work, has a total impact factor **>230**, received **>730** citations and is published in some of the top scientific journals in the field of Hematology, Pneumonology and Immunology. His most important scientific contributions have been described in the following publications: ***Nature* 2006;** 12(7):846-51 (Identification of the mutation responsible for inherited PNH); ***Blood* 2006;** 107(8):3138-44. (Regulation of normal hematopoiesis by invariant NKT cells); ***Leukemia* 2009**; 23(3):510-8 (The role of Tregs in the pathobiology of Myelodysplastic syndromes); ***Blood* 2009;** 113(11):2498-507 (The role of CD1d antigen in multiple myeloma); ***Am J Respir Crit Care Med* 2009;** 179(12):1121-30. (Treg dynamics and function in Idiopathic pulmonary fibrosis); ***Clin Cancer Res 2016*** 22(8):1958-68 (The Stat3/5 Signaling Biosignature in Myelodysplastic syndrome patients treated with hypometylationg agents);

Funding: Prof. I. Kotsianidis has secured numerous grants during his carrier abroad and in Greece that were sufficient to support all his research activities for the last 13 years. Many of these grants involved collaboration between many partners, whereas he was also principal investigator in several clinical trials.

Relapse/Refractory CLL Treatment

Ioannis Kotsianidis

Democritus University of Thrace Head of the Hematology Department University Hospital of Alexandroupolis, Alexandroupolis, Greece

Despite the established effectiveness of chemoimmunotherapy (CIT), purine analogue-refractory chronic lymphocytic leukemia (CLL) remains a challenging clinical problem associated with poor overall survival (OS). Moreover with the increasing range of therapeutic options, the exact definition of refractoriness is becoming important in the therapeutic context. It is now clear that no response or response lasting ≤ 6-12 months from last CIT, confers a particularly poor outcome; however, patients who relapse within 12-24 months after the last CIT have also reduced survival, whereas even patients with longer remissions of up to several years after CIT might have poor subsequent treatment response and survival. Several novel targeted therapeutics are now available and will be discussed herein.

The B cell receptor (BCR) pathway is critical in the survival, proliferation, chemokine-controlled migration and homing of chronic lymphocytic leukemia (CLL) cells. In line with the efficacy shown in preclinical murine models, orally bioavailable inhibitors of Bruton's tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3Kδ) induced high rates of responses in early trials and are now used in both the frontline and relapsed/refractory settings. Ibrutinib, an irreversible BTK inhibitor and idelalisib, a selective PI3Kδ inhibitor, are highly active in chemoresistant, high-risk patients, particular those with TP53 aberrations and have both been approved for such patients. Responses are typically partial and treatment should continue until disease progression or intolerable toxicity. Both agents induce a characteristic transient lymphocytosis accompanied by rapid resolution of lymphadenopathy. However, apart from the toxicity issues particularly with idelalisib, relapse demonstrating either as CLL progression or Richter's transformation is inevitable in all patients receiving TKIs. Failure of TKIs confers a grave prognosis, whereas patients who discontinue TKIs due to intolerance have a much better outcome. The role of CIT after TKI failure is very limited, whereas alternating the available TKIs and using second generation BCR inhibitors which may spare the off target effects of ibrutinib may achieve satisfactory response rates. Nevertheless, the highest efficacy in TKI relapsed/refractory patients has been shown with the bcl-2 selective inhibitor venetoclax which has recently granted approval in Europe. As regards Richter's transformation, the combination of the PD-1 inhibitor nivolumab with ibrutinib has shown promising activity in a phase II trial.

In conclusion, the therapeutic armamentarium for relapsed/refractory CLL has been expanded significantly and the treatment landscape has been radically transformed. However, since monotherapy of each one of the novel drugs is restricted by the inevitable relapse and subsequent dismal prognosis, numerous questions remain regarding the proper sequencing and combinations of these agents, whereas the extreme cost of new treatments raises concerns about potential financial toxicity to patients and health systems.

Anna Sureda

Anna Sureda, (MD, PhD) 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. In January/1991 she started 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. In January 2011, Anna Sureda moved to Cambridge University Hospital in Cambridge, UK, Addenbrookes Hospital, where she was appointed Senior Consultant in Lymphomas and Stem Cell Transplantation. In January 2013, she moved back to Barcelona where she was appointed Head of the Haematology Department of Institut Català d'Oncologia – Hospital Duran I Reynals in June 2015. She was a Visiting Physician at the University of Heidelberg, Germany in 1990 for four months and at the Fred Hutchinson Cancer Research Center of Seattle in 1993 for another period of four months.

Anna 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 achieved her PhD with the work entitled "Autologous Stem Cell Transplantation in Patients with Hodgkin's Lymphoma" in June/2008. Dr. Sureda has been an active member of the Spanish Cooperative Group of Lymphomas and Haematopoietic Stem Cell Transplantation (GELTAMO) since 1993 and during her stay in UK she was elected active member of the NCRN Lymphoma Study Group. In April/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. After stepping down as chairperson of the Lymphoma Working Party Anna Sureda was elected Secretary of the EBMT, her current position in this organization until April 2016.

Anna Sureda is a regular reviewer for the journals *Blood*, *Annals of Oncology, Bone Marrow Transplantation*, *The Hematology Journal*, *The European Journal of Hematology* and *Annals of Hematology* and has been co-authored more than 250 peer-reviewed journal articles.

Allogeneic Stem Cell Transplantation in Patients with Diffuse Large B Cell Lymphoma

Anna Sureda

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Treatment of patients with aggressive B-cell non-Hodgkin's lymphoma who relapse or who are refractory after first-line immunochemotherapy is difficult. Although autologous stem-cell transplantation is deemed to be the standard of care for these patients according to the PARMA trial,1 the CORAL trial 2 showed that even this approach often has a poor outcome, with treatment failure in more than 80% of patients. How best to achieve remission and consolidate treatment with stem-cell transplantation is still unclear, as is how patients should be conditioned before transplantation. Allogeneic stem-cell transplantation is underused for treatment of aggressive lymphomas; in the past, allogeneic stem-cell transplantation has been associated with very high non-relapse mortality,3 mainly because of the highly toxic myeloablative treatments used and patients' clinical characteristics. The introduction of reduced-intensity conditioning in the mid-1990s renewed interest in allogeneic stem-cell transplantation for lymphomas. These regimens significantly reduce non-relapse mortality, enabling the patient to benefit from the graft-versus lymphoma effect. Several retrospective analyses 4-6 have shown that reduced-intensity conditioning and allogeneic stem cell transplantation can produce long-term disease control in a highly refractory and heavily pretreated population of patients. Nevertheless, relapse is the major cause of treatment failure; donor lymphocytes cannot mount a graft-versus-lymphoma reaction quickly enough to prevent disease progression when a refractory patient only receives a minimum amount of chemotherapy. A retrospective analysis6 by the European Group for Blood and Marrow Transplantation shows that patients who receive reduced-intensity conditioning and transplantation have a higher relapse rate—but lower non-relapse mortality—than do those who receive a myeloblative conditioning regimen. Relapse is more common with reduced intensity protocols than with myeloablative ones for most cancers, although some exceptions exist (eg, chronic leukemia, follicular lymphomas). As a result, reduced-intensity conditioning should be reserved for elderly patients with co morbidities who are candidates for an allogeneic stem-cell transplantation but who might be expected to have too high a risk of non-relapse mortality with conventional conditioning protocols. More intense conditioning regimens like the one used by Glass and coworkers7 probably reduce the chance of relapse for patients with relapsing and refractory disease through improved disease control shortly after transplantation. Even though 23 (55%) of 42 patients in each group were refractory to chemotherapy, at 1 year progression-free survival was 45% (95% CI 34–55) and overall survival was 52% (95% CI 41–62). As expected, refractory disease was an independent adverse prognostic factor for progression-free survival: patients with refractory disease showed a trend to poorer overall survival at 3 years than did those with sensitive or untested response but not significantly so (38.3% vs 45.8%; p=0.134), which shows further efforts should be made to tackle the problem. In conclusion, allogeneic stem cell transplantation can be considered an adequate treatment option for patients with adverse-prognosis aggressive B-cell non-Hodgkin's lymphoma, the major challenge of this procedure still being the capacity of conventional salvage chemotherapy protocols to achieve a chemosensitive disease status before the transplantation procedure. Novel approaches should be sought to overcome this problem.

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Norbert Schmitz

Degrees

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

Positions

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

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)

Other Important Functions

1989 -	Regular reviewer for the Journal of Clinical Oncology, BLOOD, Lancet, Annals of Hematology, Haematologica, Annals of Oncology, member of the editorial board of the Journal of Clinical Oncology
1992	Co-ordinator of studies for patients with relapsed Hodgkin's disease in Germany and Europe.
2002 -	Co-Chair of the German High-Grade Non-Hodgkin-Lymphoma Study Group (DSHNHL)
1992 - 1998	Secretary of the European Group for Blood and Marrow Transplantation (EBMT)
1998 - 2004	Chairman of the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT)
2005 -	Chairman of the T-cell lymphoma subcommittee of the WP Lymphoma
2006	President of the Annual Meeting of the European Group for Blood and Marrow Transplantation
2014	President of the Annual Meeting of the German, Austrian and Swiss Societies of Hematology and Oncology

Scientific Publications

More than 400 articles in national and international journals, 420 abstracts, 50 book chapters

6th International Congress on Leukemia – Lymphoma – Myeloma

May 11 – 13, 2017 • Antalya, Turkey

ABSTRACTS

Dear Colleagues,

It is great pleasure for me to welcome you to the 6th International Congress on Leukemia, Lymphoma, Myeloma.

Scientific level of ICLLM congresses has been improving progressively year by year. I believe that this conference will represent the challenge the development of the basic studies as well as clinical researches of Hematology.

The abstracts and the educational lectures have been designated to establish an area suitable for the exchange of ideas during the meeting days. There are 92 abstracts this year. The full text content of the educational books of the meetings of International Congress on Leukemia Lymphoma Myeloma (ICLLM), will be available in the website of Turkish Society of Hematology (www.thd.org.tr) just after the end of the conference.

Besides our extensive scientific programme, we will have the chance of meeting with friends old and new, with an enjoyable social program. We will refresh our spirits, minds and hearts. Beside the scientific program, participants can enjoy the historical and natural beauties of Antalya which is one of the most beautiful cities of our beautiful country in the spring months when the nature livens up in the most beautiful time of the year, will in return will vivify our congress.

We are so glad to welcome you in this beautiful city. Our congress will come into prominence with your valuable participation.

Best regards

Prof. Dr. Güner Hayri Özsan

On behalf of 6th. ICLLM Secretary Congress & Secretary General Turkish Society of Hematology

"Abstract alignment has been arranged as to following signified abstract number"

Non-Hodgkin's Lymphoma

PS-01 Abstract Referance: 3

ACQUIRED HEMOPHILIA IN NON-HODGKIN'S LYMPHOMA DURING TREATMENT WITH RITUXIMAB AND CHEMOTHERAPY.

Vincenzo Russo[1], Fabrizio Pane[2], Amalia De Renzo[2]
[1]*A.o.u. San Martino-Department of Hematology, university of Genova, Italy*
[2]*A.o.u. Federico Ii-department of Hematology, university of Naples, Italy*

Introduction: Acquired hemophilia is a rare coagulation disorder characterized by autoantibodies against circulating coagulation factor, frequently against factor VIII. This condition may be associated in 50% of cases with lymphoproliferative disorders. We describe three patients with indolent non-Hodgkin's lymphoma (NHL) who showed isolated prolonged aPTT and PT.

Methods: Case One: A 72-year-old man referred to our Institution because of recurrent epistaxis and abnormalities of coagulation tests PT INR 2.5, aPTT ratio 2.73. No previous personal or family history of bleeding disorders, or recent surgery and new drug intake were reported.

Laboratory test showed a reduction of coagulation factors activity: FVIII C 16%; FII 44%; FV 8%; FVII 11%; FIX 10%; FX 30%; FXI 27% and appearance of antibodies against many of them. The bone marrow (BM) biopsy showed a lymphoid infiltrate and was confirmed NHL diagnosis.

Case two: A 62 year-old female came to our observation for lymphoadenopathy, hepatosplenomegaly, anemia and lymphocytosis. The patient didn't present any personal or family bleeding disorders and didn't take drugs. Laboratory tests showed abnormalities of coagulation: PT INR 3.26, aPTT ratio 4.92. They also showed a reduction of coagulation factors activity: FVIII C 2.3%; FII 32%; FVII 47%; FIX 1%; FX 43%; FXI 1% and appearance of antibodies against many of them. The BM biopsy enabled

Acute Lymphoblastic Leukemia

PS-02 Abstract Referance: 2

ACUTE LYMPHOBLASTIC LEUKEMIA PRESENTING WITH HYPERCALCEMIA IN AN ADULT: A CASE REPORT

Fehmi Hindilerden[1], Betül Erişmiş[2], Emre Osmanbaşoğlu[1], Yıldız Okuturlar[2], Mehmet Hurşitoğlu[2], Özlem Harmankaya[1]
[1]*Bakirköy Sadi Konuk Training and Research Hospital Hematology Clinic, Istanbul*
[2]*Bakirköy Sadi Konuk Trainig and Research Hospital Internal Medicine Clinic, Istanbul*

Introduction: Hypercalcemia in hematopoietic malignancies including acute lymphoblastic leukemia (ALL) is very rare and unusual, especially as the initial manifestation of disease. Herein, a 55-year-old male who presented with severe hypercalcemia prior to the onset of common and usual manifestations of ALL is described.

Case: A 55 year-old male with no previous medical history was referred to our hospital with a two weeks history of malaise, anorexia, nausea, and vomiting. On physical examination, only lethargy and pallor were noted with no other signs including lymphadenopathy and hepatosplenomegaly. Initial laboratory studies were as follows: Na: 134 mmol/L, K: 4.72 mmol/L, Creatinine: 0.54 mg/dl, Calcium: 14 mg/dl, P: 4.2 mg/dl, uric acid: 6.8 mg/dl, LDH: 2400 U/L, Mg: 1.4 mg/dl, alkaline phosphatase: 110 U/L, albumin: 3.2 gr/dl. Complete blood count included: WBC: 5.7×109/L (lymphocyte: 52%, PMN: 23%), Hgb: 10.8 gr/dl, PLT: 87×109/L. The patient was monitored for severe hypercalcemia. No significant electrocardiographic changes were noted despite sevre hypercalcemia. Aggressive hydration with normal saline and furosemide 1 mg/kg IV every 6 hours were started. Serum levels of PTH and 1.25-(OH) 2 Vitamin D were 7.5 pg/ml (10–65 pg/ml) and < 7.5 pg/ml (20–70 pg/ml),

Non-Hodgkin's Lymphoma

PS-01 Abstract Referance: 3

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Vincenzo Russo[1], Fabrizio Pane[2], Amalia De Renzo[2]
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Laboratory test showed a reduction of coagulation factors activity: FVIII C 16%; FII 44%; FV 8%; FVII 11%; FIX 10%; FX 30%; FXI 27% and appearance of antibodies against many of them. The bone marrow (BM) biopsy showed a lymphoid infiltrate and was confirmed NHL diagnosis.

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Case three: A 80 year-old man referred to our Istitution for pancytopenia and abnormalitites of coagulation tests: PT INR 2.28, aPTT ratio 3.2. No personal or familiar story of bleeding disorders. Laboratory tests showed reduction of coagulation factors activity: FII 54%; FV 68% ; FX 60%. The BM exam enabled NHL diagnosis.

Results: The patient of case one made 6 courses of chemotherapy (CHT) with R-CEOP regimen, achieved complete remission and was documented a normalization of PT and PTT. The patient of case two made 6 courses of CHT with Rituximab (R), and a slow normalization of PT and aPTT was observed. The patient underwent maintenance treatment with R. The patient of case three made 6 courses of R-Leukeran CHT and normalization of PT and PTT was documented. The patient underwent maintenance treatment with R. In all cases there was a correction of the PT and aPTT after CHT.

Conclusion: The onset of an acquired coagulation disorder can be used as diagnostic and prognostic marker of derangement of the immunologic network due to an underlying, apparently indolent, lymphoprolipherative disease. Maintenance therapy may be useful for the control of the neoplastic clone, and to reduce the risk of bleeding.

Keywords: Coagulation factors, Lymphoma, Rituximab

Acute Lymphoblastic Leukemia

PS-02 Abstract Referance: 2

ACUTE LYMPHOBLASTIC LEUKEMIA PRESENTING WITH HYPERCALCEMIA IN AN ADULT: A CASE REPORT

Fehmi Hindilerden[1], Betül Erişmiş[2], Emre Osmanbaşoğlu[1], Yıldız Okuturlar[2], Mehmet Hurşitoğlu[2], Özlem Harmankaya[1]
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Case: A 55 year-old male with no previous medical history was referred to our hospital with a two weeks history of malaise, anorexia, nausea, and vomiting. On physical examination, only lethargy and pallor were noted with no other signs including lymphadenopathy and hepatosplenomegaly. Initial laboratory studies were as follows: Na: 134 mmol/L, K: 4.72 mmol/L, Creatinine: 0.54 mg/dl, Calcium: 14 mg/dl, P: 4.2 mg/dl, uric acid: 6.8 mg/dl, LDH: 2400 U/L, Mg: 1.4 mg/dl, alkaline phosphatase: 110 U/L, albumin: 3.2 gr/dl. Complete blood count included: WBC: 5.7×109/L (lymphocyte: 52%, PMN: 23%), Hgb: 10.8 gr/dl, PLT: 87×109/L. The patient was monitored for severe hypercalcemia. No significant electrocardiographic changes were noted despite sevre hypercalcemia. Aggressive hydration with normal saline and furosemide 1 mg/kg IV every 6 hours were started. Serum levels of PTH and 1.25-(OH) 2 Vitamin D were 7.5 pg/ml (10–65 pg/ml) and < 7.5 pg/ml (20–70 pg/ml), respectively, but it was impossible to measure PTHrP. Cervical, thoracic and abdominopelvic computerized tomographic scans and tumor markers showed no sign of an underlying malignancy or the presence of bone lytic lesions. After 3 days of treatment onset regarding the serum calcium increment from14 mg/dl to 15.2 mg/dl, zoledronic acid 4 mg IV infusion was administered. Also, methylprednisolone 1 mg/kg/day was added to the previous treatment. Four days after the calcium level became normal. Furosemide and hydration were discontinued. Bone marrow aspiration was performed for anemia and thrombocytopenia and showed acute lymphoblastic leukemia (ALL) with L2 morhology. Flow cytometry of the bone marrow was consistent with pre B-ALL phenotype. Cytogenetic analysis of bone marrow showed 46, XY karyotype. Bone marrow aspirate analysis for t (9; 22), t (12; 21) and t (4; 11) using PCR method were negative. As remission induction chemotherapy, GMALL 07/2003 protocole was initiated. Methylprednisolone was continued and calcium remained within normal limits and the patient's clinical symptoms, including nausea, vomiting, weakness and lethargy resolved. Bone marrow aspiration on day 30 showed hematological remission.

Discussion: Two possible mechanisms account for hypercalcemia in hematological malignancy, either the leukemic infiltration or the paraneoplastic production of a variety of humoral factors and proinflammatory

cytokines. Physicians should be aware of this rare presentation of adulthood ALL with hypercalcemia. Given the nonspecific symptoms of hypercalcemia, it is recommended to measure serum calcium in similar cases. Prompt treatment of leukemia helps to quickly correct the hypercalcemia in addition to other therapies.

Keywords: acute lymphoblastic leukemia, hypercalcemia

Myeloprofilerative Disorders

PS-03 **Abstract Referance: 4**

ULTRASOUND IMAGING IN DIAGNOSIS OF PORTAL VENOUS THROMBOSIS IN A PATIENT WITH REFRACTORY ANEMIA (RARS-T)

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Introduction: Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) is a rare myelodysplastic/myeloproliferative disorder, that has been proposed as a provisonal entity in the 2001 and 2008 WHO classification. JAK2-V617F has been shown in the majority of these patients. Thrombotic complications can be the major cause of morbidity and mortality as portal venous thrombosis (PVT) in RARS-T. Abdominal ultrasound (US) shows the presence of hypoechoic lesions. We describe a case of PVT in a patient with RARS-T at diagnosis.

Methods: A 70-year-old woman admitted on to our hospital for normocytic anemia (Hb 9.5 g/dL) thrombocytosis (PLT 853x109/L) and mild leucopenia (WBC 2.9x109/L). Bone marrow aspirate showed increased number of megakaryocytes with dysplastic features, dyserythropoiesis and dysgranulopoiesis, ringed sideroblast was observed; polymerase chain reaction (PCR) was positive for JAK2 V617F mutation. The patient was positive to heritable thrombophilic gene mutations: G1691A Factor V Leiden, G20210A prothrombin, C677T MTHFR mutations, polymorphism of PAI-1 gene (4G/5G, 4G/4G) and lupus anticoagulant with antiphospholipid antibodies (APL-Abs).

Results: Abdominal B-mode US detected the presence of 2.3x4.1 cm hypoechoic lesion in the VI hepatic segment (Figure 1). Color doppler US showed an area with no blood supply. CT scan confirmed a portal venous thrombosis. Treatment with lenalidomide was started.

Conclusions: The clinical course of RARS-T could be better than that of RARS and worse than that of essential thrombocythemia; however, the clinical and therapeutic experience with such cases is limited, due to the rarity of this disease. The incidence of PVT among myeloproliferative disorders is 10–12%. Inherited and acquired disorders of the coagulation pathway are frequent causes of PVT and normally causes pain of varying intensity in the right upper quadrant and low grade fever. Abdominal B-mode ultrasound (US) shows the presence of hypoechoic lesions. Color doppler US may show an area with no blood supply, but CT scan is the diagnostic method which has the highest sensitivity and specificity in these cases.

Keywords: RARS-T, Ultrasound, Portal Venous Thrombosis

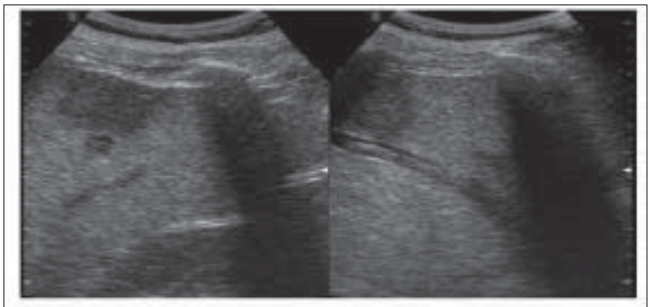

Fig.1 RARS-T with hypoechoic lesions in the V and VI hepatic segment

Non-Hodgkin's Lymphoma

PS-04 **Abstract Referance: 5**

INFECTIOUS COMPLICATIONS IN PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMA, LEG TYPE

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Introduction: Primary cutaneous large B-cell lymphoma, leg type (PCBCL) is a rare and aggressive neoplasm as defined by the recently update WHO classification of cutaneous lymphoma.

The pathogenesis of PCBCL is unclear. In Europe is evidence linking some pathogenic bacteria as *B. burgdorferi, Group B streptococcus, P. Aeruginosa* to the development of PCBCL.

We present a case of 80-year-old woman with a cutaneous lesion on her leg.

Methods: A 80-year-old woman with history of chronic hepatitis C was admitted to our hospital for evaluation of a lesion on her right leg. On presentation she was noted to have a hard, immobile, nodule palpable just under the skin surface on the right leg. Were present ulcerations and foul-smelling discharge from many of her skin lesions.

Group B streptococcus, *B. burgdorferi, P. Aeruginosa* were cultured from the lesions (Fig.).

An excisional biopsy of the lesion revealed an infiltrate of monomorphic large cells in the dermis with vesicular chromatin, prominent nucleoli, frequent mitoses.

Immunohistochemical evaluation revealed the abnormal cells to be CD20, CD22, BCL-2, BCL-6 positive, CD10 negative. The morphology and staining pattern were consistent with a diagnosis of primary cutaneous diffuse large B-cell lymphoma, leg type (PCBCL-LT).

Results: Further staging evaluation, including bone marrow biopsy and CT scan imaging was unremarkable. The patient started chemotherapy and treatment with intravenous ampicillin/sulbactam.

Conclusions: The infectious complications of PCBCL are of paramount importance since they are involved in over 50% of deaths in patients with PCBCL.

The increased susceptibility to infection by patients with PCBCL is partially due to disruption of the normal skin barrier. *Enterobacteriaceae* and *P. aeruginosa* have

been reported as important pathogens causing pneumonias and sepsis in patients with PCBCL.

Gram-negative sepsis actually remains one of the most important cause of death in patients with PCBCL.

Keywords: PCBCL, INFECTIOUS COMPLICATIONS, LEG TYPE

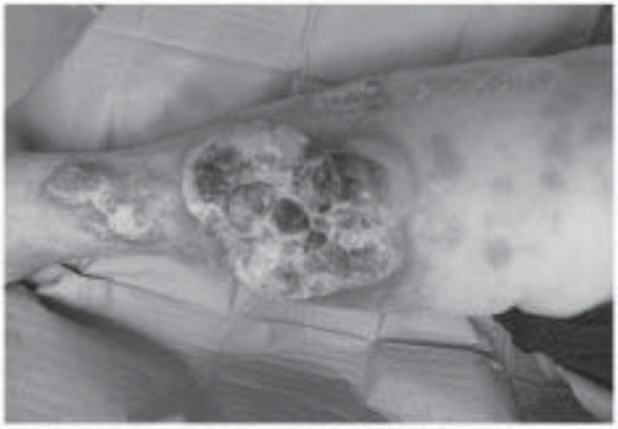

Fig. Primary cutaneous large B-cell lymphoma, leg type (PCBCL-LT) skin lesions

Non-Hodgkin's Lymphoma

PS-05 **Abstract Referance: 7**

COMBINATION INTRAVITREAL RITUXIMAB AND METHOTREXATE FOR VITREORETINAL LYMPHOMA

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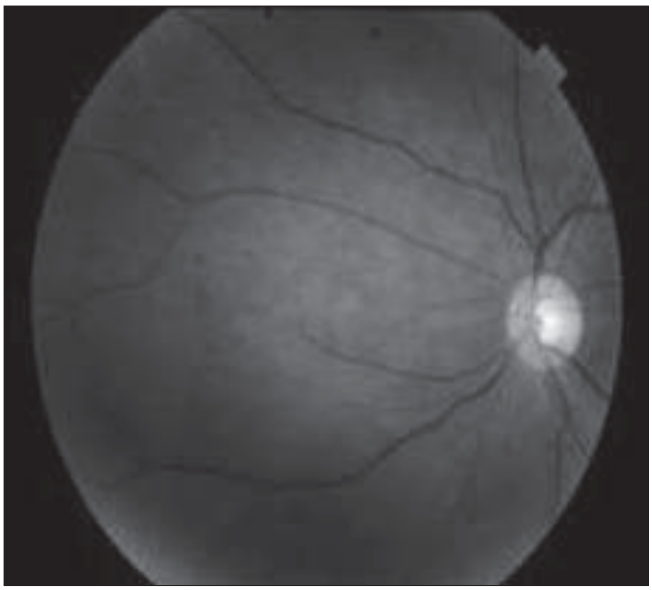
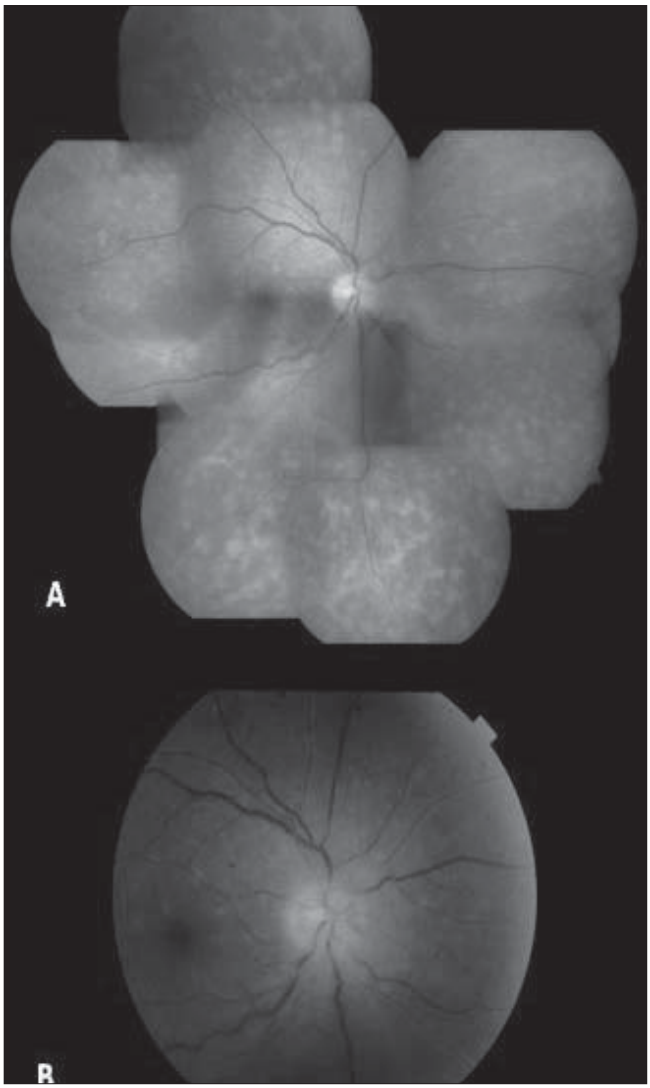
[1]*Akdeniz University*

A 38-year-old male patient with a history of diffuse B cell lymphoma in liver, bone marrow presented with progressive blurred vision in his right eye (OD) in 2 months. Visual acuities were 20/200 OD and 20/20 in left eye (OS). A relative afferent pupillary defect was present OD. Ophthalmic examination was normal OS. Trace vitritis and diffuse, confluent yellow-white subretinal infiltrates and optic disc edema were seen OD. (Figure A, B) All uveitic markers (CBC, RPR, FTA-ABS, HIV, ACE, ESR, and chest CT scan) were normal. Brain MRI was negative for CNS lymphoma. Given the medical history and clinical findings, vitreoretinal lymphoma was considered. Following ocular oncology and hematology consultations, treatment options were systemic chemotherapy, external radiation or intravitreal chemotherapy. We planned intravitreal chemotherapy because of only right eye involvement and as a sparing radiation therapy. Monthly intravitreal injections of rituximab (1 mg/0.1 ml) and methotrexate (400 mcg/0.1 ml) for 6 months were undertaken. Rapid regression of the subretinal lesions and optic disc edema were observed in first month and visual acuity improved to 20/20 OD. (Figure C) The retinal examination was stable with no evidence of central nerve system involvement.

Keywords: lymphoma, vitreus, retina, eye





Multiple Myeloma

PS-06 **Abstract Referance: 15**

LENALIDOMIDE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA, SINGLE CENTRE EXPERIENCE

Işıl Erdoğan Özünal[1], Dilek Keskin[1], Ece Vural[2], Hülya Yılmaz[2], Deniz Özmen[1], Nurgül Özgür Yurttaş[1], Sevil Sadri[1], Selin Berk[1], Ayşe Salihoğlu[1], Ahmet Emre Eşkazan[1], Şeniz Öngören[1], Muhlis Cem Ar[1], Zafer Başlar[1], Teoman Soysal[1], Nükhet Tüzüner[3], Yıldız Aydın[1]

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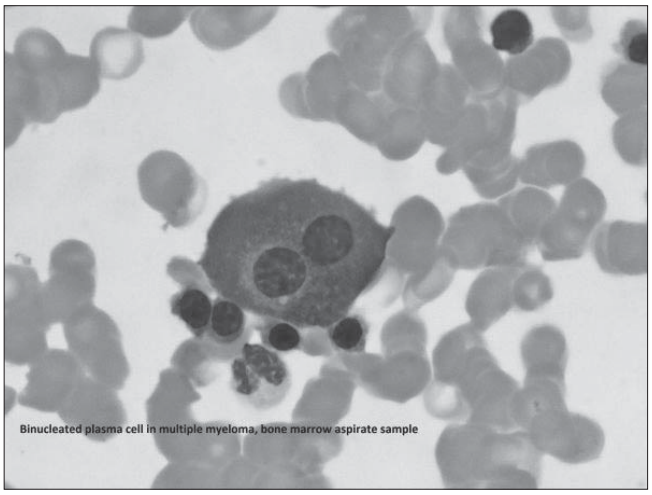
Background: There is a wide spectrum of treatment alternatives including a number of combination regimens (with immunomodulatory agents or proteasome inhibitors) or single agent therapies for relapsed/refractory multiple myeloma (RR-MM). Lenalidomide is an immunomodulatory agent approved for the treatment of RR-MM. Lenalidomide is shown to have efficacy and acceptable safety in previously treated patients with MM.

Methods: We, retrospectively, evaluated the 80 patients diagnosed with MM, between 1998–2016 in our clinic who received lenalidomide and dexamethasone due to relapsed/refractory disease.

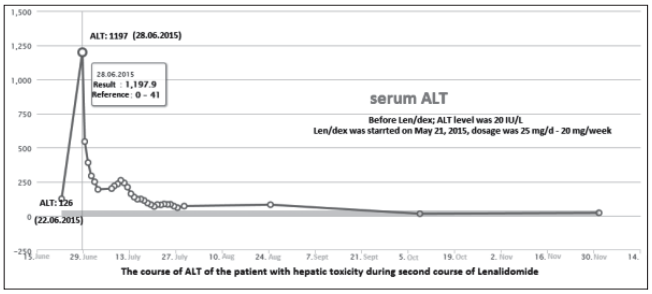
Results: Forty two patients were male (52%), median age was 59.5 (range between 35–83). Characteristics of the patients are shown in Table 1. All of the patients received dexamethasone (dose between 8 to 40 mg per week) during lenalidomide treatment. During follow-up 36 patients (45%) received autologous stem cell transplantation (ASCT). Lenalidomide was used at 2–8th line of treatment (median 3rd line) and median course number was 11 (range between 1–55 courses). Twenty nine patients received > 24 courses of lenalidomide during follow-up. In 9 patients lenalidomide was used before ASCT. Response to lenalidomide treatment is shown in Table 2. Time to next treatment was evaluated in 24 patients and range was 2–35 months (median 16 months). During treatment and follow-up 21 patients died, 31 are still on lenalidomide. Overall survival was 51 months (7–222 months). In 44 patients (55%), there were no adverse effects during treatment, but in 36 patients adverse effects were observed which required drug withdrawal or dose reduction. These included; grade 1–3 hematologic toxicity in 27 patients (34%), acute deep venous thrombosis or serebral thrombosis in 4 patients (5%), maculopapular rash in 5 patients (6%), pneumonia in 3 patients, meningititis in 1 patient and angioedema in 1 patient. One patient developed acute liver failure during second course of treatment and this required drug withdrawal. Eighteen patients (23%) had polyneuropathy before lenalidomide, this was due to previous treatment regimens containing bortezomib/thalidomide or VAD regimen. In 2 patients, polyneuropathy was absent before the onset of lenalidomide treatment, one in 14th course and the other in 18th course developed polyneuropathy and this was associated with lenalidomide.

Conclusions: Lenalidomide has been reported to be an effective treatment as single agent in heavily pre-treated multiple myeloma patients. In this study all of the patients received lenalidomide with dexamethasone in doses ranging from 8 to 40 mg per week leading to an overall response rate of 69% (CR, VGPR and PR). Eleven percent of the patients had stable disease, 13% had progressive myeloma while on lenalidomide treatment. Prospective observatory studies are needed to determine the efficacy and safety of lenalidomide in real-life setting RR-MM patients.

Keywords: Lenalidomide, relapsed/refractory Multiple Myeloma



Binucleated plasma cell in multiple myeloma, bone marrow aspirate sample



The course of ALT of the patient with hepatic toxicity during second course of Lenalidomide

Maculopapular rash due to lenalidomide treatment, right inguinal region

Table 1: Characteristics of patients

Characteristics	Patients (n=80)	
Gender	F: 38/M: 42	
Age (median/range)	59.5 (35–83)	
Diagnosis	IgG κ	37 (46%)
	IgG λ	19 (24%)
	IgA κ	8
	IgA λ	6
	λ light chain	5
	κ light chain	2
	IgD λ	2
	IgM κ	1
Stage (ISS)	I	27 (34%)
	II	23
	III	23
Stage (DS)	IA	6
	IIA	26
	IIB	1
	IIIA	31 (38%)
	IIIB	11

Table 2: Response to lenalidomide treatment

Response	Number of patients (n=80)
CR	7 (9%)
VGPR	31 (39%)
PR	17 (21%)
PROGRESSION	10 (13%)
STATIONARY	9 (11%)
UNEVALUATED	6 (7%)

Multiple Myeloma

PS-07 **Abstract Referance: 16**

PROGNOSTIC SIGNIFICANCE OF RESPONSE STATUS BEFORE AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS

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Aim: Autologous stem cell transplantation (ASCT) is a standard treatment approach in appropriate multiple myeloma (MM) patients. In this study, we aimed to evaluate the prognostic significance of the pre-ASCT response status and transplant related factors on treatment response and survival.

Methods: We analyzed retrospectively 116 MM patients who were uniformly treated with ASCT between January 2013 and June 2016 in the Department of Hematology at Ege University Medical Faculty.

Results: The most commonly used induction chemotherapy prior to ASCT was VAD (vincristine, doxorubicin, dexamethasone) and bortezomib based chemotherapy regimen (61.2%). Fifty-seven patients (49.1%) were given high dose cyclophosphamide + recombinant human granulocyte colony stimulating factor for stem cell mobilization. Preparation regimens with 200 mg/m2 of melphalan were administered (140 mg/m2 in 19 patients, 100 mg/m2 in 1 patient). Transplant-related mortality was 6.8% (n = 8). Progression-free survival probability in 2 years was 64.3% and overall survival probability in 2 years was 85.5%. Compared with pre-ASCT response status, progression-free and overall survival were found to be statistically longer in patients with complete response, very good partial response, or partial response than patients with stable disease.

Conclusion: ASCT is an effective and safe treatment without age restriction in new diagnosed MM patients with appropriate performance status. Long-term treatment response after ASCT can be achieved by obtaining a high-quality response with first-line treatment at this time of effective new agents.

Keywords: Multiple myeloma, autologous stem cell transplantation, response

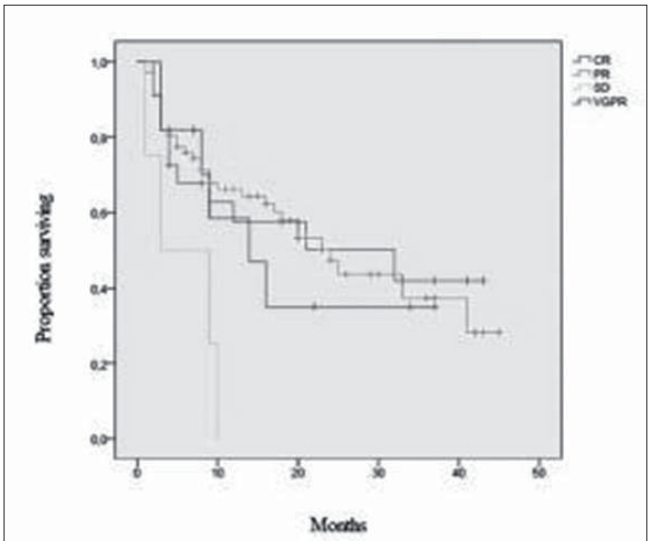

Fig. PFS: Response status before autologous stem cell transplantation

Multiple Myeloma

PS-08 Abstract Referance: 17

DOES FERRITIN AND VITAMIN B12 LEVELS HAVE PROGNOSTIC SIGNIFICANCE IN MULTIPLE MYELOMA PATIENTS?

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Aim: The aim of this study is to evaluate the effect of iron and vitamin B12 deficiencies at the time of diagnosis on complications in multiple myeloma patients.

Material and Method: The relation between iron and vitamin B12 levels with myeloma complications such as anemia, hypercreatininemia, hypercalcemia and bone lesions was analyzed with chi square in 140 multiple myeloma patients.

Findings: Vitamin B 12 deficiency was found in 29 patients (20.7%) and low ferritin level was found in 7 (5%) patients. While the rate of hypercalcemia is 37.9% in patients with vitamin B 12 deficiency, it is 18.9% in patients without deficiency. The fracture rate was 44.8% in vitamin b12 deficient group and 23.4% in the other group.

Results: Vitamin B12 deficiency at time of diagnosis is associated with hypercalcemia and bone fracture rate (p=0.04, p=0.03). There is no relation with iron deficiency and complications.

Discussion: There is no association between ferritin level and prognosis in myeloma patients. Vitamin B 12 level might have prognostic significance since hypercalcemia and fracture rate is inceased in vitamin B12 deficient group. Further studies with larger patient group are needed in this subject.

Keywords: myeloma, ferritin, vitamin b12 deficiency

Multiple Myeloma

PS-09 Abstract Referance: 9

A RARE DIAGNOSIS IN THE DIFFERENTIAL DIAGNOSIS OF PANCYTOPENIA: MULTIPLE MYELOMA

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[2]*Istanbul University Istanbul Medical Faculty Department of Pathology*

Introduction: Multiple myeloma (MM) usually presents with anemia, but pancytopenia as a presenting symptom of MM is seldomly encountered. In a patient presenting with pancytopenia, diagnosis of MM requires a high degree of suspicion to avoid delay in the initiation of treatment.

Case: An 82-years old male with no previous disease history presented with fatigue. There was no significant finding on physical examination. The complete blood count was as follows: Leukocyte: 2890/mm^3, neutrophil: 1850/mm^3, Hgb: 8.2 gr/dl, thrombocyte: 32800/mm^3. Biochemistry tests showed the following: urea: 32 mg/dl, creatinine: 0.82 mg/dl, calcium: 8.6 mg/dl, LDH: 189 IU/L, total protein: 7 gr/dl, albumin: 2.89 gr/dl and sedimentation: 97 mm/hour. On peripheral blood smear, macrocytosis and mild hypochromia were noted. For the differantial diagnosis of bone marrow (BM) failure, BM biopsy was performed. On BM biopsy, diffuse interstistial infiltrates of plasmablastic plasma cells showing lambda light chain monoclonality and grade III reticulin fibrosis were demonstrated. Serum free lambda light chain was 5.2 gr/dl and serum free kapa light chain was 0.17 gr/dl. The ratio of free kappa light chain to free lambda light chain was 0.031. Bortezomibe-thalidomide-dexamethasone was initiated as remission induction treatment for MM.

Discussion: Anemia is a common initial finding in MM. In advanced cases however, thrombocytopenia and neutropenia may be observed resulting in pancytopenia. For such advanced cases with unusual presentation, high index of suspicion supported with specific and reliable laboratory examinations are mandatory for diagnosis and to evaluate the extent of the disease. Pancytopenia in MM often results from the plasma cell proliferation replacing normal hematopoietic cells. Other causes include fas-ligand mediated apoptosis or cytokine-mediated bone marrow failure or even renal failure induced erythropoietin deficiency. MM patients are generally treated with alkylating agents, but, when associated with pancytopenia, these patients will require a mandatory addition of dexamethasone in order to avoid the hematopoietic stem cell damage by alkylating agents. Due to the risk of prolonged cytopenias and hematopoietic stem cell damage, the use of alkylating agents should be avoided in the initial treatment of MM presenting with pancytopenia.

Keywords: myeloma, pancytopenia

Non-Hodgkin's Lymphoma

PS-10 Abstract Referance: 10

NK/T CELL LYMPHOMA PRESENTING WITH HEMOPHAGOCYTOSIS: REPORT OF A CASE.

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life threatening hematologic disorder manifested by clinical findings of extreme inflammation and unregulated immune activation. HLH can occur as either a familial disorder or a sporadic condition. Malignancy associated HLH has been reported mostly in adults. Here we present a case diagnosed with HLH before recognition of NK/T cell lymphoma, nasal type.

Case: A 38 years old woman refers to the outpatient clinic with headache and weight loss. Physical examination was normal except for splenomegaly and fever. She had been diagnosed with romatoid arthritis 7 years ago. On laboratory analysis, thrombocytopenia and

hyperferritinemia were remarkable (Table 1). She was evaluated for collagen vascular diseases and p-ANCA was found to be positive. She was referred to the rheumatology department with a presumptive diagnosis of Wegener granulomatosis. Sinusoidal MRI showed a diffuse soft tissue image filling left sinusoidal compartments. The image was interpreted as chronic sinonasal infection. ENT department performed tissue biopsy. Concurrently the patient was consulted to our clinic. Her recent laboratory results were consistent with HLH (Table 1). Bone marrow biopsy was urgently and a PET-CT scan was planned. With the presumptive diagnosis of HLH, HLH-2004 protocole was initiated. On the following days the sinus biopsy was reported to be compatible with NK/T cell lymphoma, nasal type. PET-CT revealed retropharengeal and nasopharengeal mass. After the initiation of the HLH-2004 protocole, both the hemophagocytic activity and patient symptoms regressed. SMILE protocole was planned to be given to treat the NK/T cell lymphoma. Yet shortly therafter, she suffered from massive epistaxis in the concomitant presence of DIC and hyperferritinemia. The patient died on the 5th day of the SMILE protocole.

Discussion: This immune dysregulatory disorder is prominently associated with cytopenias and combination of clinical signs and symptoms of extreme inflammation. Although the individual signs or symptoms of HLH may occur in a variety of clinical circumstances the combination of these features caused by pathologic inflammation forms the pattern of HLH. Diagnosis of HLH is the first critical step but is challenging because of the rare occurrence, variable presentation and nonspecific findings of this disorder. A high rate of suspicion is necessary for early diagnosis. Our patient had been evaluated for the diagnosis of fever with unknown origin for 2 months. After the development of severe thrombocytopenia and hyperferritinemia, she was consulted to the hematology clinic with a presumptive diagnosis of HLH. HLH can cause diagnostic dilemnas because it may mask the underlying malignancy. Therefore any case of HLH needs to be evaluated for malignancy. Early treatment with immunosuppression is warranted but still poor outcome in such patients is emphasized in the literature.

Keywords: Hemophagocytosis, NK-T lymphoma

Table 1: Laboratory Results

	04.08.2016	21.09.2016	30.09.2016	07.10.2016	26.10.2016
WBC 10e3/uL	4.17	2.88	1.94	3.1	1.55
Neutrophil	2.47	1.79	0.84	1.59	0.73
Hgb g/dL	12.4	14.4	8.99	10.79	7.11
Plt 10e3/uL	137000	76500	68840	159000	26200
AST	39	84	75	18	367
ALT	27	57	46	35	107
CRP mg/dL	3.86	1.96	3.36		25.8
Ferritin ng/mL	734	3462	3670	323	4800
aPTT			35.6	30	147
PT/INR			12.5/0.98	12/0.97	20/1.74
Fibrinojen			181	241	129

Acute Myeloid Leukemia

PS-11 **Abstract Referance: 11**

EFFECT OF CAFFEIC ACID PHENETHYL ESTER ON DRUG RESISTANCE IN LEUKEMIA CELL LINES

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Objectives: Drug resistance, either preexistent or acquired, is a major obstacle for all cancer chemotherapeutic agents, as it limits treatment options. The resistant cells implicate in recurrence and mortality of myeloid leukemia. There has been no study searching for combined action of caffeic acid phenethyl ester (CAPE) with chemotherapeutic drugs in the literature, used by complementary medicine in the treatment of many diseases and previously reported to have antitumoral properties when used it alone. The aim of this study is to investigate the effect of CAPE on drug resistance in HL-60, K562 and NB-4 AML cell lines.

Method: Cells were cultured in RPMI 1640 medium and seeded into a 96-well plate. Azacitidine, decitabine, ara-C and CAPE were added to cell lines in various concentrations, incubated at 37°C for 4 days. Alterations in cell viability were assessed using CellTiter-glo luminescent assay.

Findings: The cell viability in K562 line was determined 76.4% when treated with 100 nM ara-C, 77.01% with 1 μM azacitidine and 72.3% with 0.5 μM decitabine. The viability of HL60 and NB4 cell lines treated with 50 nM ara-C was found 57.39% and 66.89%, separately. As compared to use azacitidine alone; while there has been no reduction in cell viability of K562 line with 1 μM azacitidine and 5 μM CAPE in combined, predecribed as resistant; as the same process is performed for 0.5 μM decitabine, it was detected that 60.65% viability decreased to 23.99% and this result has been found to be statistically significant ($p<0.05$). All three cell line shaving resistance to ara-C were treated in combination with 25 nM ara-C and 5 μM CAPE, it was observed that 66.30% viability decreased to 16.88% in K562 cell line and 83.24% viability decreased to 10.05% in HL60 cell line, as compared to use ara-C alone ($p<0.001$). Whereas NB4 cell line showed no reduction in cell viability with ara-C; when combined with CAPE it has been found the cell viability decreased to 42.72% ($p<0.05$). These findings have been found to be statistically significant.

Conclusion: We conclude that CAPE inhibits cell proliferation; may overcome drug-resistance with synergistic action on apoptosis, oxidative pathways and MDR gene, may increase efficacy in combination with chemotherapeutic drugs; considering ara-C and decitabine have the same metabolic pathways to be activated and have similar structures, an important reason for reverse drug resistance may be due to the effects of CAPE on kinase pathway and membrane transport and we believe the results obtained from our study should be supported by further research.

Keywords: Drug resistance, Leukemia Cell Lines, CAPE

Multiple Myeloma

PS-12 Abstract Referance: 18

ASCITES FORMATION IN THE COURSE OF MYELOMA

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[2]*Inonu University, School of Medicine, Department of Infectious Disease*

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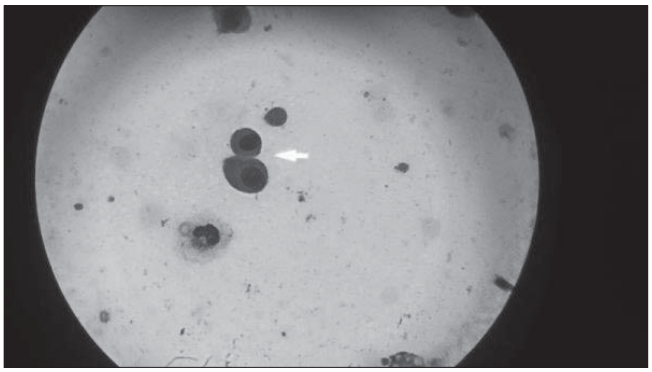
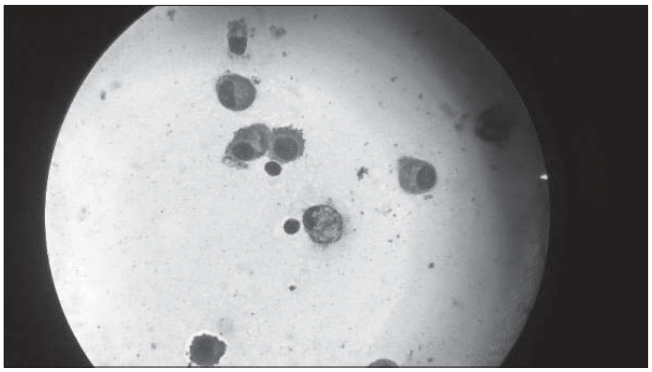
Introduction: Multiple myeloma (MM) is a plasma cell dyscrasia characterized by the malignant proliferation of a plasma cell clone. Ascites is a rare complication of MM and generally occurs because of portal hypertension due to the infiltration of liver by plasma cells. Infrequently, ascites is detected as a result of peritoneal infiltration by plasma cells. Ascites in the course of myeloma has a progressive course and is refractory to high dose chemotherapy. A refractory myeloma case with massive ascites due to peritoneal infiltration is presented.

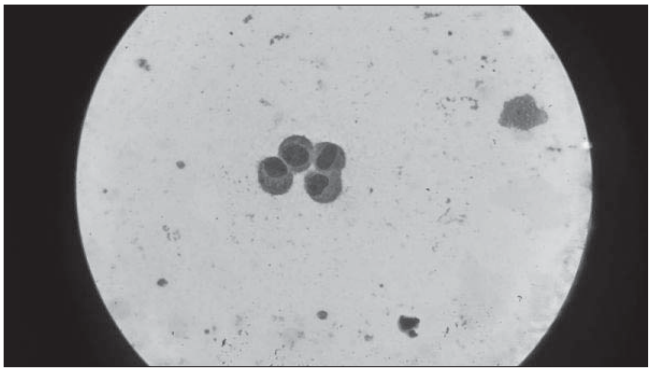
Case report: Seventy-four years old male patients was diagnosed as IgGkappa MM in March 2011. He was treated with 8 cycles VMP (Bortezomib, Melphalan, Prednole) and followed up without medication until August 2014. Tal-Dex (Thalidomide, Dexamethasone) treatment was started due to progression. Thalidomide was stoped because of grade 3 neuropathy in August 2015. Rev-Dex (Revlimide, Dexhametasone) was started but patient was used revlimide irregularly due to hematologic side effects. In November 2016 patient was presented with abdominal distention. Massive ascites was detected in physical examination and abdominal ultrasonography. Diagnostic parasynthesis was performed. Macroscopic appearance of the ascites was slightly cloudy yellow. Ascitic fluid analysis revealed total protein 5.3 g/dL, albumin 3.0 g/dL, LDH 301 U/L, WBC 800/mm^3 and serum-albumin gradient (SAAG) (serum albumin-ascites albumin) of 0.3. Gram stain and culture was negative. Small lymphocytes, polymorphonuclear leukocytes, mesotelial cells and atypical plasma cells were detected in cytological examination of the ascites. Bone marrow aspiration revealed 80% plasma cells. VCD (Bortezomibe, Cyclophosphamide, Dexamethasone) treatment was started with palliative parasynthesis.

Discussion: The patient was presented with an unusual clinical situation of relaps/refractory myeloma and he was diagnosed as peritoneal infiltration of MM, with low SAAG and atypical plasma cells in the ascites. However the reported incidence of extra-osseous manifestations in MM varies among the different series (5%-67%) ascites is a rare complication of MM and generally occurs because of portal hypertension due to the infiltration of liver by plasma cells or an increased permeability of the peritoneum. It may be rarely secondary to infectious peritonitis, or very rarely, to myelomatous peritoneal infiltration. Ascites in the course of the myeloma extremely aggressive and refractory to chemotherapy Median survival is 1.5–2 months after the ascites occurance. Cases responded to alkylating agent containing regimens and high-dose cyclophosphamide (750 mg/m^3/day for four days) was reported. Shimuzi et al. reported that ascites volume was decreased with melphalan and prednisolone treatment. Intraperitoneal injection of thiotepa, nitrogen mustard, and radioactive CR32PO4 was also used in myeloma patients with ascites and showed poor response. An alternative therapeutic approach may be warranted. When peritoneal involvement detected, intraperitoneal dexametasone injection can be used as palliation.

Keywords: Ascites, Myeloma







Multiple Myeloma

PS-13 Abstract Referance: 19

MULTIPLE MYELOMA IN PATIENTS OLDER THAN 65 YEARS: A COMPARATIVE STUDY WITH YOUNGER ADULT MULTIPLE MYELOMA PATIENTS

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Aim: To examine the clinical characteristics of multiple myeloma patients older than 65 years and to compare them with younger adult myeloma patients.

Material and Method: The study includes 74 patients older than 65 (52.9%) and 65 patients younger than 65 (47.1%). Gender, renal failure, hypercalcemia, lytic lesion, fracture, plasmacytoma, iron and vitamin B12 deficiency, VGPR and PR rates.

Findings: In geriatric patients hypoalbuminemia, vitamin B 12 deficiency, fracture, VGPR, PR rates were 51.4%, 9.1%, 19.7%, 18.5%, 85.7% respectively. The rates were 28.4%, 31.1%, 35.1%, 35.6%, 71.8% in patients younger than 65 years.

Results: Hypoalbuminemia is higher in older patients (p=0.006). Vitamin B 12 deficiency and fracture rates are higher in patients younger than 65 (p=0.002, p=0.05). Also VGPR is higher in this group (p=0.03).

Discussion: The high rate of hypoalbuminemia in older group might be related to age spesific changes and due to comorbidities. Since vitamin B 12 deficiency is widely tested and replaced in different clinics, the deficiency rates were found low in geiatric group. The high rates of fractures might be due to high plasmocytoma and lytic lesion rates. While plasmocytoma and fracture rates were expected to be higher in geriatric patients, interestingly the rates were high in younger group. Further studies with larger patients group are needed.

Keywords: myeloma complications, elderly

Acute Myeloid Leukemia

PS-14 Abstract Referance: 14

ISOLATED EXTRAMEDULLARY RELAPSE IN THE BREAST OF A PATIENT WITH ACUTE MYELOID LEUKEMIA AFTER ALLOGENEIC TRANSPLANTATION

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Introduction: Extramedullary relapse of acute myeloid leukemia (AML) shows poor prognosis and requires a combined agressive treatment approach including chemotherapy and radiotherapy. Isolated extramedullary relapse (IEMR) of AML with breast involvement after allogeneic stem cell transplantation (ASCT) has been rarely reported.

Case: A 21 years old female was diagnosed as AML with complex karytotype. Hematological remission was obtained after 2 courses of 3+7 and subsequently 2 courses of HDAC were administered as consolidation. 11 months after initial diagnosis, there was disease relapse and FLAG-IDA was given as salvage treatment. At 2nd hematological remission, she underwent ASCT from 9/10 HLA matched unrelated female donor with BU/CY as the conditioning regimen. Full donor chimerism was demonstrated on day +30. During follow up, no acute or chronic GVHD developed. 23 months after ASCT, she presented with a hard lump in the lower quadrant of her right breast. On PET CT scan, increased FDG uptake (SUV max: 8.63) was detected in the lower quadrant of the right breast. Also, there was increased FDG uptake (SUV max: 4.35) in the 1.5x1 cm lymph node at the right axilla. Trucut biopsy of the breast mass showed positivity for HLADR, CD33 and CD39 on immunohistochemistry analysis, findings compatible with extramedullary AML relapse. Bone marrow (BM) biospy showed on going hematological remission and complete donor chimerism. FLAG-IDA was administered as salvage treatment. Six courses of triple intrathecal (IT) chemotherapy were administered as CNS prophylaxis. CNS fluid cytological examination showed no disease involvement. Four weeks after completion of FLAG-IDA, a repeat PET CT scan showed no FDG uptake. Radiotherapy to the breast and axillary region was administered. A repeat BM biopsy showed no sign of medullary disease and ongoing full donor chimerism. Therore, donor lymphocyte infusion was not administered. At last follow up four months after isolated extramedullary AML relapse, she remains disease free.

Discussion: IEMR in AML after ASCT (excluding central nervous system relapse) is rare with an incidence ranging from 0.65% to 7.4%. M2 or M4 FAB phenotype, favorable cytogenetic risk group (inv[16], t[8; 21], t[15; 17]) and the use of busulfan as conditioning regimen have been associated with IERM. The proposed hypothesis for IERM after ASCT is that graft-versus-leukemia effect on leukemic cells present in peripheral tissues may be less relevant than a graft-versus-hematopoiesis effect or that its action may be more prevalent in bone marrow than at other sites. Also, full-chimerism status does not appear to protect from extramedullary relapse. Thus, the efficacy of DLI after IEMR is not clear. A close follow-up including body and central nervous system scans for early recognition of IEMR, is warranted after ASCT for AML patients carrying IEMR-associated factors. Further data is required to determine the best treatment strategy for IEMR.

Keywords: Extramedullary Relapse, allogeneic Stem Cell Transplantation

Multiple Myeloma

PS-15 Abstract Referance: 21

THE EFFECT OF GENDER ON BONE LESIONS IN MULTIPLE MYELOMA PATIENTS

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Aim: The aim of this study is to evaluate the association between gender and bone lesions such as lytic lesion, fracture and plasmocytoma.

Material and Method: The study includes 80 (57.1%) males and 60 (42.9%) females. The subjects classified whether they have lytic lesions, fracture or plasmacytoma at the time of diagnosis. The association between gender and bone lesions were anlayzed statistically.

Findings: The rates of lytic lesion, fracture and plasmocytoma were 27.9%, 53.6%, 24.4% respectively. While the fracture rate was found% 28.8 in males, it is 26.7% in females. The rate of lytic lesion and plasmocytoma is 55%, 51.7% and 32.5%, 13.3% in males and females respectively.

Results: The association between gender and bone lesions was analyzed statistically with chi square. No association was found between gender and lytic lesion and fracture rate. Plasmocytoma rate was found high in males (p=0.01).

Discussion: The association between plasmocytoma and gender was found statistically significant. Plasmocytoma was found higher in males than females. On the other hand there was no association was gender and fracture and lytic lesions.

Keywords: gender, bone lesions, Multiple Myeloma

Acute Myeloid Leukemia

PS-16 Abstract Referance: 23

SERUM CYSTATIN C IN PATIENTS WITH ACUTE LEUKEMIA AND ITS PROGNOSTIC IMPORTANCE

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Objective: Serum cystatin C may be over-expressed in some tumour cells and its high serum levels are associated with the poor outcome of disease. The aim of this study was to evaluate the serum levels of cystatin C in acute leukemia patients, explore possible correlations with prognosis.

Materıals and Methods: Serum samples of patients with newly diagnosis of acute leukemia have been collected at the time of diagnosis from February 2012 until January 2013.

Results: A total of 24 patients with acute leukemia (median age 48 years; range 19–85 years; 6 women, 18 men) were enrolled the study. The control group consisted of 24 healthy adults with similar age and gender. 84% of patients (n=20) were diagnosed with AML. Serum cystatin C was increased in acute leukemia patients compared to healthy controls [mean: 1.29±0.45 mg/l vs. 0.93±0.10 mg/l, p=0.001]. Patients who had high cytogenetic risk (n=10) had similar values of cystatin C (mean: 1.41±0.57 mg/l) compared to patients with standart cytogenetic risk (mean: 1.20±0.34; p=0.653).

Conclusıon: The level of serum cystatin C is not only a sensitive marker of renal function, but also reflects tumor burden and may delivers prognostic information in acute leukemia. Further prospective studies have to clarify the role of serum cystatin C as a new prognostic marker.

Keywords: leukemia, cystatin C, creatinine, creatinine clearence

Multiple Myeloma

PS-17 Abstract Referance: 25

NOCARDIA PNEUMONIA DEVELOPMENT IN A RELAPSED MULTIPLE MYELOMA CASE

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Objectives: Recurrent infections because of hypogamaglobulinemia, low CD4 lymphocyte level, decreasement in neutrophil migration are clinical findings of multiple myeloma. By suppressing the bone marrow; the recently used proteosome inhibitors and immunemodulatory drugs enhance the risk of infection. Among these; nocardia is a rare causative microorganism. Here, we present a relapsed multiple myeloma case that developed nocardial pnömonia during our follow-up.

Methods: A 66 year old male; who has a diagnosis of IgG kappa type multiple myelom for 5 years and a history of autologous stem cell transplantation 4 years ago, had received lenalidomide and dexametazone because of laboratory and clinical progression of disease. During the follow-up; a second relapse has occured; so bortezomibe has been added to the treatment. He had type-2 Diabetes and chronical kidney disease without dialysis. He applied with a productive cough and his lymphocyte count was determined as 1290/mm^3. Flow-cytometric analysis showed CD 45:% 97, CD3:% 63, CD5:% 68, CD7:% 90, CD4:% 28, CD8:% 56 and CD20:% 2. The lung X-ray showed 5 cm diameter opacity at 5–7th ribs on the right lung; so thorax CT was performed and; multiple nodular opacities and 39x39x45 cm diameter mass, which

contains air bronchograms at right lung superior lobe posterior segment have been detected. Direct microscopik examination of bronco-alveoler lavage sampling showed acid-rezistant branched bacillus (Nocardia). Imipenem/cilastatin and trimethoprim/sulfamethoxazole treatment started to the patient. Cranial MRI; performed to look for intracranial abcess was negative. The high-resolution CT was performed after the tenth day of the treatment and showed that infiltration findings have regressed. The case that responded to antibiotherapy is still hospitalized for follow-up.

Results: The proteosome inhibitors, that have recently been used widely for the treatment of multiple myeloma, decrease the CD8 T cell function that is essential for the cellular immunity. Bortezomib makes T cell disfunction by nuclear factor kappa-B inhibition; thus, increases the herpes zoster and hepatitis B reactivation frequency. Bortezomib provokes oppurtunistic infections such as Nocardiosis, especially lymphopenia and low IgG levels are present. The host response to nocardiosis is directly related with cellular immunity; so the risk increases when CD4 T lymphocite count is below 250/mm^3.

Conclusion: The proteosome inhibitors and immunmodulatory drugs that are used for the treatment of multiple myeloma make T cell disfunction and considering B cell disfunction is also present because of the nature of the disease; this situation tends to provoke rare opportunistic infections such as nocardiosis. Thus, in these patients; it is significant to follow the lymphocyte count closely and to keep in mind that kind of rare microorganisms.

Keywords: multipl myeloma, nocardia, lymphocyte, bortezomibe

Other

PS-18 **Abstract Referance: 26**

BLEOMYCIN-INDUCED FLAGELLATE DERMATITIS

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Bleomycin is a cytostatic, antineoplastic antibiotic that is widely used in treatment of Hodgkin lymphoma, testicular cancer, malignant pleural effusion, ovarian germ cell cancer and squamous cell carcinoma. The substance is isolated from the soil fungus Streptomyces verticillus and it shows its effects by inhibiting the incorporation of thymidine therefore cause DNA fragmentation (1).

Hydroxylase enzyme metabolizes bleomycin. This enzyme is not found in skin and lung tissues; therefore, bleomycin accumulates in those areas and cause side effects. (2) Dermatologic side effects of bleomycin may vary from onycholysis, pruritus, scleroderma-like skin changes to Stevens-Johnson Syndrome.

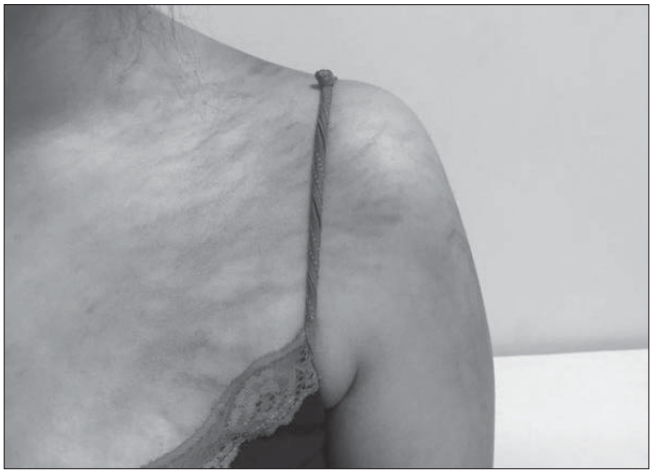
Flagellate dermatitis after bleomycin therapy was originally described by Moulin et. al. in 1970 as "Bleomycin-induced linear hyperpigmentation" (3). The characteristic symptoms are pruritic linear hyperpigmentations arranged in a flagellate pattern especially developing on the trunk. Even though the exact mechanism is not clear, minor skin traumas are thought to be responsible, since they increase blood flow to the affected area and cause drug accumulation.

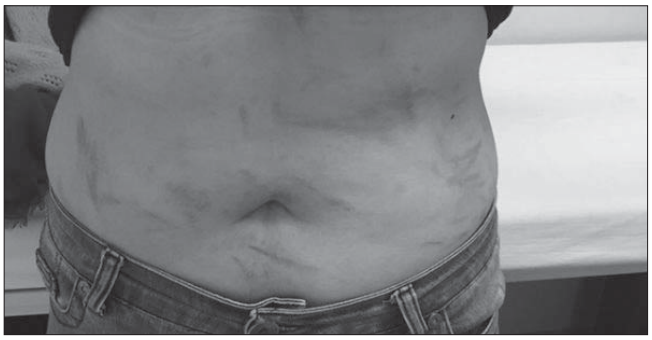
Here we present a 24-year-old female patient diagnosed in August, 2016 with Hodgkin Lymphoma stage IA (Right cervical, submandibular and bilateral palatine tonsils involvement was observed in PET-CT). Doxorubicin (25 mg/m2), bleomycin (10 mg/m2), vincristine (1.4 mg/m2), cyclophosphamide (650 mg/m2), etopside (100 mg/m2), prednol (40 mg/m2), procarbazine (100 mg/m2) (BEACOPP) chemotherapy regimen was chosen for the first line therapy.

After the second cycle of BEACOPP, the patient developed generalized and intense pruritus along with the appearance of papules and plaques on her back, shoulders, and trunk with remarkable whip-like mark formation (Figure 1–2) which evolved with hyperpigmentation. Flagellate dermatitis was diagnosed by the clinical features. BEACOPP regimen was interrupted after three cycles chemotherapy is completed. The skin lesions were already started to resolve after bleomycin including therapy suspension.

Bleomycin-induced flagellate dermatitis is a dose dependent reaction that usually occurs in total doses above *100* U (4). The lesions usually diminish 3–4 months after interrupting bleomycin treatment. Incidence of developing flagellate dermatitis and consequent hyperpigmentation after receiving bleomycin treatment is reported between 8% and 22%. (5) We found it worthy to present our case since development is rarely seen after low dose usage, lesions disappear shortly after suspension of the medication and flagellate dermatitis is not observed with the other medications our patient was receiving.

Keywords: bleomycin, flagellate dermatitis





Chronic Myeloid Leukemia

PS-19 Abstract Referance: 27

CHRONIC MYELOID LEUKEMIA AFTER CHEMORADIOTHERAPY IN A PATIENT WITH NON-SMALL CELL LUNG CANCER: A CASE REPORT

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Introduction: Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized by uncontrolled proliferation of mature and maturing granulocytes. CML accounts for approximately 15 to 20 percent of leukemias in adults. The insidance is 1–2/10000 per year. There is only one risk factor, which is ionized radiation. There are some publitions in the literature about CML development after chemotherapy and/or radiotherapy. Here we presented a case that CML occured after chemotherapy concurrent with radiotherapy in non-small cell lung cancer patient.

Case: Sixty year old man who has diagnosed inoperable lung adenocarcinoma in 2013. Carboplatin concurrent with radiotherapy was administered to him. After 2 years follow-up with no progression of disease, the level of leucocyte was started to increase. White blood cell level was 41700/ul, haemoglobin level was 14.3 g/dl and platelet level was 239000/ul. Peripheral blood smear suggested chronic myeloid leukemia. Bone marrow aspiration and biopsy was performed. The biopsy was supported chronic phase chronic myeloid leukemia. Cytogenetic analysis showed% 95 translocation (9; 22) in 20 metaphasis. BCR-ABL was detected as 60% IS. Imatinib therapy was started as 400 mg/day. Hematologic response was seen 2 weeks after imatinib treatment. After 3, 6, 12 months, BCR-ABL was detected as 27% IS, 1% IS, and 0.4 IS, respectively. The patient is still being followed as remission for both lung cancer and CML.

Discussion: Secondary cancers are increasing due to increased survival and new treatment outcomes in cancer treatment. Therapy related acute myeloid leukemia and myelodysplastic syndrome are seen at increasing rates. However, therapy related CML (t-CML) is seen rarely. One study showed that t-CML developed most often after Hodgkin disease. Less reported after breast cancer and chronic lymphocytic leukemia.

Leukoerythroblastic reaction may occur in bone marrow metastasis. If bone marrow metastasis is absent in a patient with leukoerythroblastic reaction, CML should be kept in mind. This case is the first case report of CML development after non-small cell lung cancer theratment in literature.

Keywords: Chronic myeloid leukemia, non-small cell lung cancer, chemoradiotherapy

Other

PS-20 Abstract Referance: 28

A PATIENT OF BREAST INVOLVED OF HODGKIN LYMPHOMA

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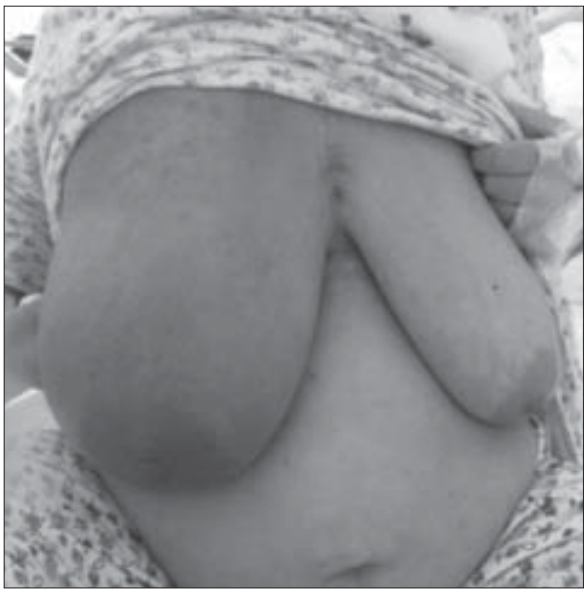
Introduction: Hodgkin's lymphoma shows bimodal age distribution, the incidence increases after age 10 and makes a peak at 20 years old, and a second peak after 45 years. The disease occurs in 90% of cases with growth in the peripheral lymph nodes and spreads through the neighborhood to the next lymph node region. It is usually straight from the disseminated mediastinum to the celiac lymph nodes, from here to the spleen, liver and bone marrow. We wanted to share our case experience, diagnosed with breast involvement at 70 years of age.

Case: A 70-year-old female patient with DM and coroner arter diseases; suffered from progressive growth, redness and pain of the right breast for the past 3 months. She lost 10% of the weight and complained about night sweats. On physical examination, the right breast enlarged more than 2 times of the left, swollen, edematous and hyperemic. There is conglomerate LAP of right axiller. Breast USG and mammography were evaluated and the right breast edema was detected. Axillary lap trucut biopsy result, hodgkin lymphoma. PET CT showed right axillary, right breast, mediastinal and bone marrow involvement. Stage 4B Hodgkin's disease was diagnosed. Adriamycin could not be given due to comorbidity and the dose-reduced EPOCH (without adriamycin) plan was followed.

Discussion: Breast cancer can be seen after radiotherapy used in the treatment of hodgkin lymphoma, but primary involvement of breast is rare. For this reason, we wanted to share our Hodgkin lymphoma case with breast involvement.

Keywords: breast involved, hodgkin lymphoma



Non-Hodgkin's Lymphoma

PS-21 **Abstract Referance: 30**

A RARE CASE OF BURKITT LYMPHOMA WITH MULTIPLE EXTRANODAL INVOLVEMENT

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Introduction: Burkitt lymphoma (BL) is a highly aggressive B cell non-Hodgkin lymphoma characterized by the translocation and deregulation of the c-MYC gene on chromosome 8. Burkitt lymphoma comprises <1% of adult non-Hodgkin lymphomas. Burkitt lymphoma involving the breast is extremely rare than the other types of B-cell lymphoma. Also, bilateral ovarian, uterine, paraspinal involvements are uncommon areas in BL.

Case report: A previously healthy 29-year-old woman was admitted to hospital with complaining of diffuse body pain and diminished motor power of bilateral lower extremities. Her laboratory examination revealed a markedly elevated lactate dehydrogenase (2293 IU/dL) and liver function tests. Renal function tests were normal with no evidence of tumor lysis. Abdomen computarized tomography (CT) showed endometrial thickening, enlargement of both ovaries (right ovary 71x45 mm, left ovary 52x42 mm), splenomegaly (long axis 137 mm), multiple hypodense solid lesions in the liver, hypodense lesions in the left iliac crest and in transverse process of L5.

At physical examination, egg sized, hard, immobile masses were detected in both breasts without overlying skin changes and with normal nipples, and nut sized, hard, mobile mass in her left axilla. Ultrasonography of the breasts revealed bilateral solid lesions of 42x16 mm sized in the right breast and multiple millimetric masses in the left breast with increased blood flow in doppler ultrasonography (correlated with BIRADS 4A). Multiple liver and bone metastatic lesions accompanying multiple breast masses initially gave the impression of metastatic breast cancer.

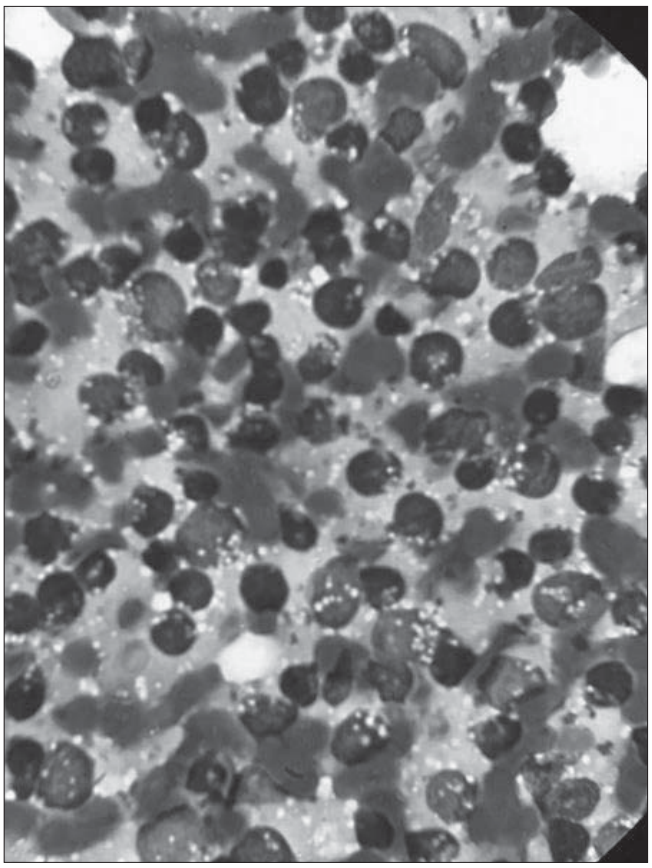
Multiple biopsies were obtained from both breasts, liver and also gastric corpus. All biopsied showed high grade B cell lymphoma with high Ki-67 proliferation index in accordance with BL. Histopathological examinations showed middle sized monotonous atypical lymphoid cells which has narrow cytoplasm containing diffuse cytoplasmic microvacuoles. Immunohistochemical studies demonstrated that the tumor cells were positive for CD20, BCL-6, CD10 but not for BCL-2, CD3, CD4, CD5, CD23, MUM1 and TdT. No blast cells were observed in the peripheral blood smear. Examination of bone marrow aspirate specimen showed diffuse infiltration with L3 type blasts (Figure 1).

An initial staging F18-FDG-PET/CT revealed high-uptake extranodal involvement in both breasts, multiple areas of liver, pancreas, uterine corpus and both ovo-adnexal region, presacral soft tissue, left cervical spinal muscle, multiple areas of skeletal system, pleural thickening in left hemithorax, localized nodule in the skin over the left shoulder and subcutaneous tissue correlated with diffuse infiltration of the primary malignancy.

The patient was started a combination of chemotherapy of rituximab, vincristine, doxorubicin, cyclophosphamide, cytarabine, methotrexate, ifosfamide and etoposide (R-CODOX-M/IVAC).

Conclusion: Extranodal involvement of both breast and pelvic organs is very rarely encountered in Burkitt lymphoma and should be considered in the differential diagnosis of other solid tumors. BL is a highly agressive disease, with a favorable outcome when treated with intensive multiagent chemotherapy and rituximab.

Keywords: Burkitt lymphoma, extranodal involvement, breast



Other

PS-22 **Abstract Referance: 31**

NIVOLUMAB EXPERIENCE IN REFRACTER HODGKIN LYMPHOMA

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Disease-free survival is predicted to be 50–60% in chemosensitive patients with autologous stem cell transplantation (HSCT) in recurrent/refractory patients, and 40–45% in chemoresistance patients. Approximately 50% of patients relapse after HSCT. New therapies are on the way during recurrence. We aimed to present our experience with nivolumab in a patient with refractory hodgkin lymphoma in our clinic.

A 48-year-old woman was diagnosed with stage 4B nodular sclerosis hodgkin lymphoma and was given 3 cycles of ABVD. Patient with partial response on interim evaluation, treatment completed 6 cycles of ABVD. The patient was obtained partial response and given the ice protocol as 3 cycles of salvage chemotherapy. Peripheral autologous stem cell transplantation with minimal response was performed. Brentuximab vedotin treatment was started after progression in the lymph nodes of the patient given mediastinal region radiotherapy after transplantation. Nivolumab chemotherapy was started on progress of 6 cycles of brentiksumab treatment. No significant difference was found in the third month of treatment, while the complete response was obtained at pet-ct at 6th month. Patients receiving a total of 24 doses of nivolumab are still under complete remission follow-up and treatment.

The PD-1 immun check-point pathway is preferred by tumors to avoid immun attack. Nivolumab is a fully human anti-pd1 IgG4 mAb capable of protecting anti-tumor immunity. It appears an active agent in the relaps hodgkin lymphoma.

Keywords: refracter, hodgkin lymphoma, nivolumab

Multiple Myeloma

PS-23 **Abstract Referance: 32**

ACUTE RENAL FAILURE ASSOCIATED WITH LENALIDOMIDE TREATMENT IN MULTIPLE MYELOMA: ABOUT 2 CASES

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Lenalidomide belongs to the group of immunomodulatory agents or IMIDs, it represents a major treatment of multiple myeloma.

Renal involvement secondary to Lenalidomide has recently been described.

We present two patients followed in the department of clinical hematology of the military hospital of Rabat, whose renal function was aggravated after the first cycle of treatment with lenalidomide.

Case 1: This is a 64-year-old patient followed for multiple myeloma with IgG Kappa symptomatic on bone and renal insufficiency, having received 8 cycles of the protocol (Cyclophosphamide + Thalidomide + Dexamethasone) Intensification and autografting. The patient relapsed 18 months after autograft with renal insufficiency, creatinine: 14.3 mg/l, was put under a 2nd line protocol based on (Velcade-Revlimid-Dexamethasone). The patient presented at 2 weeks of onset of treatment an aggravation of renal function with a clearance that increased from 64.3 ml/min to 27.23 mg/l requiring hospitalization to service with Lenalidomide discontinuation. Evolution was marked by improved renal function.

Case 2: This is a 74-year-old patient followed for multiple myeloma symptomatic with IgG Lambda, with renal insufficiency.

The patient received 6 cycles (Velcade-Dexamethasone) with partial response followed by 8 cycles (Cyclophosphamide-Thalidomide-Dexamethasone) with a 1-year VGPR followed by a relapse of the disease.

The patient was placed on a protocol (Revlimid-Cyclophosphamide-Dexamethasone). Worsening of renal function was noted 20 days after initiation of treatment, with a clearance of 54 ml/min at the start of treatment at 32 ml/min, requiring patient hospitalization and discontinuation of treatment.

Renal failure secondary to Lenalidomide is rare. The imputability of this adverse effect to Lenalidomide is difficult to prove given the multitude of causes of renal failure in patients with multiple myeloma.

Keywords: Lenalidomide, multiple myeloma, Renal failure

Non-Hodgkin's Lymphoma

PS-24 **Abstract Referance: 24**

MEGALOBLASTIC ANEMIA WITH MASSIVE SPLENOMEGALY AND MIMICKING LYMPHOMA: COMPLETE RESPONSE AFTER B12 REPLACEMENT

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Introduction: Megaloblastic anemia (MA) is a common disorder with varied manifestations. It generally results in mild to moderate splenomegaly which is due to sequestration of macrocytic erythrocytes in spleen. Massive splenomegaly is generally seen in infections, myeloproliferative diseases, neoplasms, storage disorders or hematological conditions; but is not heard of and has rarely been reported in MA.

Case: A 33 years old male presented with a two month history of dyspnea on exertion, easy fatiguability. He also reported a dragging sensation on her left upper side of abdomen and early satiety for 1 month. On physical examination, the patient was pale and subicteric. Spleen was palpable 10 cm below the left costal margin which was firm and non-tender on palpation. On evaluation his hemoglobin (Hgb) was 3 g/dL with MCV-125 fL (leucocyte count-2500/mm^3, platelets-38000/mm^3). Peripheral smear showed macrocytes, macroovalocytes with hypersegmented polymorphs and a few erythroblasts as well. Corrected reticulocyte count was% 0.4. Serum bilirubin was 2 mg/dl, AST: 24 IU/L, ALT: 32 IU/L, LDH: 4547 IU/L and other biochemistry was normal. Abdominal CT showed enlarged spleen (20 cm) and liver (17 cm) with no lymph nodes or any other abnormality. Vitamin B12 levels were reduced (50 pg/mL) with normal folic acid levels. In view of massive splenomegaly and anemia, bone marrow biopsy was performed and showed megaloblastoid erythroid hyperplasia and no sign of hematological malignancy. Parenteral B12 was initiated. At 2nd week of treatment, the following results were obtained: leucocyte: 3300/mm^3, Hgb: 7 g/dl, platelet: 120000/mm^3 and reticulocyte: 14%. By 1st month, Hgb was 13.2 gr/dl and LDH was normal. Serial USGs showed gradual decrease in splenic size which regressed to 11 cm after 3 months of treatment.

Conclusion: Massive splenomegaly is very rare in MA. Unchecked hyperplasia of reticuloendothelial system may fail to remove the defective erythrocytes and cause grossly enlarged spleen. Secondly, MA being a thrombotic state can cause splenic and portal vein thrombosis

leading to enlarged spleens due to abnormal blood flow. Thirdly, MA may predispose to or can have coexisting viral and bacterial infections contributing to splenomegaly.]Also, it is possible an immune mediated mechanism linked to disordered immune regulation in MA may contribute to massive splenomegaly. Once encountered with massive splenomegaly in MA, all efforts must be done to exclude other causes including lymphomas and a therapeutic trial of vitamin B12 must be given. Early identification and prompt treatment of will prevent anxiety of the patient and to help to avoid unnecessary investigations and therapies of this easily treatable condition.

Keywords: megaloblastic anemia, lymphoma, B12

Stem Cell Transplantation

PS-24 **Abstract Referance: 33**

LARGE UNSTAINED CELL PERCENTAGE AS A PREDICTOR OF EFFICACIOUS PERIPHERAL STEM CELL MOBILIZATION

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Introduction: Large unstained cells (LUC) are large peroxidase-negative cells that are displayed on automatic cell counters and present large lymphocytes, virocytes, blasts, hematopoietic stem cells and another abnormal cells. CD34 positive cell count by flow cytometry is routinely used for the prediction of successful peripheral stem cell collection. In this study we evaluated LUC number and percentage as a predictor of successful peripheral stem cell collection in patients who proceeded to autologous stem cell transplantation.

Patients and Method: LUC number and percentage has been studied for last two years in our institute. We evaluate 89 patients who were performed peripheral stem cell collection between September 2015 and November 2016. Siemens Hematek 3000 system was used for LUC count. LUC numbers and percentage was measured before leukapheresis. We used Pearson test for the correlation and ROC curve for cut off value.

Results: Patients'characteristics were shown in table-1. There was not a correlation between LUC number and mobilized CD34 positive stem cell number. But LUC percentage was positively correlated with mobilized stem cell number (p: 0.01). A count of 5x106/kg collected stem cells are optimal for autologous stem cell transplantation. We found 2% LUC percentage as a cut-off value for prediction of collecting optimal number of stem cells with 61% sensitivity and 60% specificity. As expected LUC percentage was negatively correlated with white blood cell count. There was no correlation between mobilized CD34 positive stem cell number and age. Both LUC percentage and mobilized CD34 positive stem cell number did not differ with underlying disease.

Conclusion: We found only one study in the literature that evaluated LUC percentage as a tool for the prediction of successful stem cell collection. They found that baseline LUC numbers negatively correlated with stem cell mobilization in healthy donors (1). But we measure LUC on apheresis day and found a positive correlation between LUC percentage and stem cell mobilization. And we found a cut-off value for optimal stem cell mobilization with acceptable sensitivity and specificity. In our study we demonstrate that LUC percentage measurement on apheresis day may be a very simple and cheap tool for the prediction of optimal stem cell mobilization.

References

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Keywords: Large Unstained Cells, Mobilization, Stem Cell

Table 1: Patients'characteristics

	n=
Age (median)	56 (20–75)
Sex (male/female)	56/33
Underlying disease (Multiple Myeloma/Non-Hodgkin Lymphoma/ testis tumor/Hodgkin Lymphoma)	67/14/3/5
Mobilization regimen (G-CSF/cyclophosphamide+ G-CSF/G-CSF+plerixafor/chemotherapy+G-CSF)	75/6/5/3
CD34+ stem cell count (median)	4.56 (0.51–32) x106/kg
LUC number (median)	0.55 (0.13–6.68) x109/L
LUC% (median)	2 (0.6–13.4)

Acute Myeloid Leukemia

PS-25 **Abstract Referance: 34**

A CASE WHO HAD A SUDDEN CARDIAC DEATH DUE TO ARSENIC TRIOXIDE

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Introduction: Arsenic trioxide (ATO) is an effective treatment for patients with acute promyelocytic leukaemia (APL) who have relapsed from or are refractory to chemotherapy. We discussed a patient who had a sudden cardiac death due to ATO.

A 78 years old woman with a history of breast cancer which was cured and followed with polyctemia vera since 2011 was diagnosed APL in April 2012. At the first cycle of remission induction treatment was given idarubucine and tretinoin. Then at the second cycle was given with mitoxantron and tretinoin. The patient was in remission and was treated tretinoin once every 3 months of 15 days for consolidation therapy. But she couldn't use medication regularly during consolidation. At October 2013 she relapsed and reinduction treatment was started with cytarabine and tretinoin. One month after the treatment,% 20 blasts was seen in bone marrow aspiration. ATO was initiated at

a daily dosage 0.15 mg/kg. Echocardiogram (ECHO) and electrocardiography (ECG) were performed before treatment and measurements was seen at normal range. ATO dosage has gradualley increased. During follow-up QT interval was seen in normal range too. ATO was given for 34 days, and tretinoin was given 43 days, patient didn't want to continue treatment. Then continued treatment with tretinoin once every 3 months of 15 days and this treatment overed in February 2016. The patient who was in remission has relapsed for 1 months later during the follow-up. Before the treatment perfomed ECHO ve ECG again and the measures was seen normal. ATO was initiated at a daily dosage 0.15 mg/kg. At the 12. day of ATO, patient had a cardiac pain and blood pressure decreased, after this performed an ECG and wasn't seen anything abnormal except for sinusal bradycardia. Pateint's blood oxygen level, cardiac biomarkers, d-dimer, magnesium and potassium level were in normal range. Then the patient who had cardiopulmonary arrest was intubated and cardiopulmonary resucitation was performed. Then spontaneous heartbeat is back. After the patient was stabilized, carotid, pulmonary, cardiac angiography were performed and thrombus wasn't detected. Patient was followed up in intensive care unit and was in remission while being discharged. After being discharged, t (15; 17) was negative in the test Results: Patient was in remission without treatment for 8 months than relapsed at January 2017.

ATO is an effective and potent agent used in patients with APL and produces dramatic remissions but this treatment has some serious side effects. In this case sudden cardiac death was considered to be associated with ATO. Past studies was showed possible mechanisms of arsenic cardiotoxicity include oxidative stress, DNA fragmentation, apoptosis and functional changes of ion channels. About this serious side effects close follow-up of patients about electrolyte imbalance and ECG changes during treatment is recommended.

Keywords: acute promyelocytic leukaemia, sudden cardiac death, arsenic trioxide

Stem Cell Transplantation

PS-26 **Abstract Referance: 35**

MYOPERICARDITIS ASSOCIATED WITH HIGH-DOSE CYCLOPHOSPHAMIDE AS TRANSPLANT CONDITIONING REGIMEN IN SEVERE APLASTIC ANEMIA

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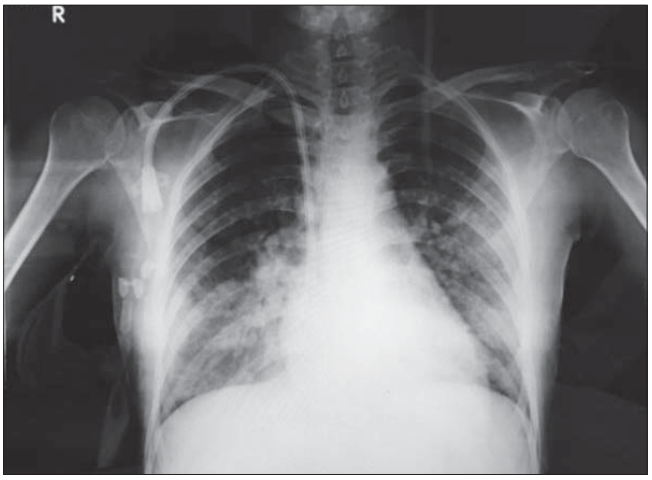
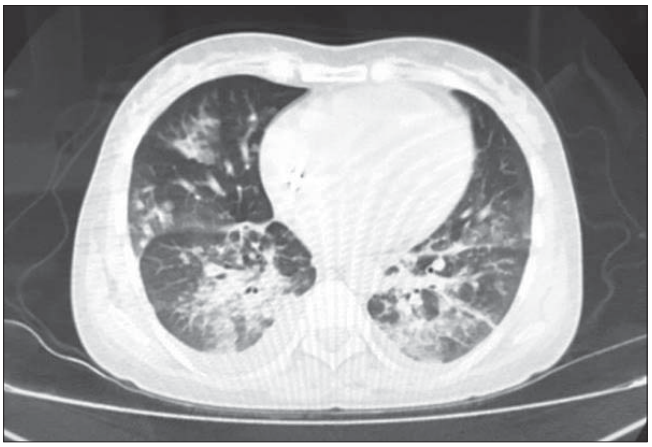
Cyclophosphamide (CPA) is a potent DNA alkylating agent. Herein, we present a case of myopericarditis resulting from the use of high-dose cyclophosphamide as the conditioning regimen (CR) in severe aplastic anemia (SAA).

31-years old female with a two-year history of systemic lupus erythematosus (SLE) was diagnosed with SAA. She had been treated with several immunosuppressive therapies for SLE including corticosteroids, mycophenolate mofetil, azathioprine and rituximab. At time of diagnosis of SAA, there was no sign of SLE activation. At 1st month of diagnosis, she underwent nonmyeloablative AHSCT from her full matched HLA-sibling male donor. Bone marrow was the stem cell source. Prior to initiation of the CR, she had no history of coronary artery disease or congestive heart failure (CHF) and had a structurally normal heart by echocardiography. The CR included CPA 50 mg/kg/day from day-5 to day-2 and ATG-F 5 mg/kg/day, 10 mg/kg/day and 20 mg/kg/day on days-3,-2 and-1, respectively. On the day of transplant, she developed dyspnea, atypical chest pain and hemoptysis accompanied by hs troponin-T elevation to 348 pg/ml (peak 435 pg/ml) and diffuse ST depression on electrocardiogram. Pro-BNP was elevated to 10736 pg/ml. Chest radiograph showed progressive pulmonary vascular distention and cardiomegaly (Figure 1). Echocardiogram evidenced a reduced ejection fraction (EF) of 42%, global hypokinesis and a high pulmonary arterial pressure of 35 mm Hg. Thoracic CT showed bilateral pleural effusion, pathcy mass lesions and ground glass opacities mostly localized to the bilateral lower lobes (Figure 2). These findings suggested worsening left ventricular function associated with high-dose CPA. Nonmechanical ventilation support was initiated for hypoxemia and acute cardiogenic pulmonary oedema. Also, Beta-blocker, corticosteroids, ACE-inhibitor and diuretic were started. After 4 days, her oxygen saturation became normal. After 7 days, hs Troponin-T and Pro-BNP decreased to 28 pg/ml and 1519 pg/ml, respectively. Repeat echocardiogram revealed an EF of 58% and mid basoseptal hypokinesis. The final diagnosis was reversible myopericarditis due to cyclophosphamide. Complete chimerism and normocellular bone marrow were detected on D28. She is still under follow-up with complete recovery of cardiac symptoms and findings.

It was reported that 5.3% of aplastic anemia (AA) patients had a history of autoimmune disease before the diagnosis of AA. Our patient was diagnosed with SAA two years after the diagnosis of SLE. Cardiotoxicity associated with high-dose CPA therapy was previously reported. Clinical presentation is the hallmark of for early recognition of CPA-induced cardiotoxicity. Acute myopericarditis will present with typical congestive heart failure symptoms, including new dyspnea at rest, elevated jugular venous pulsations, atypical chest pain, and peripheral edema. Chest radiograph often shows findings of fluid overload. In previous reports, these symptoms were often encountered after completion of a 4-day high-dose regimen, almost always within 11 days. Early diagnosis of myopericarditis on clinical presentation is critical both for treatment and prognosis, especially given the rapidly fatal course. Herein, we reported a patient who developed acute congestive heart failure and myopericarditis 2 days after completion of high-dose CPA. The diagnostic criteria presented here will guide physicians to facilitate an early clinical diagnosis.

Keywords: cyclophosphamide; severe aplastic anemia; myocarditis





Stem Cell Transplantation

PS-27 **Abstract Referance: 37**

ACUTE LUNG INJURY DURING MOBILIZATION OF PERIPHERAL BLOOD STEM CELLS WITH GRANULOCYTE-COLONY STIMULATING FACTOR

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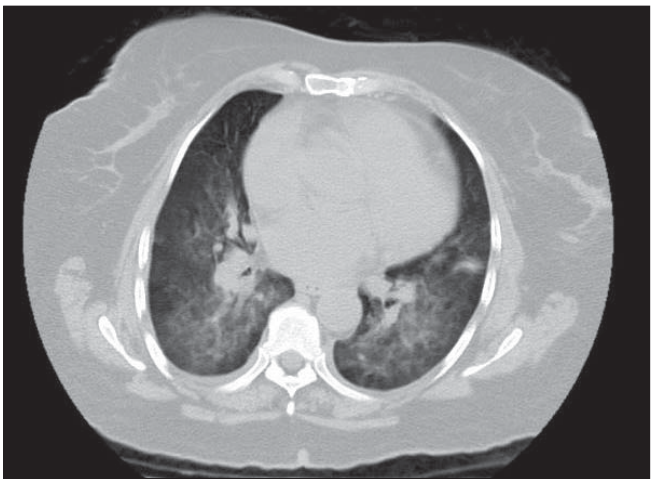
Granulocyte-colony stimulating factor (G-CSF) is commonly administered to multiple myeloma patients to mobilize peripheral blood stem cells for autologous stem cell transplantation. G-CSF-related lung injury is rare but must be considered as a possible and critical adverse event.

A 53-year-old woman was diagnosed with Durie Salmon Stage IIB, ISS Stage III IgD kappa multiple myeloma (MM). After 6 cycles of CyBorD, VGPR was obtained. She was hospitalized for mobilization of peripheral blood stem cells using subcutaneous G-CSF of 5 μg/kg G-CSF twice daily for 5 days. The patient reported no past history of respiratory or autoimmune disease. Her physical examination and chest radiography on admission were normal. At hospitalization, the following laboratory findings were obtained: white blood cell count (WBC), 5500/mm^3 (neutrophils 3800/mm^3); hemoglobin concentration (Hb), 8.8 g/dL; platelet count (Plt), 218000/mm^3; creatinin 3.7 mg/dl; serum lactate dehydrogenase (LDH), 283 IU/L; and C-reactive protein (CRP), 3 mg/L. On day 5 and 6 of G-CSF administration, a total number of 7x10^6/kg CD34 was collected. On Day 7 of G-CSF administration during routine visit, *low blood oxygen* saturation (SpO2) was noted on pulse oximeter reading. Arterial blood gas sample showed hypoxemia, with PaO2 of 51.6 mmHg in room air. Blood examination showed leukocytosis, particularly neutrocytosis, anemia, thrombocytopenia and elevated creatinine, LDH and CRP levels: WBC, 54.200/mm^3 (neutrophils 50.000/mm^3); Hb, 8.1 g/dL; Plt, 50.000/mm^3; creatinin 3.2 mg/dl; LDH, 782 IU/L; and CRP, 47 mg/L. The patient reported no symptoms or fever. Chest radiography on Day 7 of G-CSF administration revealed marked shadowy infiltrates in bilateral lung fields, particularly in the lower lobes. Chest high-resolution computed tomography (HRCT) showed diffuse ground glass opacity (Figure 1). The findings were compatible with a diagnosis of acute lung injury (ALI) attributable to G-CSF. 1 mg/kg/day methylprednisolone was begun. To exclude the possibility of acute infection, a bronchoalveolar lavage (BAL) fluid sample was collected. Bronchoscopy showed increased fragility and hemorrhage on lung tissue. BAL fluid samples excluded infections including PCP, fungal infections and tuberculosis. After 4 days of methylprednisolone administration, there was apparent regression of the infiltrative shadows on chest radiography. Chest radiography improved gradually, and arterial blood oxygen levels (PaO2) increased to normal ranges. Infiltrative shadows on chest radiography completely disappeared by Day 12 of G-CSF administration.

Adverse effects associated with G-CSF are encountered in approximately 30% of cases, including bone pain, headache, and general fatigue. Pulmonary toxicity is very rare. Pulmonary complications caused by G-CSF include cough, dyspnea, and interstitial or alveolar pulmonary edema with mild-to-severe deterioration of PaO2. Few cases of acute respiratory distress syndrome (ARDS) following G-CSF administration have been reported. The present report describes a MM patient with acute lung injury (ALI) after 7 days of G-CSF administration in whom dramatical improvement was achieved by corticosteroid therapy.

Keywords: Acute Lung Injury; Granulocyte-Colony Stimulating Factor



Multiple Myeloma

PS-28 **Abstract Referance: 38**

BONE MARROW BIOPSIES IN PATIENTS 75 YEARS AND OLDER

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Aim: Increasing numbers of bone marrow aspirates and core biopsies are done in very elderly people. The aim of this study is to evaluate the prevalence and results of bone marrow biopsies in patients over 75 years old.

Material and Method: Patients over 75 years old who underwent bone marrow biopsy between 2009 and 2016 were evaluated retrospectively. 74 patients included in the study. The bone marrow biopsy pathology reports were obtained from electronic charts. Patients were classified in two groups as benign and malign. The type of malignity and their rates were noted. The complete blood count results (CBC), vitamin B12, folate, ferritin, peripheral smear, serum protein electrophoresis and immune fixation results at the time of diagnosis were noted. The relation between these parameters and biopsy results was analyzed with chi square.

Results: 74 patients who are older than 75 years were included in the study. %58.1 of patients were male. The anemia, leucopenia, leukocytosis, thrombocytopenia, bicytopenia and pancytopenia rates were %81.1, %39.2, %10.8, %56.8, %37.8 and %25.7 respectively. While %47.3 of patients has benign biopsy results, %18.9 was diagnosed with multiple myeloma. The rates of myelodysplastic syndrom, lenfoproliferative disease, myeloproliferative disease, acute leukemia and metastatic disease rates were %9.5, %8.1, %, %6.8, %6.8 and %1.4 respectively. A relation between bicytopenia, pancytopenia and biopsy results were found (p=0.007). While the bicytopenia rate was %51.3 in malign group, the pancytopenia rate was %28.2.

Discussion: The most common indication for biopsy was one or more decreases in CBC count parameters, especially anemia. However, this indication was the least likely to yield a specific diagnosis on biopsy. The bicytopenia and pancytopenia is related with malignity and should raise a red flag. The most common diagnosis is multiple myeloma followed by myelodysplastic syndrome in elderly patients.

Keywords: Elderly, Bone Marrow Biopsy, Malignite

Multiple Myeloma

PS-29 **Abstract Referance: 39**

SEDIMENTATION RATE AND MALIGNITY RELATION IN VERY OLD PATIENTS

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Aim: The aim of this study is to evaluate the relation between sedimentation rate and malignity in patients 75 years and older who underwent bone marrow biopsy.

Material and Method: Patients over 75 years old who underwent bone marrow biopsy between 2009 and 2016 were evaluated retrospectively. 74 patients included in the study. The bone marrow biopsy pathology reports were obtained from electronic charts. Patients were classified in two groups as benign and malign. The sedimentation rate and biopsy results were noted. The relation between sedimentation rate and biopsy results was analyzed with chi square.

Results: 74 patients who are older than 75 years were included in the study. %58, 1 of patients was male. The sedimentation rates were calculated according to age. The high sedimentation rate was %59.5. While %47.3 patient was in benign group, %52.7 was in malign group. The rates of multiple myeloma, myelodysplastic syndrome, lenfoproliferative disease, myeloproliferative disease, acute leukemia and metastatic disease were %18.9, %9.5, %8.1, %, %6.8, %6.8 and %1.4 respectively. No relation has been found between high sedimentation rate and malignity (p=0.390). Also there was no relation between high sedimentation rate and malignity subtypes (p=0.616).

Discussion: Sedimentation rate is a poor marker of hematologic malignity in very old patients on the base of bone marrow biopsy

Results: The sedimentation rate rises with age, but this increase may simply reflect higher disease prevalence in the elderly.

Keywords: Elderly, Sedimentation Rate, Malignity

Other

PS-30 Abstract Referance: 40

SUCCESSFUL TREATMENT OF ACQUIRED TTP FOLLOWING MULTIPLE TRAUMATIC BONE FRACTURES, WITH TPE AND METHYL PREDNISOLONE

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Introduction: Thrombotic thrombocytopenic purpura (TTP) is a life-threatening clinical syndrome characterized by thrombocytopenia and microangiopathic hemolytic anemia (MAHA). Severe deficiency of VWF-cleaving protease ADAMTS-13 leads to the accumulation of unusual multimers of VWF which results in platelet aggregation and microthrombosis. Acquired TTP occurs by autoantibodies against the ADAMTS13. Here we report a case of acquired TTP in a trauma patient with multiple bone fractures.

Case: An 51-year-old man, construction worker, presenting with right femoral and calcaneal fractures after fall from height was hospitalized by the orthopedy department for open reduction and internal fixation. His platelet count was normal in first presentation but gradually decreased after the 4th day. At 7th day his PLT count was 31000 and he underwent the surgical procedure before checking the daily CBC

Results: Fortunately no bleeding problem was developed perioperatively. Post-op first day, hematologic consultation was requested and we assessed the patient first time. In laboratory tests; PLT: 18000, Hb: 7.0 gr/dl, LDH: 2269, PT-APTT: normal, D-Dimer: 2368, Fibrinogen: 619, Creatinin: 1.3 mg/dl and peripheral blood smear revealed 4–5% schistocytes. He had also the other components of classic TTP pentad; fever, renal impairment and neurological symptoms beside microangiopathic hemolytic anemia and thrombocytopenia. After the blood samples were collected for the measurements of ADAMTS13, total plasma exchange (TPE) was immediately started for highly suspected TTP. In the second day of TPE, his physicomotor agitation was resolved with partially recovered laboratory tests of PLT: 112000, Hb: 8.8 gr/dl and LDH: 439 Diagnose of acquired TTP was confirmed with the results of ADAMTS13 activity <0.2%, ADAMTS13 antigen: 0.04 and ADAMTS13 inhibitor titer: 57.12 U/ml. After ten consecutive days of TPE hematologic recovery was achieved with PLT: 406000, Hb: 9.4 gr/dl, LDH: 218 and no schistocytes were seen on peripheral smear. When TPE started to be performed in every other day schedule, his PLT count decreased to 158000 and LDH level increased to 331. Application for off-label use of Rituximab was made and during the approval process, methyl prednisolone therapy was administered at the dose of 1 mg/kg/day in addition to TPE. After a remarkable recovery after the first week with PLT: 538000 and LDH: 181, steroid doses were tapered and discontinued in one month. Complete hematological response is still maintaining during the third month without the need of using Rituximab.

Discussion: Although rare, acquired TTP may occur after any cause of endotelial damage like trauma and surgery and must be kept in mind in the presence of MAHA and thrombocytopenia. Early recognation is crucial and prompt diagnosis and initation of TPE is life-saving.

Keywords: acquired thrombotic thrombocytopenic purpura, bone fracture

Myeloprofilerative Disorders

PS-31 Abstract Referance: 41

A CASE OF CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML): MYELOID SARCOMA OF PROSTATE

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Myeloid sarcoma (MS) is a rare extramedullary tumor composed of immature cells of myeloid lineage that destroy the original tissue architecture in which it is found. It is most commonly identified in patients with acute myelogenous leukemia, and less often in myelodysplastic syndromes (MDSs) and other myeloproliferative disorders. It is most commonly reported in soft tissues, bone, peritoneum and lymph nodes. MS of the prostate is very uncommon with only 19 cases reported in the literature. In this case presentation MS of the prostate in a patient who was diagnosed as chronic myelomonocytic leukemia (CMML) will be discussed.

A 76 year old man had a huge left inguinal hernia and operation was planned but after they found that he had a very high white cell count he had been refered to our clinic. He had diabetes, hypertension, chronic obstructive pulmonary disease (COPD) and chronic renal failure due to nephrolithiasis. He had also had a new history of urinary frequency and hesitancy. Physical examination revealed pallor, no splenomegaly and a huge inguinal hernia. Lab: Hemoglobin 7.3 gr/dl, WBC: 85.6 mm^3/dl (neu: 52%, monocyte: 32.9%, Ly: 10.3% blast: 3%), platelet: 117000, creatinin: 3.0, LDH: 709, PSA: 42. Chronic myelomonocytic leukemia with 10% blast identifed in marrow smears. No cytogenetic anomaly was recorded. As he had a huge inguinal hernia it was very hard to reductate; for that reason he was prepared for operation by hydroxyurea and blood component supply. Additional to inguinal hernia repair; on the same operation day transurethral prostatectomy had also been performed. Microscopic examination of the protate chips showed a diffuse neoplastic proliferation through benign prostate gland. Immunohistochemically neoplastic cells were positive for CD45, CD68 and MPO, negative for PanCK, CD34, CD138, CD56, sinoptofizin, desmin, C kit, CD3, CD20, p53 and AMACR. Ki-67 was 70% positive. Myeloid sarcoma of the prostate was diagnosed. After he was discovered from the operation he was put on azasitidin 100 mgr/day for 7 days. During the follow up he had accerabation of COPD. He is still on the same treatment schema without need for urethral catherisation.

MS involving the prostate and the other urogenital organs are extremely rare and limited to case reports.

Myelomonocytic infiltration of the prostate was first reported in 1998. The definitive diagnosis is made by tissue biopsy. MS treatment consists of combining surgical intervention, with or without radiation therapy, and chemotherapy. MS; should be considered as a differential diagnosis of prostate mass in patients with a history hematological malignacies.

Keywords: chronic myelomonocytic leukemia, prostate, myeloid sarcoma

Stem Cell Transplantation

PS-32 **Abstract Referance: 42**

BIOSIMILIAR G-CSF FILGRASTIMIS AS EFFECTIVEAS A REFERENCE DRUG HOWEVER ITIS NOT AS COST EFFECTIVEAS IT SUPPOSED TO BE

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[1]*A Biosimiliar G-csf Filgrastimis As Effective As A Reference Drug However It Is Not As Cost Effective As It Supposed To Be and By The Way No Impact On The Health Care System.*

Biosimiliars are up to 1000 times the size of small molecule generic drugs and far more structurally complex. Additionally biosimiliars are manufactured in living cell lines using processes that cannot be exactly replicated from one manufacturer to the next. A biosimiliar cannot be identical to its reference biologic drug. With 67billion dollars in global sales of biologic medicines anticipated to go off patent by 2020. This lead to fast production of biosimiliar drugs. Besides, it is expected that biosimiliar drugs will be more cost effective than the reference drugs and will have a meaningful impact on health care systems around the world.

Aim: To compare biosimiliarfilgrastim (Leucostim) with two reference G-CSF filgrastim (Neupogen) and lenograstim (Granocyte) in the context of safety, efficacy and cost effectivity.

Patients and Methods: Records of patients with multiplmyeloma (MM) whom underwent autologous stem cell transplantation (ASCT) and received G-CSF sc5 mikrogram/kg/day from +day 5 until engraftment were retrospectively evaluated 60 MM patients were treated with high dose melphalan and ASCT at the Ankara University School Of Medicine Bone Marrow Transplantation Unit between 2013 and 2016. The median age was 59 (38–75 years) with 55% male. Patients were divided into three groups (n=20) whom received reference filgrastim (Neupogen), lenograstim (Granocyte) and biosimiliarfilgrastim (Leucostim): groups A, B and C respectively. The total cost of each G-CSF in dollars was calculated by one package of G-CSF multiplied by total used days. Chi-square, Mann-Whitney U and Kruskal-Wallis tests were used for analyses of variance.

Results: The percentage of patients who received melphalan 200 mg/m2 were% 80, 85, 80in groups A, B, C respectively (p=0.9). There was no statistically significant difference between the engraftment day of neutrophil 500 and 1000; platelet 20.000 and 50.000 in the groups. (p=0.07, p=0.55, p=0.33, p=0.81 respectively) Themedian numbers of G-CSF administered days were 7 (5–18), 8 (5–12), 7 (4–16) in groups A, B, C respectively. Eventhough there was no statistical difference between the numbers of days (p=0.23), the total cost in dollars was statistically difference between A vs B and C vs B (both p<0.0001) and there was no statistical difference between A vs C (P=0.89), total cost in dollars as follows: 155$ (112–288$), 416$ (260–624$) and 166$ (81–250$) for the group A, B and C respectively.

Conclusion: Our results demonstrate that biosimiliar GCSF Leucostim is highly similar to existing licenced biologic products in Turkey with no clinically meaningful difference interms of safety and efficacy. On the other hand it as a biosimiliardoes not have a meaningful impact on the cost savings to the health care system as expected when compared with reference filgrastim.

Keywords: Biosimliar,, G-CSF, filgrastim

Acute Lymphoblastic Leukemia

PS-33 **Abstract Referance: 43**

PTEN AND AKT1 GENE VARIATIONS IN CHILDHOOD T-ALL PATIENTS

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The PI3K/Akt/mTOR pathway regulates several cellular functions that are also critical for tumorigenesis, including proliferation, growth, survival and mobility. PI3K/Akt/mTOR pathway is found deregulated in a variety of tumors including leukemia. Targeted deep sequencing techniques are now helping us to clarify the molecular background of the leukemia. In this study, two major members of PI3K pathway, *PTEN* and *AKT1*, genetic variations and gene expression patterns were evaluated in the prognosis of childhood T-ALL patients. In total diagnostic samples of 50 childhood T-ALL patients, who are treated with BFM protocol were included the study. Hotspot regions of *PTEN* (exon 7 and 8) and *AKT1* (exon 2) genes were examined by using targeted next generation sequencing (454 FLX GS Junior). The gene expression levels of *PTEN* and *AKT1* genes were also analysed by quantitative real time PCR (qRT-PCR). Obtained genetic variation was compared to the clinical findings and outcomes of the T-ALL patients. Among 50 T-ALL cases, 3 patients (p. Q261*, p. R233Pfs*7 and p. Q214Rfs*11) were found to be mutated (6%) in the coding region of *PTEN* gene and in 10% of the cases a known intronic variation (rs2494748, rs2494749) of *AKT1* gene was detected. 20% of the T-ALL cases showed decreased *PTEN* mRNA expression (p=0.15) and the levels were higher in immature and cortical stage phenotype compared to mature phenotypes. *PTEN* expression levels were also found

reduced in the patients who had no steroid response and relapse. On the other hand *AKT1* mRNA expressions were increased compared to healthy thymocytes (p=0.01). Also patients who had high *AKT1* expression showed a worse disease free survival (RFS). Here we study the mutation and expression status of *PTEN* and *AKT1* genes in T-ALL patients. We found that *PTEN* mutations affect the level of *PTEN* mRNA expression and *AKT1* gene was significantly up-regulated in our cohort. These findings might be beneficial for the prediction of therapy response in the patients who are mutated for *PTEN* and *AKT* genes or different mRNA expression levels.

The present work was supported by the Research Fund of Istanbul University (Project No. 48185) and Istanbul Development Agency, Investment in the future: Project of BIOBANK (Project No: TR10/15/YNK/0093)

Keywords: leukemia, PTEN, AKT1, next generation sequencing, variation

Acute Myeloid Leukemia

PS-34 **Abstract Referance: 44**

A CHRONIC MYELOID LEUKEMIA PATIENT WITH BEHCET'S DISEASE

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Behcet's disease (BD) is a chronic, relapsing vasculitis of unknown etiology. Its association with chronic myelogenous leukemia (CML) is extremely rare. Here we reported a CML patient with BD.

He was 43 years old man. He was referred to our center with anemia and high white blood count (WBC). He had history of oral aphthae, genital ulceration and folliculitic skin lesions. The laboratory test were like that WBC: 28 000/mm^3 Hob: 11.6 gr/dl Plt: 119 000/mm^3, Ph chromosome was 100% in FISH analyses. Imatinib and colchicum treatments were started. The symptoms related to BD were disappeared after 3 months treatments. He has complete molecular response.

Thera are a few reported BD with CML, mostly in interferon area. There is no data whether tyrosine kinase inhibitors effects the outcome or symptoms of BD. Further studies are needed to get better understanding

Keywords: CML, Behcet's Disease

Stem Cell Transplantation

PS-35 **Abstract Referance: 45**

OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR HODGKIN AND NON-HODGKIN LYMPHOMA: SINGLE CENTER EXPERINCE

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Introduction: Allogeneic stem cell transplantation (alloSCT) is an option for young and fit patients with relapsed/refractory (R/R) lymphoma who were heavily pre-treated disease or after the failure of autologous stem cell transplantation (ASCT). For patients with R/R non-hodgkin lymphoma (NHL) or hodgkin lymphoma (HL) after initial chemotherapy or ASCT can cure between 20–60%. Relapse after ASCT is associated with a poor prognosis and limited therapeutic options. AlloSCT is a potentially curative therapy for lymphomas which have relapsed after AHCT.

Methods: In this study, we evaluated 14 patients with HL and NHL who had treated with alloSCT between November 2014 and January 2017 in Ege University adult hematology transplantation unit. Overall survival (OS) was measured from the date of transplant to the date of death or with censoring at the date of last follow-up. Disease free survival (DFS) was measured from the date of transplant to the date of disease progression or the date of death.

Results: There were 8 (57.1%) males and 6 (42.9%) females with a median age 41.5 (range, 20–56) years at the time of alloSCT. Five (35.7%) had HL and 9 (64.3%) had NHL. Histologic subtype of NHL was evaluated as T cell lymphoma (66.7%), mantle cell lymphoma (11.1%), diffuse large B-cell lymphoma (DLBCL) (11.1%) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL (11.1%). All histologic subtype of HL was determined as nodular sclerosis. The median number of prior treatment before alloSCT was 3 (range, 1–4). Nine (% 64.3) patients had prior ASCT. Ten patients had refractory disease, 2 patients were in complete remission (CR) and 2 patients were in partial remission (PR) before alloSCT. The median time from diagnosis to alloSCT was 22 (range, 8–144) months. Peripheral stem cell was used for stem cell source in all of them. The median CD34-positive cell count was 6.33 × 106/kg (range, 4.17–10× 106). Patients received alloSCT from matched related donor (n= 10), matched unrelated donor (n= 3) and mismatched donor (n= 1). Non-myeloablative regimens were preferred more frequently as conditioning regimens (non-myeloablative% 64.3, myeloablative% 35.7). Fludarabine plus total body irradiation plus cyclophosphamide was the most commonly used for conditioning regimen as non-myeloablative. Neutrophil engraftment was occurred median of 15 (range, 10–21) days. Graft versus host disease (GVHD) prophylaxis was applied all of them as cyclosporine plus methotrexate (n=12), cyclosporine plus mycophenolate mofetil (MMF) (N=1), tacrolimus plus MMF (N=1). GVHD was occurred in 64.3% of them (44.4% acute GVHD, 44.4% chronic GVHD and 11.2% both of them). Venoocclusive disease (VOD) was occurred in 1 patients who received prophylaxis for VOD. Transplant related death was observed in 3 patients. Nine patients were evaluated in CR, 1 patient in PR and 1 patient in stable disease after alloSCT. OS and DFS were evaluated as median 6.5 (range, 0–22) and 4.5 (range, 0–22) months, respectively. Five patients are alive without disease.

Discussion: In recent years, the increased options of treatment for lymphoma especially the use of targeted therapies had improved life expectancy. However R/R lymphoma or after the failure of ASCT have poor prognosis. In this group alloSCT may be the only curative approach. The patient group should be selected well because of the risk of transplant-related mortality.

Keywords: hodgkin lymphoma, non-hodgkin lymphoma, allogeneic Stem Cell Transplantation

Other

PS-36 Abstract Referance: 46

THE EFFECTS OF MCP-1A251G AND CCR2V641 GENE POLYMORPHISMS IN THE PATIENTS WITH MYELODYSPLASTIC SYNDROME

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Background: Myelodysplastic syndromes (MDS) are a group of hematologic malignancies of bone marrow characterized by morphologic and functional abnormalities in hematopoietic stem cells and with various degrees of cytopenias in peripheral blood. It is with one or more cytopenias depending on bone marrow dysfunction. Chemokines are the cytokines that help the leukocytes and stem cells for chemotaxis in case of inflammation and homeostasis.

Purpose: In this study we aim to investigate the polymorphisms of MCP-1A251G and CCR2V641 genes in MDS. These genes were related with solid tumors but have not been studied in MDS yet.

Methods: Thirty-nine MDS patients were included in this study and compared with 110 healthy volunteers.

Results: There was a significant difference between patient and healthy groups in frequencies of MCP-1A251G genotypes and gene alleles (p: 0.001 and p: 0.0002). But there was no difference in CCR2V641 genotype (p>0.005).

Also the frequencies of MCP-1 AA genotype were higher in MDS patients versus healthy controls. The individuals with MCP-1 AA genotype have five-fold increased risk for the development of MDS (p: 0.000; x^2:13.60; OR: 5.30; % 95 CI: 2.05–13.66).

The frequencies of MCP-1 AG and MCP-1 G+ genotypes were higher in healthy controls versus MDS patients (p: 0.002; x2:9.39; OR: 0.24; % 95 CI: 0.094–0.62 and p: 0.000; x2:13.60; OR: 0.189; % 95 CI: 0.073–0.48).

Conclusion: The genotypes of MCP-1AA have higher risk for MDS but MCP-1 AG and MCP-1 G+ were significantly higher in healthy population and may have a protective role versus the development of MDS. Our study was the first study investigating the role of MCP-1A2581G and CCR2V641 gene polymorphism in MDS population. These effects should be further studied in larger group of patients for determining the exact role of these genes.

Keywords: Myelodysplastic syndrome, Chemokines, Gene polymorphism

Figure.1.The frequencies of MCP-1A2518V genotypes

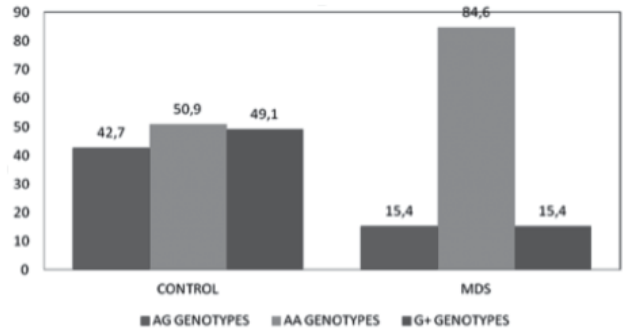

Table.1. Baseline Characteristics

	Healthy (n =110)	MDS (n =39)	p-value
Median age, years	69,02±4,97	68,48±9,71	0,658
Female/Male	48/62	22/17	0,170
MDS subtypes (WHO)		(%)	
MDS-U		2,6	
RA		30,8	
RAEB-1		10,3	
RAEB-2		5,1	
RA-IZOLEDEL5Q		5,1	
RARS		10,3	
RCMD		33,3	
RCUD		2,6	
Cytogenetic Evaluation			
11Q23(DEL)		2,6	
46XX		33,3	
46XY		5,1	
46XX		7,7	
46XY		30,8	
47XX+8		2,6	
ADD(1)P32-36[18]		2,6	
DEL(11)(Q13Q23),DER5,DER1		2,6	
DEL(20)(Q11,2)		2,6	
DEL(5)(Q31Q35)+8,-18		2,6	
DEL5(Q12Q33[16]		2,6	
DEL5Q		2,6	
Not available		2,6	
IPSS			
0		34,8	
0,5		47,8	
1		8,7	
1,5		4,3	
2		4,3	

Table.2. Distribution of genotype frequencies in control and MDS groups

Polymorphism	Control (n:110)		MDS (n:39)		P-value
	N	%	N	%	
MCP-1A2518G					
AA	56	50,9	33	84,6	0,001
GG	7	6,4	0	0	
AG	47	42,7	6	15,4	
A	159	72,27	72	92,3	0,0002
G	61	27,72	6	7,69	
CCR2V64I					
GG	85	77,3	32	82,1	0,330
AA	6	5,5	0	0	
GA	19	17,3	7	17,9	
G	189	85,90	71	91,02	0,24
A	31	14,09	7	8,97	

Chronic Myeloid Leukemia

PS-37 **Abstract Referance: 47**

A CML PATIENT WITH SECONDARY CANCER

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Treatment of chronic myeloid leukemia (CML) has been profoundly improved by the introduction of tyrosine kinase inhibitors (TKIs). Long-term survival with TKIs is excellent with a 8-year survival rate of ~88%. Long-term toxicity of TKI treatment, especially carcinogenicity, has become a concern. Here we presented a CML patient with secondary cancer.

He was 60 years old man. He was referred to our center with fatigue and high white blood count (WBC). He had no chronic disease history. The laboratory test were like that WBC: 79 000/mm^3 Hob: 7.6 gr/dl Plt: 368 000/mm^3, Ph chromosome was 100% in FISH analyses. Imatinib treatment was started. Due to muscle cramps and bone pain after 1 month imatinib was stopped and nilotinib was given. But muscle cramps and bone pain still continued after nilotinib treatment and dasatinib was started. After 3 months BCR-ABL was negative. Four years later cough started and there was a mass in lung X-ray. Biopsy from that mass revealed squamous cell carcinoma. Chemotherapy was started.

There is insufficient data to assess that there is an increased risk of developing SM after TKI therapy as well as to elucidate the mechanisms through the drug can facilitate carcinogenesis. CML patients are simply more carefully monitored than the average population for secondary cancer. Moreover, further molecular studies evaluating carcinogenicity of TKIs would be useful.

Keywords: CML, SECONDARY CA

Acute Lymphoblastic Leukemia

PS-38 **Abstract Referance: 48**

DOES TUBB2A EXPRESSION HAVE A PROGNOSTIC EFFECT IN CHILDHOOD T-ALL PATIENTS

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Introduction: Microtubules that take part in several cellular functions like cell shape, motility and intracellular trafficking are important components of cytoskeleton. Since microtubules are involved in the formation of mitotic spindle within proliferating cells they are among targets of anticancer agents. Tubulins are found in cells as different isotypes and in human there are several genes encoding α-and β-tubulins. In this study, microarray data consisting of childhood T-ALL and control group of thymocytes was evaluated for differential gene expression of tubulin transcripts, particularly TUBB2A and its clinical correlation.

Material and Method: Microarray data generated by our research group (GSE46170, T-ALL n= 31, thymocyte subset n= 7) was used for differential gene expression analysis. Data normalization, fold change and adjusted p value calculations were performed in R 3.3.2. Cohort of 51 T-ALL patients who were treated with BFM protocol, with mean age = 9, 38 male and 13 females and mean 100 000 WBC count at diagnosis were included the validation study. The mRNA expression of TUBB2A was evaluated by qRT-PCR.

Results: Differential gene expression analysis showed that TUBB2A was significantly increased in T-ALL patients compared to control group of thymocyte subsets. None of the other tubulin isotypes were found to pass adj. $p < 0.05$ threshold. qRT-PCR was performed to validate TUBB2A's expression in a separate childhood T-ALL cohort and found to be increased by 2.8 fold in T-ALL patients compared to thymocyte subsets (p= 0.0012 by Mann Whitney test). In the normal T-cell development we identified that the mature cells express higher levels of TUBB2A than immature stage cells. CD3 (-) T-ALL cases showed significantly higher levels of TUBB2A expression compared to CD3 (-) healthy controls (p=0.02). The patients with higher TUBB2A expression levels showed worse overall survival rates and the cox regression analysis showed a significant correlation with relapse (p=0.018) and day 33 response (p=0.011).

Conclusion: TUBB2A protein is one of the important members of microtubule structure and found significantly high in T-ALL cases. There could be two major consequences of this finding; firstly, microtubule organization is strictly in balance and malign transformation destroys the balance. Since vinca alkaloids that used in the standard treatment protocols are a set of anti-mitotic and anti-microtubule alkaloid agents, in line with our findings TUBB2A expression might predict the treatment response

Keywords: Microtubules, T-ALL, expression, prognosis

Chronic Lymphocytic Leukemia

PS-39 **Abstract Referance: 49**

IBRUTINIB EXPERIENCE IN RELAPSED/ REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND MANTLE CELL LYMPHOMA

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Introduction: Bruton tyrosine kinase (BTK) is a critical signaling molecule in the B-cell receptor signaling pathway and functions. Ibrutinib is a new and first agent that is BTK inhibitor. It is approved for the treatment of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia. Ibrutinib is frequently used (single agent or in combination) in the relapsed and/or refractory CLL or MCL. We evaluated safety and efficacy results of ibrutinib in limited patients groups.

Methodology: In this case series, we evaluated retrospectively 12 relapsed and/or refractory CLL/SLL and MCL patients who were used single agent as ibrutinib between October 2015 and January 2017 in Ege University Hematology department.

Results: Patients were identified that CLL was 8 (66.6%) and MCL was 4 (33.4%). Eleven of them were male, 1 was female. The median age was 63 (range, 38–83) years. All of MCL patients had advanced stage. Four patients had stage 4, 1 patient had stage 2 and 2 patients had stage 1 as RAI staging system in group of CLL. One patient had 17p deletion in CLL. All patients received least 1 prior treatment before ibrutinib. The median line of ibrutinib was 4 (range, 2–7). Patients received continuous oral ibrutinib daily as 420 mg per day for CLL and 560 mg per day for MCL. The median duration of treatment for ibrutinib was 4.5 (range, 1–12) months. During the treatment, side effects were observed in 5 patients. Four patients had hematologic side effects, 1 of them with grade 3 thrombocytopenia, grade 2 anemia, grade 3 neutropenia who died because of pneumonia and 1 of them with grade 3 neutropenia. Lymphocytosis was observed in 2 patients in the first cycle. Non-hematological side effects were observed in 1 patient due to the subarachnoid hemorrhage (grade 4). The adverse events rate was 41.6%. During the follow-up, 3 patients had progressive and 1 patient had stable disease under ibrutinib treatment. The overall response rate (ORR) was 50%. The median overall survival (OS) after ibrutinib and event free survival were 7 (1–18) and 3.5 (0–12) months, respectively. Nine patients (62.5%) are still alive. Treatment related mortality was occurred in one patient.

Conclusion: Ibrutinib is a new agent that has demonstrated efficacy and safety in recurrent/refractory B-cell malignancies. There are publications reporting ORR as 68%. Our clinical experience had a limited number of cases and our data were low OS according to the literature. Our profile of side effects was consistent with the literature. In our case, grade 3 or higher bleeding was reported as 6% in the literature and it is a serious side effect of the newly used agent. Although overall response rate was lower than literature, ibrutinib is seems as a safe and effective agent in relapsed/refractory CLL and MCL.

Keywords: ibrutinib, mantle cell lymphoma, Chronic Lymphocytic Leukemia

Non-Hodgkin's Lymphoma

PS-40 **Abstract Referance: 50**

IBRUTINIB EXPERIENCE IN RELAPSED REFRACTORY MANTLE CELL LYMPHOMA

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Mantle cell lymphoma (MCL), one of the B cell non-Hodgkin lymphomas (NHL), has a variable course. Therapy for MCL is not curative and virtually all patients will have refractory or recurrent disease. We aimed to present the response obtained with ibrutinib therapy in relapsed refractory patient who received 4 serial of treatment beforehand.

A 60-year-old man who was diagnosed with stage 4 B-mantle cell lymphoma was treated with 6 cycles of R-CHOP and 2 cycles of Rituximab therapy. Relapse developed in the patient who remained in remission for 3 years. Autologous transplantation was planned after salvage chemotherapy (R-DHAP). The patient was diagnosed with an abdominal aortic aneurysm during autologous transplant preparations, then operated. After operation he relapsed again. Bendamustine, gemcitabine, fludara-based 3 series of treatment was given but did not respond despite treatment. Emergency radiotherapy was given to the patient who developed mediastinal conglomerate lymph nodes causing vena cava superior syndrome during follow up. Treatment of ibrutinib in the patient who did not respond to standard chemotherapy, whose blastoid variant transformation was detected in the investigations. On the third day of treatment, a dramatic response was obtained in the lymph nodes and in the performance of the patient. Evaluation of the third-month response revealed a reduction of % 75 in lymph nodes and improvement in the pancytopenia pattern. The patient is stil being followed.

Targeted agents instead of standard cytotoxic therapies offer promise in the treatment of MCL. Ibrutinib, which is a Bruton's tyrosine kinase inhibitor, is one of these.

Keywords: ibrutinib, refractory, relapse

Chronic Lymphocytic Leukemia

PS-41 **Abstract Referance: 51**

CHRONIC LYMPHOCYTE LEUKEMIA AND ACUTE MYELOID LEUKEMIA TRANSFORMATION

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Introduction: Secondary malignancies may occur during chronic lymphocyte leukomia (CLL) illness and also treatment. After FCR treatment, secondary malignancy can be seen more frequently and Fludara is most accused of these agents. There are AML, ALL, and MDS among secondary malignancies, but AML is rare. In our case diagnosed with CLL, we wanted to share our AML transformation experiment.

Case: A 69-year-old woman with a diagnosis of CLL who developed treatment indications in 2001 had 4+ direct coombs positivity and anemia during the diagnosis. Between 2001 and 2016, she received chemotherapy of chlorambucil, cyclofosfomid and CVP at different times. She did not receive fludarabine treatment due to direct coombs positive autoimmune hemolytic anemia. She also did not complete the chemotherapy with the reason of incompatibility. She applied with anemia and deep thrombocytopenia in 2016. Bone marrow biopsy pathology; conformed to CLL infiltration. Bone marrow FISH was evaluated as 17p negative, 11q positive and 13q positive. 6 cycles of R-CVP applied. Pancytopenia developed after treatment. A control bone marrow biopsy was performed on the basis that there was no improvement in the cytopenia of the patients. Pathology; CLL involvement. Bendamustine chemotherapy was administered to the patient who was treated with primary refractory CLL.

Pansitopenis deepened further. A blast rate of 60% was detected in the peripheral spread of the patient and flow cytometry was concluded in agreement with AML.

Discussion: Secondary malignancies associated with primary or treatment related of CLL may be seen. The most important agent responsible for the secondary malignancy is fludarabine. In our case, fludarabine is not used and the use of short-acting alkylating agent may be a cause for the development of secondary AML. AML transformation; The primary may be in the course of CLL, or the treatment may have developed in the second.

Keywords: CLL, FLUDARABINE, AML transformation

Acute Myeloid Leukemia

PS-42 **Abstract Referance: 52**

EXTRAMEDULLARY RELAPSE OF AML PRESENTED WITH ORBITAL, TESTICULAR, RETROPERITONEAL, GINGIVAL GRANULOCYTIC SARCOMA

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Myeloid sarcoma also known as granulocytic sarcoma (GS) or chloroma is an extramedullary (EM) tumor of immature myeloid cells. The most common sites of GS are soft tissue, bone, periosteum, and lymph nodes. Central nervous system (CNS) involvement is rare. Isolated EM relapse is rare and often heralds systemic relapse. Here we report a case of several isolated extramedullary relapses during the AML treatment/follow-up period. A 21-year-old man diagnosed as 46-XY AML M5, in 1996, and treated with 2 cycle idarubicin (Id) and Cytosine Arabinosid (CA) induction + 3 cycles high dosage CA consolidation regimen. Bone marrow was in remision with <1% marrow blast at the end of the treatment. In 2010 gingival mass biopsy reported as GS but get in remission after gingival surgery. In 2015 patient admitted with jaundice and impaired liver function tests PET-CT revealed retroperitonel/pancreatic/unilateral testiculary involvement. Pancreatic biopsy and Testis spacemans reported as GS (CD34 (+), MPO (+) diffuse blastoid infiltration). Bone marrow blasts were <% 1 in 2010 and 2015.2 cycles Ida-CA induction regimen given after unilateral orchiectomy. In March 2016 allogenic hematopoietic cell transplantation (HCT) with TBI/Cyclophosphamid conditioning regimen performed after remission. Diplopia + Orbital swelling developed 7 months after HCT during immune suppressive (IS) tapering period without any GVHD. Cranial MR imaging + PET-CT revealed 3 cm contrast enhanced orbital mass lesion with SUV-Max: 7.9. Orbital mass resected and reported as GS relapse while bone marrow examination showed off myeloid blasts <1% and 100% donor chimerism. The incidence of GS after HCT has been reported to be 0.2%-1.3%. The outcome of these patients is poor, and there is no standard treatment guideline. Donor Lymphocyte Infusion (DLI), Impaired Field Radiotherapy (IFRT), systemic high dosage chemotheraphy, hypomethilating agents, clinical trials considered as treatment alternatives. We tapered IS and after 2 cycles FLAG regimen + IFRT patient is still in remission without any GVHD/visual impairment. Myeloid blasts were <1% and donor chimerism was 100% in bone marrow examination so that we didn't prefer to treat with DLI.

Keywords: AML, Sarcoma, Extramedullary, Orbita, Pancreas, Testis, Retorperiton

Other

PS-43 **Abstract Referance: 53**

A RARE LEUEKEMIA TYPE IN CHILDHOOD: LARGE GRANULAR LYMPHCYTIC LEUKEMIA

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Large granular lymphocytic leukemia (LGL) is a chronic leukemia type that is more commonly seen among adult age group, which may sometimes present with a more agressive course. Autoimmune diseases may accompany in upto 40% of the LGL cases and the median age of diagnosis has been reported as 60 years. On the other hand, LGL is extremely rare in childhood.

Herein, we present a 5 year-old boy presented with lymphocytosis, hepatosplenomegaly and autoimmune hepatitis and was diagnosed to have LGL.

The personel history revealed an otherwise healthy boy upto 4 years of age who was found to have hepatosplenomegaly during a routine visit. The hemaogram revealed Hb 9.3 g/dl, Hct 33.5%, MCV 65 fl, WBC 37x109/L, platelets 172x109/L with peripheral blood smear containng 78% of large granular lymphocytes. Since persistent hypertransaminasemia was detected liver biopsy was performed and pathology was compatible with autoimmune hepatitis. The diagnosis of T cell-LGL was confirmed with flow cytometry and positive TCR-rearrangement indicating clonality. After the initiation of steroid treatment leukocytosis and hypertransaminasemia subsided and hepatosplenomegaly subsided.

The diagnosis of LGL should be considered in patients with absolute lymphocytosis, splenomegaly, associated autoimmune disorders and the diagnosis can be confirmed with the positive clonality.

Keywords: pediatric, large granular lymphocytic leukemia

Non-Hodgkin's Lymphoma

PS-44 **Abstract Referance: 54**

IMMUN THROMBOCYTOPENIA IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENT FOLLOWED BY REMISSION AFTER AUTOLOGOUS TRANSPLANTATION

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Non-hematological autoimmune disorders are occasionally associated with malignant lymphoma but autoimmune thrombocytopenia is rare in patients with malign

lymphoma. Active lymphoma and immuno-thrombocytopenia are more common in the literature. We aimed to present immun trombocytopenia in a diffuse large b-cell lymphoma patient followed up in our clinic in remission after transplantation.

A 36-year-old man with stage 4B diffuse large b-cell lymphoma (with lung involvement) underwent partial remission after 6 cycles of R-Chop chemotherapy and completed 8 cycles. Partial remission was obtained on response evaluation. Peripheral autologous stem cell transplantation was performed with TEAM (thiotepa-containing protocol) protocol with partial response after 4 cycles of ICE salvage chemotherapy. Was assessed in a partial remission on the third month response evaluation. Deep thrombocytopenia developed at 10th month. We excluded the active disease with PET-CT and excisional biopsy from available lymph nodes. No involvement in bone marrow biopsy. Immune thrombocytopenia was considered in a patient with normal cytogenetic and MDS panel without any other organic cause to explain thrombocytopenia. In the patient resistant to steroid treatment, a complete response was obtained after 4 weeks of rituximab therapy.

More than 30% recurrence is observed in DBBHL patients during follow-up. Immunopathologies should be considered in cases of post-transplantation cytopenia. At this point, rituximab treatment seems to be an effective agent.

Keywords: Immun thrombocytopenia, lymphoma

Non-Hodgkin's Lymphoma

PS-45 **Abstract Referance: 56**

PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA LOCALIZED TO THE NASAL CAVITY AND LACRIMAL SAC

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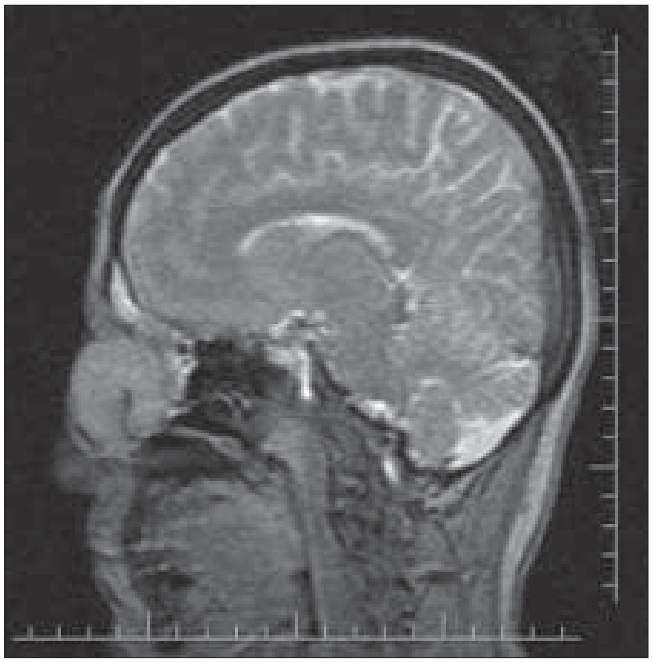
Introduction: Diffuse large B-cell lymphoma (DLBCL) represents a heterogeneous disease that depends mainly on the primary site of involvement. Patients with DLBCL that arises in many different sites. In contrast to lymphomas of the Waldeyer ring or paranasal sinuses, which are predominantly diffuse large B-cell lymphomas, nasal lymphomas are mainly of a natural killer (NK)/T-cell origin. Primary nasal cavity and lacrimal sac DLBCL is extremely rare. We aimed to present a case of a DLBCL originating within the right orbit, specifically within the lacrimal sac laining to nasal cavity, which is a rare and atypical presentation.

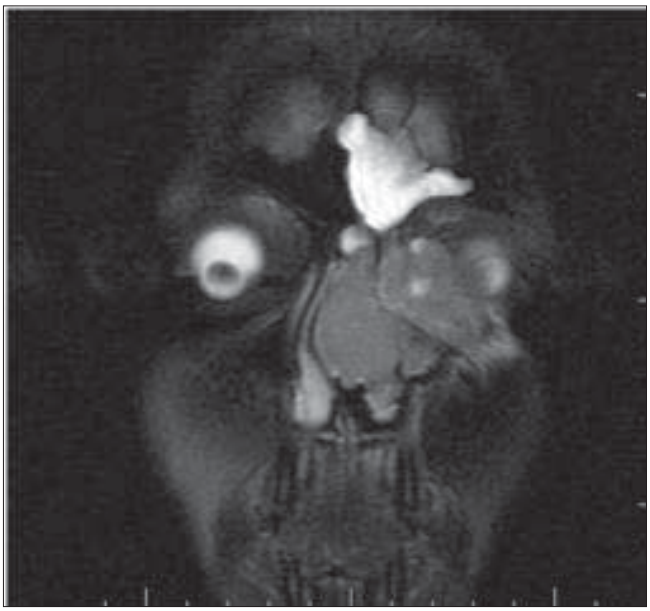
Case Report: 18 years old woman who has been on lactation for two months and an unremarkable past medical history, presented with epiphora, nasal obstruction and a growing mass on her left eye for 2 weeks. She denied any nasal pain, epistaxis, visual disturbances or numbness. she denied any systemic or B symptoms. The physical examination reveals mass which is obliterating the nasal cavity on the superior region. MRI exam shows a 45*35*34 mass, which is expanding the nasal septum and skin, started from the lacrimal sac and laining to nasal cavity, destructing the orbital bone. (Fig-1.2) During the tumor excision, a capsularized heterogenous pink soft mass over the lacrimal sac, infiltrating the orbital bone was observed. The lacrimal sac was totally removed. The pathological results revealed a diffusely infiltration of medium-size to large neoplastic cells with a high mitotic activity. The immunohistochemical stains showed the characteristics CD20 (+), BCL-6 (+), CD3 (−), CD5 (−), and CK (−), compatible with the diagnosis of diffuse large B cell lymphoma. A whole-body fludeoxyglucose (FDG) positron emission tomography scan demonstrated increased FDG uptake in the inferior medial aspect of the left orbital cavity, starting from the ethmoidal sinus, laining to nasal cavity. (SUV-max: 33) Posterior nasopharynx wall demostrated an increased FSG uptake. (SUV-max: 20). (Fig-3) A bone marrow examination revealed no bone marrow involvement. Stage IIAE, low IPI score DLBCL NHL was diagnosed and R-CHOP treatment with intratecal prophylaxis was started.

Discussion: Most of the malignancies in the sinonasal tract are epithelial carcinoma. For the lymphoma subtypes, the nasal cavity is the predominant site of involvement in T-cell and NK/T-cell lymphomas, whereas sinus involvement without nasal disease is more common in B-cell lymphomas. According to previous case reports and small studies, the vast majority of nasolacrimal lymphoma can be seen with advanced stage disease and in elderly patients with 2/1 male/female ratio. Adversely, our patient is a young female adult, and nasolacrimal involvement accompanies with early stage disease.

In conclusion, malignant lymphomas of the lacrimal sac are rare and they can mimic other diagnosis. A differential diagnosis using neuroimages and biopsy is essential in making an accurate diagnosis. The current treatment of choice for lacrimal sac DLBCL is the R-CHOP regimen.

Keywords: diffuse large b cell lymphoma, lacrimal sac, nasal cavity





Stem Cell Transplantation

PS-46 **Abstract Referance: 59**

IMMUNE HEMOLYTIC ANEMIA RELATED TO IMATINIB MAINTANENCE AFTER ALLOGENEIC TRANSPLANT IN BLASTIC CHRONIC MYELOID LEUKEMIA

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Introduction: Taking into account the high relapse rates up to 30% to 40% in accelerated or blastic phase chronic myeloid leukemia (CML) after allogeneic hematopoietic stem cell transplantation (AHSCT), posttransplant monitoring and prophylactic or therapeutic strategies in this setting continue to gain more importance. Imatinib mesylate showed adequate efficacy and acceptable tolerance in patients with CML after AHSCT. Herein, we report a rare patient presenting with immune hemolytic anemia associated with imatinib mesylate after AHSCT.

Case: A 54-year-old man was diagnosed with blastic phase CML. He was treated with imatinib and 7+3 induction therapy followed by 2 courses of intermediate dose ARA-C consolidation. Subsequently, he underwent myeloablative peripheral blood stem cell transplantation (PBSCT) (Flu, Bu, ATG-F as conditioning regimen) from his full matched HLA-sibling female donor. At time of PBSCT, he was in first molecular, cytogenetic and hematological remission. Full donor chimerism was detected at the 1st and 3rd month of AHSCT. Since the initial presentation of disease was advanced phase CML, imatinib maintanence was started at 3rd month. Imatinib was started as low dose (200 mg/day) and increased to 300 mg/day and 400 mg/day after 2 weeks and 4 weeks, respectively. After three months, he presented with anemia (Hb: 7.1 g/dl, reticulocyte count: 9% and haptoglobin: 8 mg/dl). Direct antiglobin test (DAT) was positive for IgG. Autoimmune markers and cancer screening tests were negative. The final diagnosis was immune-mediated hemolytic anemia induced by imatinib mesylate and methylprednisolone (MP) 1 mg/kg/day was initiated. After one week, his Hb level rose to 10.4 g/dl. MP was progressively decreased as the Hb level increased. One month after the initiation of MP, the patient's Hb level was found to be 12.9 g/dl. Yet, the Hb level was not sustained and decreased to 9.2 g/dl after two months. Imatinib was discontinued and the maintanence treatment was switched to dasatinib. Dasatinib was started as a dose of 70 mg/day. After one week, Hb level was increased to 12.1 g/dl. The dose of dasatinib was increased to 140 mg/day. Hb level was sustained. DAT became negative. He still maintains complete chimerism and complete cytogenetic, molecular and hematological response. At his last follow-up 10 months after AHSCT, Hb was 12.5 g/dl and DAT remained negative.

Conclusion: Imatinib is generally a well tolerated agent. Nausea, edema, diarrhoea, cramps, vomiting, rash, headache, fatigue, arthralgia, neutropenia and thrombocytopenia associated with the use of imatinib have been reported in more than 5% of patients. Few cases of immune hemolytic anemia due to imatinib have been previously reported. The case presented herein, whose hemolysis resolved after withdrawal of imatinib, reconfirms the previous observations suggesting that imatinib mesylate may induce hemolytic anemia. As depicted in our case, second-generation TKIs such as dasatinib may be safe in case of imatinib induced immune hemolytic anemia.

Keywords: Immune hemolytic anemia, imatinib, Chronic Myeloid Leukemia

Non-Hodgkin's Lymphoma

PS-47 **Abstract Referance: 60**

ANAPLASTIC LARGE T-CELL LYMPHOMA PRESENTING WITH SEVERE HEMOPHAGOCYTOSIS

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Introduction: Anaplastic large cell lymphoma (ALCL) is a rare type of NHL. Patients with systemic ALCL are divided into two groups, depending on whether or not their cells have an abnormal form of a protein on their surface called anaplastic lymphoma kinase (ALK). Hemophagocytic syndrom is characterized by clinic presentation with cytopenias, fever, hyperferritinemia and hepatosplenomegaly. We report a rare case of Anaplastic Large T Cell Lymphoma (ALCL) with hemophagocytosis on bone marrow and lymph nodes in a 69-year-old man with an aim to expand our knowledge of hemophagocytos on both bone marrow and lymph nodes in case of non-Hodgkin's lymphoma.

Case Report: A 69-year-old man was admitted to outpatient clinic, complaining of fewer, weight loss and fatique for three months. The patient also had night sweats with body temperature fluctuating from 38°C to 39°C. The patient had lost about 10 kg of body weight since his illness began, with enlargement of lymph nodes, liver and spleen found upon palpation. His medical history included abdominal surgery, radiotherapy for prostat carcinoma and coronary artery disease. Physical exam

showed a temperature of 39°C, blood pressure of 100/65 mmHg, pulse of 110 beats per minute. Painless swelling of right inguinal lymph node and hepatosplenomegaly was found. Laboratory findings were revealed severe pancytopenia, hyperferritinemia, extreme elevation of lactate dehydrogenase and transaminases. An abdominal ultrasound revealed hepatomegaly of 160 mm, splenomegaly of 200 mm. Positron-emission tomography (PET) scanning showed multiple hypermethabolic lymphadenopathies on right common iliac, internal and external iliac, obturator and inguinal region with the biggest size of 3.3x3.2x4.0 mm (SUVmax: 17.8).

Both of Bone marrow aspiration and biopsy was compatible with hemophagocytosis. CRP was within normal limits and in laboratory findings there was no evidence of tuberculosis and other infections. Patient with cytopenia and hemophagocytosis was treated intravenous immunglobulin (400 mg/kg/day) during five days. The patient was discharged in a good clinical condition. A week later the patient's platelet level was $150x10^9$/L and his condition was very good. Three weeks later the patient's blood counts were all in normal ranges. After excisional biopsy taken from right inguinal lymph node, subsequently diagnosis was found to be non-Hodgkin's lymphoma of ALK-positive anaplastic large T cell type (ALCL) with hemophagocytosis on the lymph node too. He was treated with etoposide, cyclophosphamide epirubicin, vincristine, prednisone. Complete remission was achieved after 6 cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) therapy and the patient was followed up every month after chemotherapy.

Discussion: In conclusion, ALCL is a rare but biologically well-characterised disorder with a wide spectrum of presentation. It may present with hemophagocytosis on bone marrow. Recognition of a combination of symptoms including pancytopenia, fewer, weight loss and fatique in the presence of hemophagocytosis on bone marrow biopsy should trigger aggressive clinical work up to rule out the possibility of lymphoma. A careful examination of early biopsies based on CT and MRI of lymphnodes or deeply situated soft tissue are recommended to yield an early diagnosis of ALCL. It should be keep in mind that lymphoma patients may present with hemophagocytosis with pancytopenia.

Keywords: Anaplastic Large T-Cell Lymphoma, Hemophagocytosis

Acute Lymphoblastic Leukemia

PS-48 **Abstract Referance: 61**

INDUCTION FAILURE IN ACUTE LEUKEMIA OR PARVOVIRUS B19 INFECTION?

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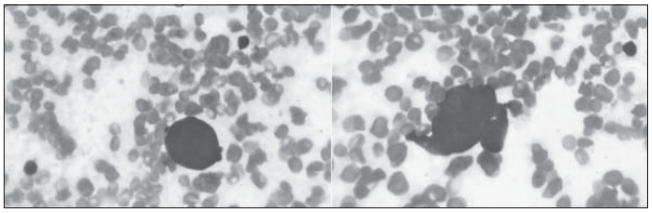
Introduction: Complications due to viral infections can be seen during the treatment of childhood hematologic malignancies. Parvovirus B19 infection can cause severe clinical signs and prolonged, unexpected cytopenia in acute leukemia patients that may lead to misinterpretation of the remission status.

Case report: An 8-year old girl had the diagnosis of pre-B cell acute lymphoblastic leukemia (ALL) and treatment was started according to ALL-BFM 2000 protocol. Her prednisone response was good but 15th day bone marrow aspiration (BMA) revealed 6% blasts. At the end of the induction (33rd day), BMA was performed and showed lymphoid predominancy with no myeloid regeneration and giant proerythroblasts with absence of late erythroid precursors (Figure 1). The patient was evaluated as having induction failure and parvovirus B19 DNA was also sent based on the bone marrow findings. Her clinical status deteriorated; she complained of severe myalgia, bone pain, abdominal pain, and developed hepatomegaly, anemia, hyperbillirubinemia and elevation in the transaminases. Abdominal ultrasonograpy showed sinusoidal obstruction syndrome, treatment with defibrotide was started. Parvovirus B19 DNA PCR analysis was consistent with Parvovirus infection. Intravenous immunglobulin was administered (1 g/kg). Her clinical findings resolved in one week and repeated BMA revelaed a normocellular bone marrow with trilineage regeneration and no blasts. MRD was also negative at time point 2 (33rd day) and time point 3 (78th day).

Conclusion: Parvovirus infection may be seen in acute leukemia patients and clinical findings and cytopenia caused by the viral infection may complicate the evaluation of the remission status. The typical bone marrow findings should alert the physician about Parvovirus B19 infection.

Keywords: acute lymphoblastic leukemia, child, parvovirus B19 infection



Stem Cell Transplantation

PS-49 **Abstract Referance: 62**

ECULIZUMAB IN THE TREATMENT OF TRANSPLANTATION ASSOCIATED THROMBOTIC MICROANGIOPATHY

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Introduction: Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (TA-TMA) is a systemic disease with long-term morbidity and high mortality and characterised by generalized endothelial dysfunction leading to microangiopathic hemolytic anemia, thrombocytopenia and multiple organ damage.

The anti-C5 monoclonal antibody eculizumab, also used in children, can prevent tissue damage by blocking the membrane attack complex. Here we present two pediatric cases in which TA-TMA was successfully treated by using eculizumab.

Case 1: An 8-year-old male patient with high-risk group (HRG) pre-B ALL underwent allogeneic stem cell transplantation from a full-matched sibling donor after a conditioning regimen with total body irradiation (TBI) and etoposide. The patient had tonic convulsions with hypertension on the post-transplant 37th day. The brain magnetic resonance imaging was normal. Cyclosporine was substituted with mycofenolate mofetil and antihypertensive and antiepileptic medications were started. In his clinical follow-up, persistent trombocytopenia and severe refractory anemia together with reticulocytosis, elevated LDH, decreased haptoglobulin and presence of schistocytes led us to consider the diagnosis of TA-TMA. ADAMTS 13 activity was normal. Plasmapheresis was performed for several times but was unsuccesful. Eculizumab was started with a dose of 900 mg per two weeks. On follow-up, the need for transfusion decreased, findings of hemolysis and cytopenia improved and eculizumab treatment was withheld after ten doses. The patient is now off immunosuprresive therapy in his post transplant 24th month with no active problems.

Case 2: An 16-year-old male patient with HRG pre-B, Ph (+) ALL underwent allogeneic stem cell transplantation from a full-matched sibling donor after a conditioning regimen with total body TBI and etoposide. He developed Grade 3 skin GVHD despite use of cyclosporine and steroid. Cyclosporine was stopped; mycophenolate mofetil and tacrolimus were started and mesenchymal stem cells were given for two times. GVHD improved but he had still persistent severe thrombocyopenia and mild anemia at the 4th month. Thrombocytopenia and a compensated non-immune hemolytic anemia with presence of schistocytes in the peripheral blood smear led us to consider the diagnosis of TA-TMA. Eculizumab was given with a dose of 900 mg per two weeks for the initial two doses and then given as 1200 mg per 4 weeks for two additional times. On follow-up, the need for transfusion decreased, findings of hemolysis and cytopenia improved and eculizumab treatment was withheld after 4 doses. The patient is now off immunosuprresive therapy in his post transplant 12th month with no active problems.

Discussion: It has been shown in the literature that the use of agents that provide complementary pathway blockade, such as the monoclonal human anti-C5 antibody eculizumab, may stop multiple organ damage and improve the prognosis of the cases. Consistently, TA-TMA was succesfully treated with eculizumab in our patients.

Keywords: thrombotic microangiopathy, stem cell transplantation, eculizumab

Acute Myeloid Leukemia

PS-50 **Abstract Referance: 63**

CD30 EXPRESSION IN ACUTE MYELOID LEUKEMIA TRANSFORMED FROM MYELODYSPLASTIC SYNDROME: CASE REPORT

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Background: The CD30 antigen, also known as Ki-1, is a member of the tumor necrosis factor receptor superfamily. In physiologic states, CD30 expression is restricted to subpopulations of activated B-and T-cells. In neoplastic diseases, CD30 is best known for its being expressed in classical Hodgkin lymphomas and anaplastic large cell lymphoma. Additionally, CD30 is also expressed by embryonal carcinoma, a subset of diffuse large B-cell lymphomas and peripheral T-cell lymphomas. Relatively little data for CD30 expression in myeloid neoplasms are available with few cases studied. Acute myeloid leukemia (AML) in elderly secondary to myelodysplastic syndrome (MDS) responds poorly to conventional therapy. It is suggested that CD30 could be a target for therapy by using anti-CD30 antibodies in a subset of patients with AML. We present a case of AML transformed from MDS with aberrant CD30 expression of myeloblasts.

Case Report: An 81-year-old female patient with pre-diagnosed myelodysplastic syndrome (MDS) presented with widespread ecchymosis and melena and deep pancytopenia was detected. Bone marrow trephine biopsy was hypercellular and infiltrated by neoplastic cells of blastoid morphology. Blastoid cells were positive with CD34 and CD43 by immunohistochemistry and focal CD30 expression was observed. Myeloperoxidase, CD117, CD10 and Tdt was negative. Flow cytometric analysis detected blasts with CD13, CD33, CD34, HLA-DR and CD117 antigenic expression. The patient was diagnosed as AML transformed from MDS. The patient could not be given chemotheraphy because of very old age and further deterioration in her general condition. She died on the 18th day of admittance.

Conclusion: MDS has a high risk of developing blastic transformation into AML. Patients with MDS-AML have specific biological characteristics and a worse prognosis. Blastic cells of AML rarely express CD30 and anti-CD30-targeted therapy might be an option for high-risk AML/MDS patients with very few treatment options left.

Keywords: acute myeloid leukemia, CD30, myelodysplastic syndrome

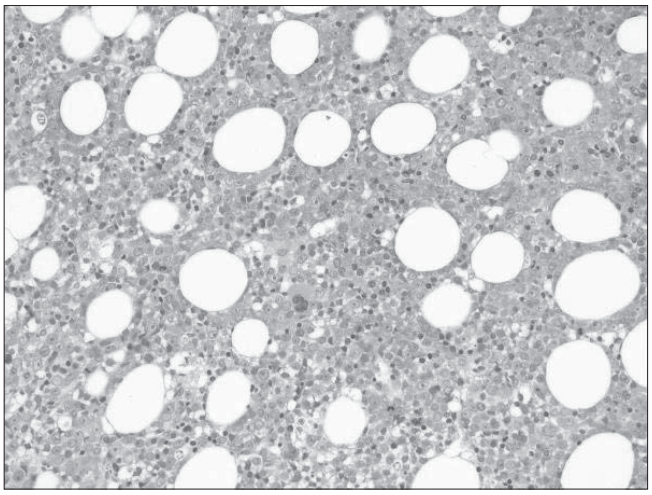

Figure 1: Diffuse infiltration of blastic cells in bone marrow trephine biopsy (H & E 40X).

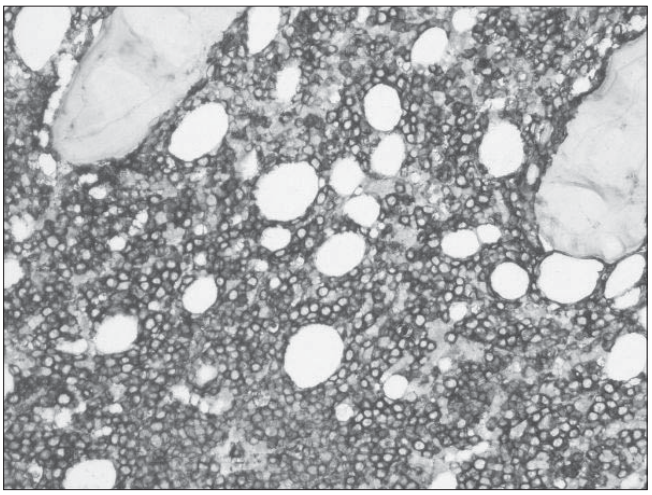

Figure 2: CD34 expression of blastic cells (CD34 immunostain 40x)

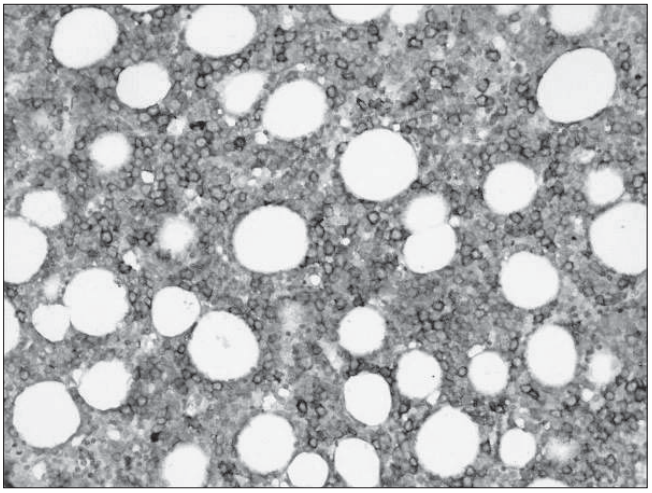

Figure 3: Aberrant CD30 expression of blastic cells (CD30 immunostain 40x)

Other

PS-51 **Abstract Referance: 64**

ABERRANT MYELOPEROXIDASE EXPRESSION IN KIKUCHI'S DISEASE: CASE REPORT

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Background: Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is an uncommon, idiopathic, generally self-limited cause of lymphadenitis. It is mainly a disease of young adults (20–30 years), with a slight bias towards females. The most common clinical manifestation of KFD is cervical lymphadenopathy, with or without systemic signs and symptoms. KFD is characterized by cortical and paracortical necrotizing nodules, apoptotic debris, proliferation of histiocytes and immunoblasts, abundant CD8+ T cells, and an absence/paucity of neutrophils. Myeloperoxidase (MPO) expression of the histiocytes is very rarely reported. Differential diagnosis with a myeloid tumor may be difficult in MPO positive cases. In this study we report the occurrence of large numbers of histiocytes expressing MPO in KFD in a male patient presenting with servical lymph node enlargement.

Case Report: A 41-year-old man presented to his physician with an enlarged cervical lymph node, fever and weight loss of 3 weeks duration. No other adenopathy or abnormalities were identified. The lymph node was excised and the initial diagnosis was necrotizing lymphadenitis. Representative paraffin blocks of the lymph node were admitted to our laboratory for consultation. Morphologically, the lesion affected the cortical and paracortical areas of the node with foci that have "clear" appearance at low magnification and were composed of varying amounts of histiocytes, small-to medium-sized lymphocytes and immunoblasts, abundant karyorhectic and granular eosinophilic debris, and coagulative necrosis without any neutrophils. By immunohistochemistry, the histiocytic component was characterized by the expression of the CD68 antigen, whereas the lymphoid component carried a T-cell phenotype with a prevalence of $CD8^+$ cytotoxic cells. Histiocytes were also positive with MPO (Figure1–3).

Conclusion: Kikuchi-Fujimoto disease (KFD) is a rare, self-limiting disorder that typically affects the cervical lymph nodes. Recognition of this condition is very important, especially because it can easily be mistaken for inflamatory diseases like tuberculosis, and neoplastic diseases like lymphoma and leukemia. Morphological and immunohistochemical evaluation is the key for diagnosis, and aberrant expressions must be kept in mind in order to avoid misdiagnosis and inappropriate treatment.

Keywords: Kikuchi's disease, aberrant expression, Myeloperoxidase

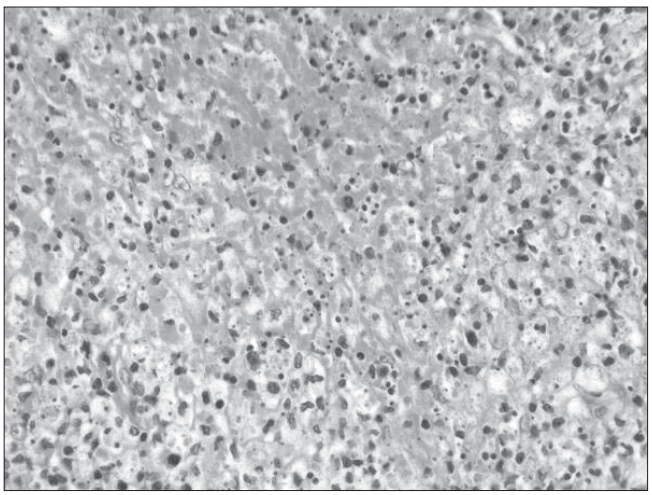

Figure 1: High power view of the lymph node demonstrating necrosis surrounded by karyorrhectic debris, histiocytes and plasmacytoid lymphocytes (H & E 40X).

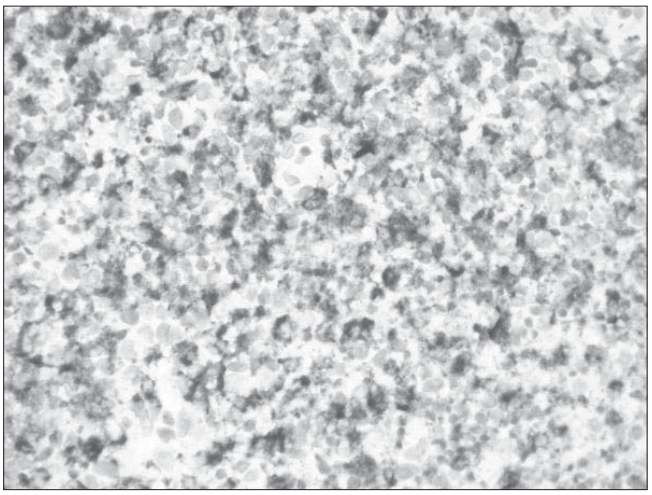

Figure 2: CD68 expression of histiocytes (CD68 immunostain 40x).

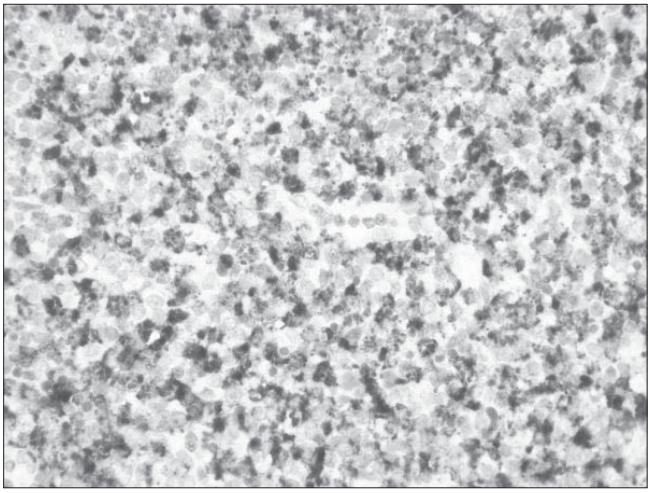

Figure 3: Aberrant Myeloperoxidase expression of histiocytes (Myeloperoxidase immunostain 40X)

Multiple Myeloma

PS-52 **Abstract Referance: 65**

A CASE WITH MULTIPLE SOLITARY PLASMACYTOMAS SECRETING MONOCLONAL PROTEIN

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Multiple solitary plasmacytomas are rare manifestations of plasma cell neoplasm which is characterized by the absence of bone marrow myeloma infiltration as well as absence of organ damage. Some patients have low level of monoclonal proteins. We present a case with multiple plasmocytomas which secrete monoclonal protein.

Case: A 54-year-old man was admitted to neurosurgery department with back pain. On computerized tomography imaging, an expansile mass (sized 5x4 cm) was detected on the left 3rd costa. Tru-cut biopsy of the mass revealed plasmacytoma. Bone marrow investigaton did not reveal any monoclonal plasma cell infiltration. Serum protein electrophoresis revealed M peak and immunofixation revealed IgG kappa monoclonal protein. Multiple lytic lesions on vertebras, costas and pelvic bones were detected on PET-CT (suvmax: 4.8–43.6). The patient was started systemic therapy with bortezomib, cyclophosphamide and dexamethasone.

Discussion: In this case, since there wasn't any monoclonal plasma cells in the bone marrow, with high probability, the source of monoclonal protein was the plasmacytomas. Another interesting feature is the presence of both plasmacytomas and lytic lesions at the same time. Unlike solitary plasmacytomas which are mainly treated with radiotherapy alone, systemic chemotherapy or high dose therapy supported with autologous stem cell transplantation is recommended for multiple plasmacytomas. Bortezomib containing combined therapies are suggested as first choice of treatment. In addition, immunomodulatory drug based therapies may upgrade the response.

Keywords: Multiple solitary plasmacytoma

Stem Cell Transplantation

PS-53 **Abstract Referance: 67**

HODGKIN'S LYMPHOMA IN A SCID PATIENT AFTER HAPLOIDENTICAL HEMATOPOETIC STEM CELL TRANSPLANTATION

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Objectives: Severe combined immunodeficiency (SCID) is a rare congenital syndrome characterized by profound deficiencies of cellular and humoral immunity. Bone marrow transplantation, is the standard of care for SCID. Patients with immunodeficiencies have an increased risk of developing malignancy, the overall risk is estimated at 4–25%. The type of malignancy depends on the primary immunodeficiency, the age of the patient and possible viral infection. Non-Hodgkin's lymphomas predominate, then respectively Hodgkin's disease and Leukaemia.

Case Report: A 4.5 month-old male patient who was diagnosed with SCID T (-) (B-) (NK+) was brought to Istanbul University Faculty of Medicine, Our Leukemia Children's Foundation BMT center in May 1999. His physical examination was unremarkable, the blood count parameters were as follows: RBC: 3.5 x10 6/mm^3, HGB: 7.8 gr/dL, HCT: 24.7%, PLT: 168 x 103/mm^3, WBC: 3700/mm^3, Lymphocyte:% 7, Flowcytometry was as follows: CD3 1.50%, CD4: negative, CD8:4.5%, CD10: negative, CD19:2.94%, CD20: negative, CD: 56:60%. The

immunglobulin levels; IgG: 296.9 mg/dl, IgA: <25.8 mg/dl, IgM: <18.3 mg/dl, IgE: >1030 iu/ml. The patient's HLA groups did not match with his sisters, so T-cell-depleted haploidentical parental marrow from the father was transplanted, the patient received $33x10^6$/kg CD34+ progenitor cells and $3.6x10^4$/kg T-lymphocytes. No conditioning regimen or GvHD prophylaxis was given. Engraftment and partial immune reconstitution was detected.

After transplantation mix chimerism was seen, because of the low immunoglobulin levels, IvIG is continued for years.

In May 2016, after 16.5 years, the patient admitted to the hematology-oncology clinic with lymphadenopathy. Left Cervical LAP excisional biopsy results were as follows: Classical Hodgkin's lymphoma (Mixed cell type).

The laboratory tests were as follows: WBC: 8000/mm^3, Neutrophil: 5500/mm^3, Lymphocyte: 1270/mm^3, HGB14.7 g/dL, HCT43.9%, PLT 259 x!03 mm^3, T. Protein 8.2 g/dL (5.7–8), Albumin 5.5 g/dL (3.5–5.2), Globulin 2.7 g/dL (2.9–3.1), GGT 54U/L (2–42), Calcium 11.2 mg/dL (8.8–10.6), Ferritin 129.5ng/mL (23.9–336), CRP 5.38 mg/dL (0–5).

The stage was evaluated as stage 2A, and 4 cycles of ABVD treatment was given. The patient tolerated with chemotherapy well and entered the remission.

The therapeutic process for patients with immunodeficiency is not different from other patients with the same malignancy.

Conclusion: Patients with immunodeficiencies have an increased risk of developing malignancy due to a defective immunity towards cancer cells. We suggest that SCID can successfully be transplanted and treated with routine chemotherapy even if malignancy develops.

Keywords: SCID, haploidentical stem cell transplantation, Hodgkin's lymphoma

Multiple Myeloma

PS-54 **Abstract Referance: 70**

STEM CELL MOBILIZATION FOR AUTOLOGOUS TRANSPLANTATION WITH CYCLOPHOSPHOMIDE 2.5 G/M2 IN MULTIPLE MYELOMA PATIENTS

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Introduction: Even in the era of new anti myeloma drugs autologous stem cell transplantation is still the first line therapy for myeloma patients. Different doses of cyclophosphomide regimens (1.5–4 g/m2) before stem cell collection is being used and there is no optimal dosing. Here were reported our results with cyclophosphomide 2.5 g/m2.

Methods: We retrospectively analyzed the impact of cyclophosphomide 2.5 g/m2 (Cy2.5 g/m2) in 14 myeloma patients (median age 57.3 years, rang 52–70 years). Enough stem cell harvest was defined as a stem cell yield of at least 2 million CD34 cells per kg body weight. The mobilization kinetics are evaluated.

Results: All patients were in PR/VGPR status of multiple myeloma. Successful stem cell mobilization was achieved in 7 of 14 (50%) patients with Cy2.5/GCSF. The other 50% of patients mobilized with plerixafar after Cy2.5/GCSF induction failure. There was 1.6 episodes of apheresis sessions. The median CD34 content of stem cell harvest 6.8 million CD34 cells per kg bodyweight for all cohort and 4 million cells with only Cy2.5/GCSF. While 9 patients had no febrile event, 28% (n=4) patients had febrile neutropenic episodes. Time to stay at hospital 12.2 days.

Conclusion: In conclusion the rate of unsuccesful mobilization with only Cy2.5/GCSF is high as 50% in our small sized study. This result is independent with the disease status. The apheresis session time, febrile neutropenic episodes, collected cell amount are in acceptable ranges when compared with other studies

Keywords: Multiple Myeloma, Cyclophosphomide, Mobilization

Table 1

Median Age	Median number of treatment	Number of apheresis sessions	Stem cell collected CD34+ (Mu/kg)	Plerixafar used patients
57.3	1.7	1.6	6.8	7

Multiple Myeloma

PS-55 **Abstract Referance: 71**

EFFECT OF CYTOKINE GENES IN THE PATHOGENESIS AND ON THE CLINICAL PARAMETERS FOR THE TREATMENT OF MULTIPLE MYELOMA

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Objective: In this study, we aimed to explore the association among gene variants of five cytokine, Tumor necrosis factor alpha (TNF-α), Transforming growth factor beta-1 (TGF-β1), Interferon gamma (IFN-γ), Interleukin-6 (IL-6), and Interleukin-10 (IL-10), and clinical parameters and prognosis in patients with multiple myeloma (MM) treated with novel therapeutic drugs in Turkish population for the first time except TNF-α.

Patients and Methods: We analyzed five cytokine genes in 113 cases with MM and 113 healthy controls. Cytokine genotyping was performed by the polymerase chain reaction-sequence-spesific primer method.

Results: AG genotype associated with high expression in TNF-α gene (-308) variant was found to be significantly higher (p: 0.019) and GG genotype associated with low expression in TNF-α gene (-308) variant was significantly lower in MM group as compared to controls (p: 0.012). IFN-γ (+874) variant TT genotype was increased (p: 0.037) and AA genotype was decreased (p: 0.002) in MM group in contrast to controls. IFN-γ (+874) T allele was higher in MM patients compared to controls (OR: 1.985, p: 0.000), while A allel was significantly lower (OR: 0.5037, p: 0.0005). On multivariate analysis revealed that factors associated with 5-year Overall survival (OS) were only IPI III (RR: 1.630, p: 0.018) and

thrombocytopenia (RR: 2.207, Cox p: 0.021) while 5-year event free survival (EFS) was associated with IPI III (RR: 1.524, p: 0.022), thrombocytopenia (RR: 2.902, p: 0.002), APSCT treatment (RR: 1.729, p: 0.035) and female gender (RR: 0.435, p: 0.002) with negative prognostic values. CONCLUSIONS: Our results suggested that TNF-a gene (-308) AG genotype and IFN-γ (+874) TT genotype and T allele may have a role on MM but not other cytokines were associated with the risk of MM.

Keywords: Multiple Myeloma, cytokine genes expression, prognostic factors.

Stem Cell Transplantation

PS-56 **Abstract Referance: 72**

OUTCOME OF AUTOLOGOUS TRANSPLANTATION IN PATIENTS YOUNGER THAN 50 YEARS WITH MULTIPLE MYELOMA

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Multiple myeloma is an uncommon disease in young population. The incidence increases with age. In the retrospective analysis of International Myeloma Group age was an independent risk factor for conventional chemotherapy but did not effect the outcome of autologous transplantation 1. Although survival seems significantly better compared to older patients, young patients have shorter survival after finding were corrected for differences in life expectancy 2.

We retrospectively analyzed the outcome of 13 myeloma patients younger than 50 years transplanted between years 2014–2017.

The median age was 46 (37–50); 7 male, 6 female. Subgroups were 7 IgG, 2 IgA and the others were light chain disease. Most of the patients got bortezomib combination protocols before transplantation. Four patients were in CR after CyDex before transplantation. The disease status of the patients were 5 progressive disease (PD), 4 complete remission (CR), 4 very good partial remission (VGPR) and 1 partial remission (PR). Eight patients have bone involvement with lytic lesions and the conditioning regimen was MEL200 except one patient with chronic renal failure.

All patients engrafted, mean neutrophil engraftment day was 12.6 (10–20) days. Only one patient died early after transplantation on 39th day due to rapidly growing multiple plazmasitomas. Mean progression free survey was 10.3 (1.3–35.2) months and 5 patients were refractory to combination therapies including pomalidomide and carfilzomib and second transplantation was performed. Remaining 8 patients got short term consolidation therapies and radiation therapy. Mean overall survival was 18 months (1.3–35.2) for all patients. The mean overall survival of the 5 patients after second transplantation was 5 months (0.83–15.9).

We cannot make a statistical conclusion with this small cohort of patients but depending on our observation this young population has a short progression free survival. Although we have a short follow up period, 5 patients needed second transplantation in two years in average 4 patients are under combination therapies, only four patients are treatment free.

In conclusion we may say that these younger population will survey shorter when we consider life expectancy compared to the elderly patients.

Keywords: multiple myeloma, autologous Stem Cell Transplantation

Acute Myeloid Leukemia

PS-57 **Abstract Referance: 73**

A CASE REPORT: ACUTE MYELOID LEUKEMIA DIAGNOSIS WITH MAGNETIC RESONANCE

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Introduction: Patients with Acute Myeloide Leukemia (AML) usually present with symptoms associated with complications of pancytopenia (eg, anemia, neutropenia and thrombocytopenia), Bone pain is one of this rare symptoms in adults with AML, also some patients describe sternal discomfort or tenderness, sometimes pain in long bones, These symptoms can be particularly serious as we know due to the expansion of the medullary space in the lower extremities through the leukemic process,In this case, we will review that the patient who although non invasive tests performed,do not provide any data to suggest leukemia, the suspicion of leukemic infiltration in the vertebral MR taken with the complaint of low back pain without the underlying hematologic symptom and its finding; further tests have been performed and the diagnosis of acute promyelocytic leukemia has been made.

Case: A 21-year-old male patient in November 2016, lumbar MR taken by reason of low back pain, “all the vertebral T1-weighted images suggest a leukemic infiltration with hypointense areas in the spotted appearance” applied to our clinic with this report, Except for waist pain, there was no pathological finding other than an additional complaint and physical examination of the vertebrae except tenderness, In the complete blood count, WBC: 6,60/mm^3 NEU: 3,81 mm^3 LYM: 1,98 mm^3 Hb: 16,3 g/dl PLT: 209,000/mm^3 The coagulation tests were normal in the peripheral smear of the patient with normal leucocyte formula and no atypical mononuclear cells, Biochemical tests showed no evidence other than a slight elevation of LDH, Significant increase in promyelocytes, loss of maturation, 50% AMNH was detected in bone marrow aspiration evaluation, HLA-DR negative, CD15, CD13, CD33, CD34, CD117, CD15, MPO positive and AML-M3 were found to be compatible with the atypical cell population of 62% in flow cytometry, The patient`s FISH showed t (15–17) 15% positivity, The patient is currently undergoing treatment with a low-risk APL diagnosis, During induction, grade 4 neutropenia and thrombocytopenia developed and the DIC table was not developed, The transfusion was not needed, The waist pain disappeared with induction chemotherapy of the patient, Cytopenia did not develop in the patient during consolidation, The patient is currently undergoing treatment with molecular and hematologic remission.

Discussion: Dynamic material-enhanced magnetic resonance (DCE-MR) has been used in hematological and oncologic malignancies as a noninvasive quantitative technique for tumor vascularization in recent years. Semiquantitative findings obtained with MR and clinical data correlated with remission in 51 AML patients, However, there is no study showing the correlation of MR imaging method in the diagnosis of active systemic leukemia, Most of the cases in the literature show that cases with extramedullary involvement can be detected by MR, In our case, the heterogeneous appearance of all vertebrae in the imaging field with MRI and T1 sequences was defined as leukemia and we directed clinicians to advanced examination, This is a very striking example that we often never encountered the «hematologic disease» reports on the MR.

Keywords: MR AML

Non-Hodgkin's Lymphoma

PS-58 **Abstract Referance: 74**

CORRELATION OF PLASMA EXOSOME CONCENTRATIONS WITH STAGE IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Objectives: Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma among adults and is characterized by heterogeneous clinical, immunophenotypic and genetic features. The studies on exosomes in DLBCL are still very limited. The aim of this study was to investigate differences in plasma exosome concentrations of DLBCL patients with differen stages.

Methods: Forty-nine patients with DLBCL and 21 age-and sex-matched healthy controls were included in the study. Blood samples were drawn from the right antecubital vein using a large (>21-gauge) needle and processed within 30 minutes. An ultracentrifugation-based procedure was used to isolate exosomes form plasma samples. The exosomes were characterized by electron microscopy, specific markers including CD63, CD81, and TSG101 used for exosome detection, and protein quantity.

Results: All exosome samples showed typical morphology and expressed the exosomal markers. The plasma exosome concentration was almost six-fold higher in DLBCL patients than in healthy controls (p=0.00). DLBCL patients had higher concentration of total exosomal proteins, when compared to healthy controls (p=0.00). It was also found significant differences in the exosome concentration comparing all stages of the disease with healthy controls (p< 0.05 for all). Interestingly, patients at stages III-IV of disease had significantly lower exosome concentrations compared with patients at stages I-II (p=0.03).

Conclusion: Our results showed that the centrifugation-based procedures assessed in this study are able to isolate high quality, analyzable exosomes in DLBCL patients. We have observed a significant inverse relation between exosome concentrations and disease stage of DLBCL patients. Further studies are necessary to clarify the molecular mechanisms underlying the removal of exosomes from plasma in patients with advanced stage.

Keywords: DLBCL, exosome, quantification

Non-Hodgkin's Lymphoma

PS-59 **Abstract Referance: 75**

PROSTATE INVOLVEMENT IN A PATIENT WITH FOLLICULAR LYMPHOMA: A CASE REPORT

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Introduction: While the extranodal involvement is observed in 50% of the cases of non-Hodgkin's lymphoma, the prostatic involvement is rare. Prostatic lymphoma accounts for 0.09% of all prostate neoplasms and 0.1% of all non-Hodgkin's lymphomas.

Case: Patient was monitored for 4 years, had stage 4BS disease follicular lymphoma (bone marrow involvement, mesenteric lymph nodes in the abdomen the largest of which was measured as 9*4 cm, cervical and mediastinal lymph nodes, splenomegaly and B symptoms) at the time of diagnosis, received CVP, CHOP and gemcitabine therapy, respectively, had the symptoms of lower urinary tract symptoms during the follow-up and hypertrophic prostate was palpated during the physical examination. PSA value was measured to be 8.3 (0–4) ng/mL. Urinary analysis showed microscopic haematuria. Ultrasound examination detected a prostate volume of 60 cc. Transurethral resection of the prostate (TUR-P) pathology result showed a diffuse lymphocytic infiltration and positive staining for CD20, CD10, CD5 and BCL-2 (Image 1–2). The symptoms of the patient regressed after treatment with rituximab plus bendamustine.

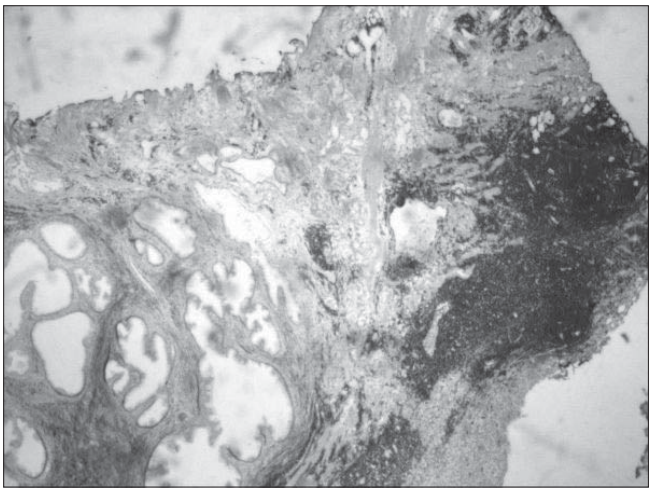
Discussion: Prostate cancer is the most common cancer among men worldwide. There are 1.618.000 cases with 366.000 deaths in 2015. Prostatic lymphoma is a rare condition that accounts for 0.09% of all prostate neoplasms. While the extranodal involvement is observed in about 50% of the cases of non-Hodgkin's lymphoma, the prostatic involvement is rare. The usual clinical manifestations of prostatic involvement in lymphomas are lower urinary tract symptoms and acute urinary retention. High serum PSA levels are not typical for prostatic lymphoma. Our patient presented with high PSA levels.

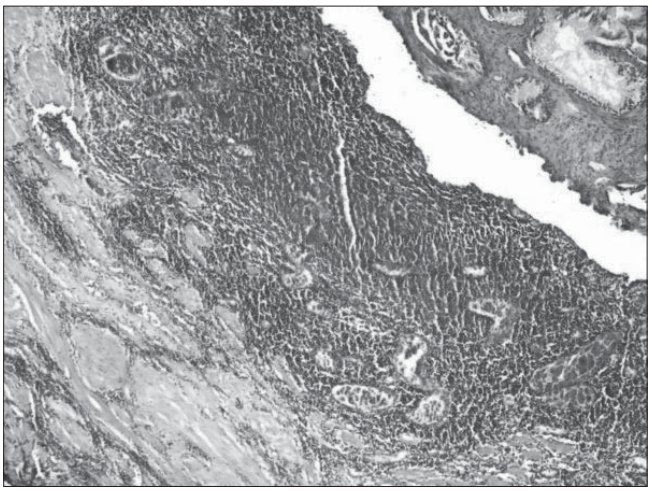
A study that investigated prostate materials from 4.831 subjects determined lymphoma in 29 subjects (0.6%). 11 (0.23%) subjects had the history of concurrent lymphoma. In patients with prostate cancer, the

incidence of non-Hodgkin's lymphoma of prostate was observed to be 0.2% in a series of 4.319 radical prostatectomy cases and 1.19% in another series of 1.092 cases.

In conclusion, prostatic lymphoma is clinically difficult to distinguish from benign prostatic hyperplasia and prostatic carcinoma as it occurs in the same age group and presents with similar symptoms and thus, the histopathological and immunohistochemical findings in TUR-P material are important. An early and proper treatment improves the quality and the length of life.

Keywords: follicular lymphoma, extranodal, prostatic involvement





Acute Myeloid Leukemia

PS-60 **Abstract Referance: 76**

QUALITY OF LIFE IN LOW-RISK MYELODYSPLASTIC SYNDROME

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Objectives: Chronic cytopenias, especially anemia, frailty comorbidities, and age may alter the physical status significantly in patients with myelodysplastic syndrome (MDS). Erythropoietin-stimulating agents (ESAs) and red blood cell transfusions are the treatment options for patients suffering from anemia.

Methods: Patients with low-risk MDS were included in the study. One physician completed FACT-An, Hematopoietic Stem Cell Transplantation-Comorbidity Index (HCT-CI), and G8 frailty questionnaires in all patients. Demographic data were collected from patients'chart records.

Results: A total of 66 patients were screened. Fourteen patients were excluded due to high-risk MDS or indefinite diagnosis. In one patient, informed consent could not be obtained. Finally, 51 patients were included in the study. Median age was 66 years old (interquartile range [IQR]: 55–77). Twenty-one out of 51 patients (41.2%) were male. Most prevalent MDS subtype was MDS-refractory anemia (47%). All patients had very-low/low (86.3%) or intermediate-risk (13.7%) MDS according to age-adjusted IPSS-R (IPSS-RA). Median time from the diagnosis of MDS was 113 (IQR: 53–170) weeks. Twenty-eight patients (54.9%) were transfusion-dependent. Ten patients had a high transfusion burden, which was defined as transfusion requirement ≥4 units (U) over 8 weeks. Median transfusion duration was 112 (IQR: 31–173) weeks for transfusion-dependent patients. Median red blood cell transfusion during eight weeks was 1.5 (IQR: 0–4.5) U. Median hemoglobin concentration was 10.0 (7.9–11.3) g/dL for all patients. A total of nineteen patients (37.3%) were ESA-user/responder. Most of the patients (80.4%) had a low (<11 years) education level. Thirty-eight (74.5%) patients were living with their parents or partners. A half of the patients had an ECOG performance status ≤2. Sixty per cent were frail and 39% had significant (≥2) comorbidities.

In univariate analyses, older age (β:-0.740, 95% CI:-1.138;-0.341, p<0.001), higher transfusion burden (β:-7.235, 95% CI:-14.279;-0.190, p=0.044), intermediate risk IPSS-RA (β:-8.113, 95% CI:-15.715;-0.511, p=0.037), lower educational status (β:-19.625, 95% CI:-32.565;-6.684, p=0.004), lower ECOG performance status (≥2) (β:-14.385, 95% CI:-24.805;-3.964, p=0.008), frailty (β:-13.740, 95% CI:-24.518;-2.962, p=0.014), and being ESA-user/responder (β:-15.431, 95% CI:-26.141;-4.722, p=0.006) were associated with worse FACT-An total scores.

Multivariate analyses revealed that age (β:-0.738, % 95 GA:-1.101;-0.374, p<0.001) and being ESA-user/responder (β: 15.368, % 95 GA: 6.040; 24.697, p=0.002) were the only independent predictors of QoL in patients with low-risk MDS.

Model stability was tested in 5000 bootstrap replicates of dataset. Age and being ESA-user/responder were included in 40.6% and 38.2% of all models.

Conclusion: These data indicates that age and ESA use are independent parameters of QoL in low-risk MDS. Impact of ESA use on QoL is independent from the hemoglobin level.

Keywords: Myelodysplastic Syndrome, Quality of Life, Erythropoietin-stimulating agents

Chronic Myeloid Leukemia

PS-61 Abstract Referance: 77

MOLECULAR CYTOGENETIC PROFILE OF COMPLEX/ VARIANT TRANSLOCATIONS IN CHRONIC MYELOID LEUKEMIA

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the presence of the Philadelphia (Ph) chromosome resulting from the reciprocal translocation t (9; 22) (q34; q11). In 5%-10% of newly diagnosed CML cases, one or more additional chromosomes are added to 9 and 22 and are involved in the translocation, and this is termed variant translocation.

In total, 878 patients were evaluated at initial diagnosis between 2009–2016. Chromosome-banding analysis was performed on peripheral blood (n=397) or bone marrow (n=481) cellsafter short-term culture (24 and/ or 48 hours). Twenty metaphases were analyzed and the karyotype was described by standard ISCN nomenclature. FISH was performed on the cells prepared according to standard cytogenetic techniques and using BCR/ ABL Dual-Color, Dual-Fusion (D) Translocation Probe (Cytocell) or the Double-Fusion Signal D-FISH BCR/ABL Probe (Oncor-QBiogene).

The typical D-FISH pattern for classict (9; 22) (q34; q11) translocation was seen in 26 (3%) patients while 156 (18%) patients showed different patterns of complex/ variant rearrangements involving more than the chromosomes 9 and 22. We were not able to determine a cluster of breakpoints on specific chromosomes, because a number of chromosomes were involved as the third or fourth chromosomes in the variant translocations.

There is still no consensus on the prognostic significance of complex or variant Ph translocations involving several partner chromosomes. The breakpoints on the partner chromosomes might contain important genes involved in leukemogenesisor contribute to genome instability. It is necessary to further elucidate the prognostic significance of complex or variant Ph translocations in patients with CML.

Keywords: CML, complex/variant translocation, Philadelphia chromosome

Myeloprofilerative Disorders

PS-62 Abstract Referance: 78

PRIMARY BUDD-CHIARI SYNDROME ASSOCIATED WITH MYELOPROLIFERATIVE DISEASES

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Budd-Chiari syndrome (BCS) is characterized by an obstruction of the hepatic venous outflow tract in the absence of right heart failure or constrictive pericarditis (1). BCS is further separated into secondary BCS when related to compression or invasion by a lesion originating outside the veins (benign or malignant tumor, abscess, cyst, etc.); and primary BCS when related to a primarily venous disease (thrombosis or phlebitis). Philadelphia-negative myeloproliferative neoplasms (MPNs) are the most frequent underlying prothrombotic factor in BCS and portal vein thrombosis (PVT), with a reported prevalence of 30%-50% and 15%-30% respectively (2,3).

Here we present 67 years old female with primary BCS diagnosed as JAK2 (+) MPN afterwards. In 2015, when she was 65 years old, she applied to hospital with ascites. In further examinations, laboratory and imaging interventions; she was diagnosed as BCS. She was treated with low molecular weight heparin bridging with oral K vitamin antagonist. She was referred to our hematology clinic after two months later for further investigations.

She had splenomegaly, hepatic vein thrombosis, leukocytosis (16.000/mm^3) and polycythemia (Hgb: 16.5 gr/dl) when she applied to our clinic. We had revealed bone marrow examination, thrombophilia tests (Factor V Leiden, Prothrombin gene mutation, antiphospolipid syndrome), JAK2 and bcr-abl for differential diagnosis.

The bone marrow examination was hypercellulary with erythroid and megakaryocytic hyperplasia. On genetic tests JAK2 was positive and bcr-abl negative. All other thrombophilia tests were also negative. She was diagnosed as JAK2 (+) MPN, polycythemia vera (PSV) due to WHO 2008 criteria (JAK2 (+), bone marrow associated with PSV, Hgb>16.5 gr/dl and normal EPO levels).

She is treated with cytoreductive agent (Hydroxiurea) according to risk status (age and prior thrombotic event) and oral anticoagulant therapy. She is still stable after two years follow up.

Conclusion; there is a high prevalence between BCS and MPNs. Such as in this case, MPNs must considered as one of the main differential diagnosis in BCS.

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Keywords: Budd-Chiari Syndrome, Myeloproliferative Neoplasms, JAK2

Non-Hodgkin's Lymphoma

PS-63 **Abstract Referance: 79**

MYELOMA AND RELAPSED MANTLE CELL LYMPHOMA; SYNCHRONOUS MALIGNENCIES IN A PATIENT

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Introduction: The association between a multiple myeloma and a secondary solid tumor is not well established. The occurrence of Mantle Cell Lymphoma (MCL) and Multiple Myeloma (MM) in the same patient is very rarely reported in the literature. Clonal relationship is the major factor need to be investigated. The question about the clinical significance of t (11; 14) and the overexpression of cyclin D1 shared by MM and MCL seems to be settled, its role in tumorigenesis is an ongoing area of investigation. Here we report synchronous malignencies of myeloma and mantle cell lymphoma in a male patient.

Case Presentation: A 72-year-old male patient referred on May 2014 with the complaint of diplopia, and on his cranial MR a right parietal mass was identified and operated. A diffuse infiltration of neoplastic small lymphoid cells with irregular nuclear contours was noticed in all surgical materials removed, including the meninges, parietal bone, soft tissues overlying the cortex and the skin. On immunohistochemical evaluation the neoplastic cells were positive for CD5, CD20, bcl-2, and cyclin D1, thus diagnosed as mantle cell lymphoma (MCL). The patient was staged as 4BS. A total of 6 cycles of chemotherapy, two cycles of CHOP (Cyclophosphamide, Vincristine, Doxorubicin, Methylprednisolone) and four cycles of R-CHOP (Rituximab-CHOP), was given. After chemotherapy cranial radiotherapy was performed. Control PET/CT and bone marrow biopsy of the patient was assessed as full response, so the patient was undertaken for follow-up. In June 2016, neck ultrasound taken for routine controls revealed pathological lymph nodes increased in number and size. Left cervical lymph node biopsy was performed and neoplastic infiltration of lymphoid cells with blastic morphology were noticed, positive for CD5, CD20, bcl-2, cyclin D1, and SOX11 on immunohistochemical examination, so the case was diagnosed as blastoid MCL. The patient was evaluated as recurrent MCL, PET/CT scanning and bone marrow biopsy was performed for staging. PET/CT scanning revealed cervical and abdominal pathological lymphadenopathies. On bone marrow biopsy, increase in plasma cells with intracytoplasmic Russell bodies and Mott cells, and rare macrophages with phagocytosis of erythrocytes and erythroblasts were found. A focal nonparatrabecular infiltration of lymphoid cells was identified, mostly consisting of CD3 and CD5 positive T-cells, with rare CD20 and PAX5 positive B-cells, negative for both CyclinD1 and SOX11. On immunohistochemical evaluation the plasma cells were monotypically positive for IgG and lambda light chain, so the diagnoses were given as multiple myeloma (MM) infiltration of bone marrow and hemophagocytosis. After 6 cycles of Rituximab-Bortezomib-Cyclophosphamide and Dexamethasone (R-VCD), patient achieved a complete remission for MCL. VCD therapy is still administered for treatment of myeloma to get VGPR or CR.

Discussion: This case of MCL, with atypical clinical presentation of diplopia, recurrence as blastoid variant MCL with simultaneous development of myeloma on two years of follow-up, with a diagnostically challenging abnormal plasma cell morphology, most presenting as Mott cells, is evaluated in the light of literature. Unfortunately, molecular studies for clonal relationship could not be undertaken in our patient because of lack of adequate samples.

Keywords: Mantle Cell Lymphoma, Myeloma

Myeloprofilerative Disorders

PS-64 **Abstract Referance: 81**

"SEARCH, LOOK AND SEE"

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The idiopathic hypereosinophilic syndrome (HES) is characterized by a persistently high eosinophil count (> $1.5x10^9$/L), signs or symptoms of organ involvement and no secondary causes such as allergies, atopic diseases and asthma, infections (mainly helminthic), autoimmune disorders, exposure to toxins, solid or hematopoietic neoplasias. Increased blast counts in blood or bone marrow and/or detectionof clonal abnormalities lead to a diagnosis of chronic eosinophilic leukemia (CEL). Genetic analysis has recently identified a cryptic del (4) (q12), producing the FIP1L1/PDGFRA fusion protein.

We report here a case with chronic cough which was induced by asthma bronchiole and also he has hypereosinophilia since two months. The patient's history has begun four years ago with cough and he had been treated with antiasthmatic drugs. While he has leukocytosis with hypereosinophilia, has been consultationed by hematologist. He was evaluated for HES and 90% eosinophil was detected in the peripheral blood smear without blastic cells. In the bone marrow smear and flow cytometric analyses were revealed 23% eosinophil no blastic transformation. There was no infiltrative processes in term of the other malignancies. The conventional cytogenetic and molecular analyses were done for differential diagnosis; there were no positive result in term of BCR-ABL and JAK2 V617F mutation. There was no abnormality in karyotype analysis of bone marrow cells culture for 24 and 48 hours for 20 metaphases by GTG banding method. The fusion of FIB1L1 and PDGFRA was found negative by interphase-FISH. The organ damage by eosinophil infiltration was not detected in the gastrointestinal system with endoscopic review and endoscopic biopsy. Helicobacter pylori wasn't seen in the gastric mucosa. The biochemical assays in term of hepatic and renal function were normal range, hepatic viral markers were negative. There was no abnormality in the ultrasonographic evaluation of abdomen. High resolution chest tomography was revealed no marked pathology except minimal linear sequel changes. Echocardiographic evaluation was normal. At the end of the research 1 mg/kg metilprednisolon was initiated to the patient but no any regression in eosinophilic leukocytosis.

The patient admitted to our center in this situation. It seems that everything have been done for possible clonally hypereosinophilia. While we were reviewing all of the examinations, we recognized one point. FIB1L1and PDGFRA fusion was found to be negative in the FISH analysis with one month interval, but as a remarkable result, 4q12 deletion was found in 74% of the cases after 24%. We investigated this deletion and found that a cryptic deletion of 4q12 producing the FIP1L1/PDGFRA fusion gene, identifies a distinct CEL subgroup. There were some cases in the literature who response to tyrosine kinase inhibitory 'imatinib mesylate'treatment. We get approval off-label use for imatinib from Ministry of Health and immediately started it. We obtained complete hematologic response in three month and complete cytogenetic response in six month with 100 mg po imatinib. The cytogenetic response was continuous for 18 months.

Keywords: Hypereosinophilic syndrome, cryptic de l4q12, imatinib

Multiple Myeloma

PS-66 **Abstract Referance: 84**

MULTIPLE MYELOMA AND THROMBOEMBOLISM IN THE PERSPECTIVE OF AGE AND PERFORMANCE

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Introduction: The relation with cancer and thromboembolism (TE) are well documented. Within cancer types, hematological malignancies, especially Multiple Myeloma (MM) show a propensity towards TE with its disease biology, disease burden and treatments. We aimed to evaluate the risk factors of TE and MM with a perspective of age and clinical performance.

Methods: Data regarding Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance scores, patient, disease and treatment related properties of patients with MM between 2010 and 2016 were recorded.

Results: Of the 125 MM patients, 60 were female (48%) while 65 were male (52%). Median age was 65 years. VTE was observed in 28 patients (22.4%). In patients <65 years, poor ECOG and Karnofsky scores were strongly related with VTE (p values 0.003 and 0.000). Polypharmacy and LDH elevation was observed to be a risk factor in all ages (p values 0.002 and 0.000), in poor ECOG (p=0.005 and 0.037) and Karnofsky performance (p=0.002 and 0.003) while radiotherapy and pneumonia during TE episodes were observed to be risk factors for TE regardless of age and performance (p values 0.016 and 0.000). Antimicrobial use during TE episode was observed to be a risk factor in younger patients (p=0.000) who are fit by both scales while bedrest and presence of fractures were observed as risk factors in younger patients with poor performance scores.

Conclusion: Performance assessment should be considered as fundamental for TE evaluation and adequate prophylactic treatment for TE should be commenced in frail young patients.

Keywords: Multiple Myeloma, Performance, Thromboembolism

Table 1. Thromboembolism Risk Factors with Respect to Age and Performance

Risk Factors	All ages	<65 years	≥65 years	ECOG Performance 3–4 (poor)	ECOG Performance 1–2 (fit)	Karnofsky performance ≤50 (poor)	Karnofsky performance >50 (fit)
Polypharmacy	p=0.002	independent of age	independent of age	p=0.005	not significant	p=0.002	not significant
Radiotherapy	p=0.016	independent of age	independent of age	p=0.016 independent of performance	p=0.016 independent of performance	p=0.016 independent of performance	p=0.016 independent of performance
Pneumonia during episode	p=0.005	independent of age	independent of age	p=0.005 independent of performance	p=0.005 independent of performance	p=0.005 independent of performance	p=0.016 independent of performance
Bedrest	p=0.02	p=0.017	not significant	p=0.015	not significant	p=0.02	not significant
Antimicrobial treatments	p=0.000	p=0.000	not significant	p=0.005	not significant	p=0.000	not significant
Fracture	p=0.000	p=0.000	not significant	p=0.001	not significant	p=0.042	not significant
LDH elevation	p=0.000	p=0.000 independent of age	p=0.000 independent of age	p=0.037	not significant	p=0.003	not significant

Non-Hodgkin's Lymphoma

PS-67 **Abstract Referance: 85**

DEPRESSION AS THE PRESENTING SYMPTOM OF CENTRAL NERVOUS SYSTEM LYMPHOMAS IN NORTHWESTERN TURKEY

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Primary Central Nervous System Lymphomas (CNSL) represents approximately 4 percent of newly diagnosed primary central nervous system (CNS) tumors, with an age-adjusted incidence rate of four cases per million persons per year. Antecedent flu-like or gastrointestinal illnesses or a history of autoimmune diseases were reported. Presenting symptoms may include focal neurologic deficits, neurophyschiatric symptoms, signs of increased intracranial pressure, seizures or ocular symptoms. Neurophyschiatric symptoms like depression, apathy, psychosis, confusion, memory impairment, slowness of thought are generally undernoticed or underestimated due to the increased rates of depression and tendancy towards antidepressant use.

We aimed to evaluate the presence of depression and antidepressant use before the diagnosis of CNS lymphoma and emphasize the duration between the diagnosis of depression and lymphoma.

Data of 40 patients with CNS lymphoma were evaluated in a retrospective manner. From their national health records, prescription for antidepressant and anxiolytic drugs with their psychiatric diagnosis, time before the diagnosis of CNS lymphoma, the branch of the prescribing physician, presenting symptoms from their medical files, type and treatment of lymphoma and survival were recorded. OECD international statistics as well as Turkish Statistical Institute data for national antidepressant use were collected and interpreted.

Of the 40 patients, 14 were male (35%) while 26 were male (65%). Mean age was 60.5 years (38–78). 7 patients were alive (17.5%). Method for diagnosis was radiological imaging (magnetic resonance imaging) in 27 patients (67.5%) while in 13 patients, diagnosis was supported with histopathological confirmation (32.5%).

Mean survival was 8.6 months (2–24 months). As the complaint for medical help seeking, 4 patients presented with neurophyschiatric symptoms while 16 patients presented with headache (40%) and 20 patients (50%) presented with neurological defects. On the other hand, prior to lymphoma diagnosis, 7 patients were diagnosed as anxiety disorder and 13 as depression (total, 19 patients, 47.5%) and were prescribed antidepressant and anxiolytic medications. The mean duration between prescription of antidepressants and diagnosis of lymphoma was 2.6 months (0–10 months). Within the patients who were on antidepressants, 6 were female and 14 were male.

OECD Health at a Glance data revealed that in 2013, the defined dose per 1000 per day is 35, range of Europe is 21–88. According to our data of Ministry of Health, use of antidepressants in the general population is 10.52%, mostly in women. Within these patients, 42.37% were anxiety disorders and 22.99% were depression. In the last five years'statistics, 30% of our population was prescribed for an antidepressant. The major group of physicians presciribing these medications was family and general physicians (>45%). The most striking finding of our study was the majority of male patients receiving antidepressants before the diagnosis of CNS lymphoma with a mean delay of diagnosis as 2.6 months (0–10 months). Depression and anxiety disorders are the leading diseases of disability and the importance of organic and underlying conditions should not be underestimated relying on the increasing need of antidepressants.

Keywords: CNS lymphoma, depression

Chronic Lymphocytic Leukemia

PS-68 **Abstract Referance: 87**

SUCCESSFUL TREATMENT OF INVAZIVE MUCORMYCOSIS FOLLOWING CHEMOTHERAPY IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Mucormycosis is a fungal infection mainly affects immunocompromised patients with diabetes mellitus type II or malignant hematologic diseases. Fludarabine causes T-helper cell depletion which is important in defending against invasive fungal infection and has been suggested to increase risk of invasive fungal infections in leukaemia patients. We herein report a CLL patient with invasive fungal sinusitis.

Case Report: A 70-year old man admitted to our hematology department of hospital with the complaint of fullness in the left upper abdomen and severe fatigue. His radiological investigations revealed that he had multiple enlarged lymphadenopathies and splenomegaly 25 cm in diameter. We performed left axillary lymph node excisional biopsy resulted as small lymphocytic leukemia (SLL). He had severe B symptoms, anemia and trombocytopenia on laboratory tests (Hb: 8.5 gr/dl, Plt: 47000x10^3/ml, WBC: 17100x10^3/ml, Lymp: 14700x10^3/ml). Flow cytometry was compatible with chronic lymphocytic leukemia (CLL). Bone marrow biopsy showed involvement of atypical lymphoid cell infiltration. We diagnosed patient as CLL/SLL stage 4 (RAI), stage C (Binet). His performance was fit. Genetic analysis of 17p deletion has not been resulted yet. We gave dosage adjusted Fludarabin and Cyclophosphamide chemotherapy as first cycle. Two weeks after chemotherapy he was admitted to emergency department with neutropenic fewer. We hospitalized the patient and started ampirical antibiotic treatment and G-CSF. On the seventh day of hospital stay, he had headache, left eyelid swelling and periorbital edema. He had still neutropenia despite G-CSF usage. Paranasal sinus computerized tomography (PNCT) revealed soft tissue lesion on left nasal cavity that oblitarates nasal passage and borders can not clearly be distunguished from middle concha. Cranial MRI showed lesion 23x33 mm in diameter on the level of left anterior ethmoidal cell, lamina propricea, left bulbus oculi which is adjacent to medial rectus muscle, left half of nasal bone involves left nasolacrimal gland and also has air spaces and no contrast enhacement. We performed soft tissue biopsy from that lesion and immediately started on ampirical liposomal amphotericin-B treatment for opportunistic fungal infections. But his eye swelling, periorbital edema and headache progressed so that surgical resection was performed by otolaryngologists due to consideration of invasive fungal infection spreading from paranasal cavity to orbital region. Lesion biyopsy resulted as mucormycosis and we continued Amphotericin-B and G-CSF treatment. His neutropenia recovered on the 14th day of hospital stay and his other complaints improved progressively. Cranial MRI scan also showed significant improvement on the 30th day of stay. We are still going on Amphotericin-B treatment.

Discussion: Rituximab - fludarabine - cyclophosphamide therapy is first line treatment in fit CLL patients. Our patient had invasive fungal infection within 21 days of receiving fludarabine in spite of taking only one cycle of chemotherapy regimen. He was treated successfully with extensive surgical debridement and intravenous liposomal amphotericin B. This case showed us that fludarabine-based regimens can cause severe immunosuppression and fungal infections even after first cycle of chemotherapy. Mortality is better than past in mucormycosis if we start antifungal antibiotics and perform surgical resection as soon as possible.

Keywords: Mucormycosis, Chronic Lymphocytic Leukemia, Fludarabine

Multiple Myeloma

PS-69 **Abstract Referance: 88**

ATYPICAL RECURRENCE PRESENTATION IN A PATIENT WITH MULTIPLE MYELOMA: SPHENOIDAL AND ETHMOIDAL SINUS INVOLVEMENT

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Introduction: Plasma cell neoplasms of the head and neck region can be extramedullary plasmacytoma (EMPs)

or solitary plasmacytoma of the bone, and local manifestations of multiple myeloma. Involvement of sphenoid sinus and ethmoidal sinus has been rarely reported in multiple myeloma. We report herein a multiple myeloma recurrence after first line therapy with involvement of ethmoidal and sphenoial sinuses leading to rigth eyeball proptosis and eye swelling.

Case report: A 49-year-old man admitted to hematology department of our hospital with the complaints of fatigue and right eyeball proptosis. His medical history revealed that firstly the patient was referred to another hospital in September 2016 with pain on lumbosacral region and weakness. On investigations he was diagnosed as lambda light chain Multiple Myeloma based on aspiration of bone marrow which showed 40% plasma cells. PET-CT revealed multiple lytic lesions on humerus, costovertebral bones, bilateral iliac bones and right inferior pubic bone. The patient has been started on treatment of Cyclophosphamide and Dexamethasone. After 2 cycles of induction treatment bone marrow biopsy was performed there and revealed 3% of monoclonal plasma cells. Third cycle of treatment was given in December 2016 and referred to our center for autologous stem cell transplantation. We accepted patient and decided to begin stem cell mobilization as soon as possible. But after a short time, he admitted to our department with the complaints of right eyeball proptosis, eye swelling and redness, and severe bone pain on lumbosacral region. Vision field test was normal. Paranasal sinus CT revealed an opacification resulted totally loss of air flow and resorbtion of lamellar bone and lamina propricea on right ethmoidal sinus. MRI scan of cranial and paranasal region showed multiple cranial bone lytic lesions and multifocal soft tissue lesions on ethmoidal and sphenoidal sinuses. We also detected a mass of 16 cm in diameter between T6-T11 vertebral region that destructed costal cartilage and paravertebral muscles on thoracolumbar MRI scan. We performed again PET-CT and it revealed enhanced activities on soft tissue lesion fullfilling right sphenoidal and right ethmoidal sinuses and on mass between T6–11 vertebral bones. His urine protein electrophoresis resulted M spike and lambda monoclonal band found on urine immunfixation. Serum IFE and PE was normal. He had elevated serum calcium level. We performed bone marrow biopsy and there was 90% plasma cells. We diagnosed patient as relapsed multiple myeloma with multiple lytic bone lesions, involvement of paranasal sinuses and thoracal vertebral region. Radiotherapy was given on thoracal mass and we started on Bortezomibe, Cyclophosphamide and Dexamethasone chemotherapy regimen.

Discussion: Plasma cell neoplasms are unusual tumors of the head and neck region. Extraosseous manifestations of MM may also found at these sites. Our patient presented with multiple myeloma relapsed with sphenoidal and ethmoidal sinus involvement. The gold standart treatment of MM is autologous stem cell transplantation so we again noticed in this case that we must perform ASCT as soon as possible before relapse occurence.

Keywords: Multiple Myeloma, Sphenoid Sinus, Ethmoid Sinus

Non-Hodgkin's Lymphoma

PS-70 **Abstract Referance: 89**

A RARE CASE OF DIFFUSE LARGE B-CELL LYMPHOMA DIAGNOSED BY SPLENECTOMY

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Introduction: Diffuse large B-cell lymphomas (DLBCL) are a heterogeneous tumour group which consisting of transformed and large B cells accounting for 30 to 40 percent of Non-Hodgkin lymphomas. Incidence increases with age and the median age at diagnosis is seventh decade. DLBCL usually occurs as de novo and can also arise as a result of histologic transformation from an indolent lymhoma. The disease typically presents as an exponential nodal or extranodal mass with systemic symptoms. Approximately 50 to 60 percent of patients present with advanced stage. Our case, which is diagnosed by splenectomy, is presented as a contribution to the literature.

Case: The patient was a 45-year-old man. Hepatic dysfunction was found in August 2016. A splenic tumor was suspected based on his pain in the left side of the abdomen. He was admitted to our hospital for close inspection and medical treatment. Positron emission tomography-computed tomography (PET-CT) showed strong fluorodeoxyglucose (FDG) accumulation in the splen, lung, stomach and supradiyafragmatic and abdominal lymphadenopathy (suv max 34 in the splen). The serum levels of LDH were elevated (518 U/L), and therefore a diagnosis of malignant lymphoma was suspected. Due to the risk of splenic rupture, a splenectomy was performed. After pathological examination, the patient was diagnosed with diffuse large B-cell malignant lymphoma (DLBCL). Bone marrow biopsy did not reveal any abnormalities. Ann Arbor stage IV AES and IPI score was 4. He was successfully treated with 6 courses of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, and treated 6 courses of the intratekal methotrexat, and maintains a complete remission.

Conclusion: We report our experience of a patient who had diagnosed with splenecyomy, with discussion of the literature.

Keywords: Diffuse large B-cell lymphoma, Splenectomy

Non-Hodgkin's Lymphoma

PS-71 **Abstract Referance: 90**

DIFFUSE LARGE B-CELL LYMPHOMA MANIFESTING AS A BREAST MASS

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Introduction: Extranodal lymphomas constitute 25–50% of all lymphomas. Extranodal lymphomas can be seen in any organ but more frequent in gastrointestinal

system, stomach, skin and head-neck areas. The breast is an uncommon site of lymphoma, which may occur as a either secondary involvement of systemic lymphoma or a primary lesion. In this report, we talked about our patient who applied with a breast mass and who had a biopsy resulting Diffuse Large B Cell Lymphoma.

Case: The patient was a 41 years old-woman. She was admitted because of a mass on the right breast, to the surgery clinic. Breast magnetic resonance imaging reveals a mass lesion of 56x30 mm in size with fine septic and peripheral enhancement. After pathological examination, the patient was diagnosed with diffuse large B-cell malignant lymphoma (DLBCL). CD20 (+), CD10 (+), Bcl6 (+), MUM1 (+), LCA (+). Ki-67% 70. CD5 (-), CD23 (-), CD3 (-), CD38 (-), Bcl2 (-), cyclinD1 (-), CD30 (-), sitokeratin (-). The patient had no B symptoms at the time of referral. Positron emission tomography-computed tomography (PET-CT) showed strong fluorodeoxyglucose (FDG) accumulation in the right breast, right axilla, pleural area, bone marrow (suv max 33 in the breast). The serum levels of LDH were elevated (315 U/L). Ann Arbor stage IV and IPI score was 3. The patient was treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy and intratekal methotrexat for central nervous system prophylaxis.

Conclusion: Diffuse Large B Cell Lymphomas present a highly variable clinical course and marked biological heterogeneity. The primary reason for the rare occurance of primary breast lymphoma is that the lymphoid tissue is low in the mammary gland. if there is a mass in the breast, the lymphoma should be conceived and treatment planning should be done rapidly in this disease which has poor prognosis.

Keywords: Diffuse Large B-Cell Lymphoma, breast mass

Multiple Myeloma

PS-72 **Abstract Referance: 91**

A RARE CASE OF IG D KAPPA MYELOM

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Introduction: Multiple myeloma (MM) is a plasma cell (PC) disorder that induces anemia, skeletal destruction, renal failure and hypercalcemia. IgD MM constitutes ≤2% of all MM cases, displays generally an aggressive phenotype (often with renal failure) and is usually characterized by poor prognosis. IgD-κ occurs only in 3–4% of all IgD MM cases, and is also associated with the difficulty of obtaining a reliable diagnosis. The diagnostic panel for IgD-κ MM should include PC flow cytometry characterization, fluorescence in situ hybridization (FISH), serum protein electrophoresis (SPE), serum immunofixation electrophoresis (sIFE), measurement of serum free light chains (sFLCs) and total heavy chain IgD, and urinary IFE for Bence Jones (BJ) protein. This rare case which Ig D Kappa Myelom is provided for the contribution of the literature.

Case: A 65-year-old woman was admitted for inflammatory low back pain. The symptoms had been present for 4 months. Laboratory test abnormalities included an erythrocyte sedimentation rate of 40 mm/h, anemia, thrombocytopenia. Tests were negative another immunological markers. Serum protein electrophoresis showed hypergammaglobulinemia, kappa monoclonal peak. Immunoelectrophoresis, however, detected a faint IgG kappa band in the blood and but serum Ig G, Ig M and Ig A levels decreased revealed and homogeneous kappa band in the urine. Bone marrow biopsy was found to contain 30% of malignant plasma cells, biopsy for amyloidosis were negative, and neoplastic plasma cells were found positive with Ig D and Kappa and megakaryocytes were found dysplasic. Bone osteolytic lesion not detached. However, the case was accepted as Ig D Kappa Myeloma. The treatment and follow-up of the patient continues

Conclusion: IgD kappa myeloma is a severe variant of myeloma often associated with extraosseous lesions, renal failure, and amyloidosis. The monoclonal component is absent or faint by serum protein electrophoresis, making the diagnosis difficult. The pathogenesis is unclear and the prognosis grim. This rare case which Ig D Kappa Myelom is provided for the contribution of the literature.

Keywords: IG D KAPPA MYELOMA, MULTIPL MYELOM

Other

PS-73 **Abstract Referance: 92**

A CASE OF HODGKIN LYMPHOMA WITH BLEOMYCIN RELATED LUNG TOXICITY

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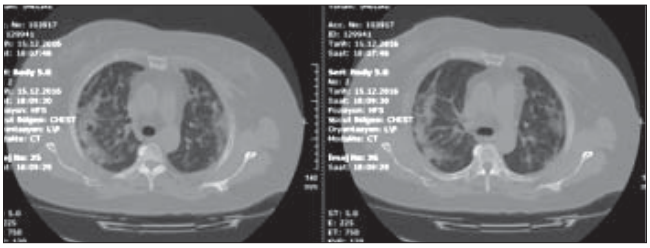
Introduction: Hodgkin's lymphoma is one of the curable cancers and the standard treatment regimen involves combination chemotherapy involving bleomycin. One of the fatal side effect of bleomycin is pulmonary toxicity. Here we present a case of Hodgkin's lymphoma treated with ABVD chemotherapy who had pulmonary toxicity.

Case: The patient was 55 year-old women. She presented with mobile lymph nodes in her right neck, left axillary. The patient had no B symptoms at the time of referral. After pathological examination and imaging the patient was diagnosed with Hodgkin's lymphoma, Ann Arbor stage III and IPS-3 and was started on 4 cycles of ABVD (Adriamycin, Bleomycin, Vincristine, Dacarbazine) regimen. Vincristine treatment was discontinued due to neuropathy during chemotherapy. Before interim evaluation patient got admitted with complaints of dry cough and exertional breathlessness. On examination she was tachpnoeic with coarse crepitations and oxygen saturation was decreased. High-Resolution Computed Tomography (HRCT) thorax was done, which showed interlobar septal thickening and ground glass

attenuation. Diffusing capacity of the lungs for carbon monoxide (DLCO) was decreased. Considering bleomycin-induced pulmoner toxicity, metilprednisone therapy (1 mg/kg/gün) was started and bronchoalveolar lavage was applied. But pneumothorax developed after the procedure and later she died.

Conclusion: Pulmonary toxicity due to bleomycin is one of the fatal side effect on this drug in the treament of Hodgkin lymphoma. The frequency is 10–25%. Risk factors are, cumulative bleomycin dose, renal insufficiency, pulmonary radiation, tobacco history, concomitant use of G-CSF. Bleomycin toxicity should be kept in mind if respiratory distress develops in patients with Hodgkin's lymphoma who are receiving treatment.

Keywords: HODGKIN LYMPHOMA, BLEOMYCIN TOXICITY



Other

PS-74 **Abstract Referance: 94**

METASTATIC GASTRIC CARCINOMA-PRESENTATION AS THROMBO-MICROANGIOPATHIC SYNDROME WITH BONE MARROW NECROSIS

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Thrombo-microangiopathic syndrome tends to be a rare paraneoplastic syndrome in metastatic carcinomas. To contribute to the relevant literature, in the present case report, we focused on a 35-year-old pregnant patient who was admitted to the university hospital with a thrombo-microangiopathic syndrome and did not respond to all the treatments. To specify, the case with metastatic gastric carcinoma had a coagulation necrosis in the bone marrow biopsy. The patient was admitted to our clinic due to fatigue at the 36th week of her pregnancy. The examination results were as follows: Wbc: 7930/mm^3, neu: 6040/mm^3 hb: 8.4 g/dl, plt: 52.000/mm^3, ldh: 1158 U/L, direct coombs (-), indirect coombs (-) bilirubin was moderately high, coagulation parameters were normal. From the examination of the patient, abdominal CT showed a large number of LAM appearance starting from retrokrural distance and filling the stomach small curvature level, sediment axis, portocaval level, paraaortic and aorticaval level. The 36-week patient was delivered by the normal vaginal route. In the peripheral spread, erythroid precursors, fragmentation, anisocytosis, poikilocytosis and polychromatic cells were seen. The platelet count was 2–3 in each area and also rarely large thrombocytes were seen. Our pre-diagnosis was the thrombo-microangiopathic syndrome induced by the pregnancy. The patient had progressive thrombocytopenia and anemia. There was no bleeding diathesis. Plasmapheresis and 0.5 mg/kg/day steroid treatment were initiated. 21 sessions of 18 unit plasmapheresis were performed. Unexpectedly, despite this application, the patient did not respond to the treatment. Anemia and thrombocytopenia were further deepened in the patient with daily platelet and erythrocyte replacement. All the tests for the ethiology of thrombo-microangiopathic syndrome were conducted in the patient with no PNH clone and had a normal ADAMTS 13 activity. Autoimmune, infectious causes, drug use, HUS/TTP, malignant HT and vasculitis were ruled out. Bone marrow biopsy was performed to account for progressive cytopenias. The outcome of pathology of bone marrow biopsy showed the coagulation necrosis. That is why, the presence of malignancy was questioned. For malignancy examination, abdominal USG, skeletal surveillance, abdominopelvic CT and neck CT were planned. Multiple neck lymph nodes in the lower cervical chain and supraclavicular area in the left neck of the neck CT, multiple lymph nodes in the upper abdominal CT were observed in the thoracic and abdominal levels, which reminds us of the lymphoproliferative disease. From the examination of the patient, abdominal CT showed a large number of LAM appearance starting from retrokrural distance and filling the stomach small curvature level, sediment axis, portocaval level, paraaortic and aorticaval level. Left cervical lymph node biopsy was performed. The biopsy result was metastatic adenocarcinoma. The patient was referred to an oncology clinic for solid organ malignancy for chemotherapy. All in all, as haematologists we suggest that in the ethiology of thrombo-microangiopathic syndrome which has not been determined, occult malignancy should be taken in to account.

Keywords: Thrombo-microangiopathic syndrome, bone marrow necrosis, metastatic adenocarcinoma

Multiple Myeloma

PS-75 **Abstract Referance: 97**

THE NEW PROGNOSTIC SIGNIFICANCE OF PLATELET-TO-LYMPHOCYTE RATIOS IN PATIENTS WITH MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is the second common hematologic malignancy that 1% of all tumors in the adults and with a prevelance approximately 15% of hematologic malignancies. Recently, the international staging system (ISS) is using in patients with MM which combines serum β2 microglobulin and albumin levels to classify in three groups. However the platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) have reported as an independent prognostic marker in solid and hematologic malignancy. Therefore our study

aimed to investigate an association between PLR and NLR in the survival time of patients with multipl myeloma.

Materials and Methods: The retrospective study analyzed of 186 patients with diagnosed MM between 2005 and 2015 in Department of Hematology, Dokuz Eylul University. We described including age at diagnosis, gender, disease staging, immunoglobulin (Ig) subtypes, overal survival of all patients. We examined complete blood count (CBC) and biochemical laboratory (calcium, albumin, creatinine and β2 microglobulin) at the diagnosis of patients in this study. ISS was used the staging criteria for patients. The PLR was defined by platelet count divided by the absolute lymphocyte count and NLR was defined by the absolute neutrophil count divided by the absolute lymphocyte count.

Results: The baseline characteristics of patients are listed in Table 1. Among 186 MM patients, 56% were male and 44% were female. The median age was 60 years. (range 29–89) ISS staging of patients had been diagnosed with stage I% 24, stage II% 28 and stage III% 35. (notevaluated% 13) The most prevelant MM type was Ig G (51%), 23% Ig A, 14% of patient light chain disease and others 12%. Among the patients, 41 patients (8%) had severe renal failure. Mean platelet count was 228x103/µL (range36–547x103/µL) mean lymphocyte count was 2000^3/µL (range 200–7.500^3/µL) mean neuthrophil count 4000^3/µL (range 800–12000 ^3/µL). Over median follow-up of 44 months for all patients, 82 deaths 44% were recorded at the last follow-up. The median OS was 44 months (2–146 month). Patients were divided into high and low NLR and PLR groups according to cutoff points from the receiver operating characteristics curve (1.91 and 120.00) The low PLR group experienced inferior overal survival compared with the high PLR group (p 0.005). However there was no significant difference in overall survival between high and low NLR groups (p 0.94).

Conclusion: We conclude that PLR is an independent prognostic factor for OS in Myeloma.

Keywords: Platelet-to-Lymphocyte Ratios, Multiple Myeloma

Non-Hodgkin's Lymphoma

PS-76 **Abstract Referance: 99**

COMPARATIVE ANALYSIS OF THE LEUKEMIC PHASE B CHRONIC LYMPHOPROLIFERATIVE NEOPLASMS

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Introduction: B-cell non-Hodgkin lymphomas mostly present as disseminated diseases involving lymph nodes, spleen, liver, often the bone marrow, in different percent peripheral blood (leukemic phase). Evaluation of the prognostic factors are of high importance for selecting the best type of therapy.

Aim: The objective of this study was to evaluate immunophenotypic profile and clinical characteristics in patients with leukemic phase lymphoma (10 follicular lymphoma (FL), 46 marginal zone lymphoma (MZL) and 44 mantle cell lymphoma (MCL) patients), their possible influence on overall survival (OS), also to evaluate validity of international prognostic indices (IPI).

Methods: Immunophenotyping of peripheral blood by flow cytometry was performed in all (100) patients Statistical analyses were performed to determinate prognostic factors and the impact of analyzed parameters on OS.

Results: In our 3 lymphoma groups male dominate. Median age was 48.9 y (FL), 65.5 y (MZL) and 61.5 y (MCL). Three groups had different median of survival (FL-non achieved, MZL-72 months, MCL-31 months). In small cohort of FL (10 patients), overall response rate was good (9/10), prognostic factors were not identified. In MZL group (28 splenic, 10 nodal and 8 extranodal MZL), nodal MZL had poor overall response, comparing with splenic and extranodal. MCL distribution of patients according to prognostic indices (IPI, s-MIPI) confirmed validity of IPI validity. Cut off value 8 inside MIPI score had predictive significance and divided MCL patients into the 2 groups. Multivariate Cox regression identified >1 EN localization and s-MIPI index with cut off value 8 as predictive markers.

Conclusion: Leukemic phase of FL is rare event that could be analyzed by using multicenter studies. In our group t IPI index had prognostic significance for MZL, for MCL t s-MIPI index was powerful prognostic factor. Among others analyzed parameters we identified some with prognostic significance. New knowledge about lymphoma biology may lead to targeted therapy.

Keywords: Key words: Leukemic phase, MCL, FL, MZL, prognostic factors, IPI, s MIPI, FLIPI

Multiple Myeloma

PS-77 **Abstract Referance: 100**

RARE PRESENTATION OF KIDNEY EXTRAMEDULARY PLASMACYTOMA, THERAPY APPROACH

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Background: Plasmacytomas are malignant plasma cell tumors which are characterized by the proliferation of plasma cells clone that produce monoclonal immunoglobulins. Plasmacytomas can be either or diffuse (multiple myeloma and plasma cell leukemias) or localized (solitary plasmacytoma of bone or extramedullary plasmacytomas). Extramedullary plasmacytomas typically affect patients during middle age (55–60 years) with male predominance (male: female 3 : 1) A renal extramedullary plasmacytoma is rare clinical presentation with small number of cases reported in the literature.

Case report: a 59-year-old male presented with fracture of right femur on April 2009. y, and immobilization had been performed. NMR finding revealed expansive lesion of right femur. Bone scintigraphy demonstrated increased activity also in left tibia and left femur. Biopsy of the expansive lesion of right femur revealed plasmacytoma. Clinical and laboratory findings confirmed the diagnosis of Myeloma Multiplex with Durie-Salmon stage IIIA, IgA type. The patient was treated with six cycles of VAD plus bisphosphonates followed with radiotherapy of the right femur, then until the May of 2012. y. he was treated with Tal-Dex protocol achieving remission of disease. Response maintained until December 2014. y. when patient complained the pain in left hemiabdomen. CT scan of abdomen revealed a 82x94 mm expansive inhomogeneous mass expanded from medial curvature of

left kidney, with pyelon compression, also vessels compression and extension to peripancreatic and periaortic areas, and caudal communication with m. illiopsoas. Biopsy of the mass had been performed and confirmed diagnosis of plasmacytoma. Following this unexpected diagnosis, various examinations were performed including bone marrow aspiration, but there was no evidence of systemic plasma cell disease. taking in consideration his comorbidity (cardiovascular patient and DM type 2) and due to involvement of the surrounding tissues and tumor mass including vessels up to the psoas muscle and following multidisciplinary team discussion, it was decided that initial management was applying chemotherapy. His renal function was intact. He was treated with six cycles CTD protocol without response, than with four cycles of Vel-Dex protocol making progression of disease. CT scan in November 2015. y. showed enlargement of the mass up to 201x 112 mm. We decided to apply new therapy modality with Ribomustin-Pronison therapy and after III cycles we have the satisfactory response with reduction of the mass to 53 mm. We plan to go on with 3 more cycles, than to make new estimation of therapy response.

Conclusion: There are no guidelines for the treatment of renal plasmacytoma. Treatment modality include surgery, chemotherapy and radiotherapy, either alone or in combination. Optimal treatment strategies are difficult to formulate because of the rarity of the tumors. At present, there is no standard treatment for extramedulare plasmacytoma involving the kidney, but the current experiences of treating indicate that combined surgery and radiotherapy is an accepted treatment, depending on the resectability of the lesion. In case of none resectable lesion chemotherapy approach may be therapy option like in our patient.

Keywords: Extramedularis plasmacytoma, therapy

Multiple Myeloma

PS-78 **Abstract Referance: 101**

REMISSION OF PATIENT WITH MAXILLARY SINUS PLASMACYTOMA

Enisa Zaric
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Background: Plasma cell neoplasms have been classified as diffuse (multiple myeloma), or localized disease (solitary plasmacytoma and extramedullary plasmacytoma). The solitary plasmacytoma of the maxillary sinus is rare presentation of disease.

Case report: a 64-year-old male presented on February 2016. year with epistaxis. His anamnesis include Diabetes mellitus type 2 and stabile angina pectoris. Radiographics examinations revealed lesion of mucosis invading left maxillary sinus. Otorhinolaryngologist did biopsy of the lesion. PH finding of resected lesion was plasmacytoma. Patient was hospitalized to hematology department and we performed additional analyses. Bone marrow biopsy did not confirmed bone involvement. Laboratory findings pointes hypercalciemia (Ca 2.6 mg/dl), all other findings were within reference range. PET CT has been performed and confirmed uptake of radiopharmaceutical in left nasal region (SUV max 6.86), also diffuse uptake in bone marrow (8.63). MR of skeleton pointed increased inhomogeneous increased signal in region of spine, also in pelvic bones. Patient was treated with local radiotherapy, than with systemic chemotherapy (4 cycles of VCD protocol) and achieved complete remission. Also autologous stem cell transplantation has been performed.

Conclusion: There are no guidelines for the treatment of solitary plasmacytoma. Treatment modality depend on localization and involved structures and may include surgery, chemotherapy and radiotherapy, either alone or in combination, including autologous transplant procedure. Our patient was threated with radiotherapy followed with chemotherapy and autologous stem cell transplantation. This strategy may be optimal approach taking in consideration complete remission in our patient.

Keywords: Maxillary sinus plasmacytoma, radiotherapy, chemotherapy

Other

PS-79 **Abstract Referance: 102**

IMMUNE THROMBOCYTOPENIC PURPURA ASSOCIATED WITH ULCERATIVE COLITIS

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Background: Ulcerative colitis (UC) have many extraintestinal manifestations, on rare occasions, immune thrombocytopenic purpura (ITP) has been reported as associated. ITP influence of UC clinical course increasing number of bloody bowel movements as one of the important criteria of disease severity. A possible explanation for this association is antigenic mimicry between a platelet surface antigen and bacterial glycoprotein.

Case report: A 33-year-old female presented with weakness, epistaxis, spontaneous bruises over upper and lower extremitates, 2 days of 4 bloody bowel movements per day. Her medical history include UC developed 5 years prior to hospital admission (previously treated with sulfasalazine and corticosteroids in two episodes), also chronic maxillary sinusitis and renal calculosis. On admission, her white cell count was 6.36/µL, hemoglobin of 70 g/dL, and platelet count was 2000/µL. The peripheral smear showed two large size platelets. Coombs tests were negative, serology for virus infections and H. pylori were negative, as well as tumor markers and Lupus anticoagulant antibodies. Stool analyze pointed positivity for Clostridium difficile toxin. Bone marrow aspiration revealed presence of normal number of megakaryocytes with absence of splenomegaly on abdomen ultrasonography. After examination we concluded that her diagnoses is Immune thrombocytopenic purpura. Thyroid gland examination revealed Hashimoto`s thyroiditis. Initially she was treated with intravenous corticosteroids (2 mg per kg of weight), intravenous immunoglobulin (0.4 g per kg of weight 5 days) and tranexamic acid without therapy response (platelet count on day 5 was 6000/µL). Frequency of bloody bowel movement increased, with consultation of gastroenterologist she received oral sulfasalazine, metronidazole and probiotic. Hereafter pulse dose of corticosteroids were administered (40 mg of dexamethasone intravenous per day, 4 days). On day 10 of hospitalization her platelet count increased to 240 000/µL. We go on with corticosteroids therapy, 1 mg per kg of weight, with stepwise reduction. Frequency of bloody stool decreased significantly on day 12 and

repeated test of Clostridium difficile toxin was negative. The patient was discharged after 15 days hospitalization with oral dose of steroids of 40 mg per day and plan of further stepwise reduction, finally with dismiss of corticosteroids. On outpatient follow up 6 months after discharge her thrombocytes level was in reference range. Six months follow up from side of gastroenterologist pointed bad control of UC, also recidivism of Clostridium difficile infection, presence of Candida albicans and Giardia lamblia in stool. Because UC was corticosteroid resistant she started treatment with Infliximab infusion.

Conclusion: Treatment of severe ITP associated with UC with high dose of corticosteroids seems to be effective for ITP control. The use of biological agents is an acceptable alternative in a steroid-resistant case of UC associated with ITP.

Keywords: Immune thrombocytopenic purpura, ulcerative colitis, therapy

Acute Myeloid Leukemia

PS-80 **Abstract Referance: 103**

FUSARIUM ENDOPHTHALMITIS, UNUSUAL AND CHALLENGING INFECTION IN AN ACUTE LEUKEMIA PATIENT

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Introduction: Fusarium species are generally present in soil and organic debris, and they are common pathogens of plants. Though they are occasionally responsible in allergic reactions in immunocompetent individuals, in immunocompromised individuals (especially in patients with hematological malignancies and transplant recipients due to prolonged and profound neutropenia after treatment with highly cytotoxic chemotherapy) invasive fungal infections represent a major complication. Here we present a primary refractory acute myeloid leukemia patient presenting with retinal fusarium endophthalmitis.

Case: 28-year-old male patient with de novo acute myeloid leukemia was admitted to our Hematology clinic. Under the prophylaxis of posaconazole, standard first line intensive treatment with 7+3 (cytarabine+Idarubicin) for remission induction was followed by FLAG-IDA (fludarabine, cytarabine, idarubicin) due to remission failure. Prophylactic posaconazole was switched to empirical voriconazole during febrile neutropenia and probable invasive fungal infection determined with thorax tomography. On the fourth week of second line treatment, remission was not obtained, a full match sibling was determined as eligible for allogeneic transplantation and clofarabine-cytarabine was selected for bridging therapy under the coverage of voriconazole. Before the initiation of chemotherapy, patient complained of blurred vision with the right eye. Fundoscopic exam showed signs of bilateral retinal hemorrhage. Local antibiotic and corticosteroid treatment was initiated. Cranial and orbital MRI showed leukemic infiltration of thalamus and right eye. Conjunctival and intraorbital sample culture showed fusarium infection on the right eye. Liposomal amphothericin B was added to voriconazole for 3 weeks and a control orbital MR scan was performed showing progression of infection. Clinically, intractable severe edema of the eye with progressive infection required enucleation of the right eye. Pathological evaluation of the enucleated eye showed fusarium hyphae with hyaline and septate filaments which dichotomize in abrupt and right angles.

After the debridement of the infected tissue and dual antifungal treatment, the patient was stable in regard of the infection. He underwent allogeneic transplantation and died due to pneumosepsis. The course of the disease was depicted in Table 1.

Discussion. Invasive and opportunistic fungal infections play a major problem for treatment of myeloid leukemia patients. Although prophylactic antifungal treatment shows benefit in reducing the risk of fungal infections atypical and fusarium like species can be encountered in this group of patients. *Fusarium* causes serious morbidity and mortality, and may mimic aspergillosis. Targeted antibiotherapy should be the main goal of treatment and isolation of responsible stains should be supported in every immunocompromised patient

Keywords: acute myeloid leukemia, invasive fungal infeciton

Table 1. Follow-up and course of the disease

Time	Diagnosis	+1 month	+3 months	+4 months	+5 months	+6 months
Event	AML	Refractory AML	Refractory AML, Probable fungal infection with Thorax CT	Refractory AML blurred vision with the right eye-infiltration in thalamus and right eye.	Refractory AML Enucleation and debridement of right eye	Allogeneic stem cell transplant from HLA matched sibling
Treatment	Posaconazole 200 mg (5 mL) PO TID Remission induction 7+3 (cytarabine-idarubicin)	Posaconazole 200 mg (5 mL) PO TID Remission induction FLAG-IDA (fludarabine-cytarabine-idarubicin)	Voriconazole 6 mg/kg IV q12 hr for first 24 hours, then 4 mg/kg IV q12 hr Bridging therapy for allogeneic stem cell transplantation (Clofarabine-Cytarabine)	Voriconazole 4 mg/kg IV q12 hr + Liposomal amphothericin B 5 mg/kg IV qDay	Voriconazole 4 mg/kg IV q12 hr + Liposomal amphothericin B 5 mg/kg IV qDay	Died +21 day of transplantation due to pneumosepsis

Non-Hodgkin's Lymphoma

PS-81 **Abstract Referance: 104**

CALR MUTATION IN A SPLENIC MARGINAL ZONE LYPMHOMA PATIENT

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Calreticulin (CALR) is a ubiquitin, cheparone protein; synthesized by CALR gene which is mainly located in chromosome 19. Mutations in exon 9 of CALR gene are found in JAK-2 negative myeloproliferative neoplams (MPN); %15–30 in ET (essential thrombocytosis) and% 20–30 in MF (Myelofibrosis). Therefore CALR mutations are associated with bone marrow fibrosis, splenomegaly, and anemia. Besides MPNs CALR mutated genes are detected in rheumatologic disesases such as SLE and Sjögren syndrome. CALR mutations are not associated with lypmhocytosis or lymphoma devolopment.

Splenic marginal zone lymphoma (SMZL) is a low grade lyphoma which accounts less than %1 of non

hodgkin lypmhomas. Cytopenias, splenomegaly and bone marrow infiltration is commonly seen in the disease course. Autoimmun manifestations, Hepatitis C seropositivity described in SMZL cases. Antigenic stimulation, NOTCH signaling NF-KB pathway, IGVH somatic hypermutations are thought to contribute the pathogenesis In SMZL. But CALR mutatons stands nowhere near this argument. To date no cases with CALR mutated SMZL reported. Here we try to describe the first patient with CALR mutation and SMZL.

Sixty five year old female patient was admitted to our hospital fatiuge, early satiety and lassitude. Phycial examination revealed a splenomegaly below 5 cm costa curve and bilateral 1.5 cm non tender servical lypmhadenopathies. Laboratuary studies found an anemia, lymphocytosis and thrombocytopenia Hgb 8.1 gr/dl leukocyte count 10.300 mm^3 lymphocyte 7000 mm^3 and thrombocyte count 104.000. Kidney, liver funcitons and biochemical studies are found normal except for LDH which was found 532 U/L (125–220 U/L normal reference). Peripheral blood film demonstrated atypical lymphocytes larger than normal lypmhocytes with basophilic cytoplasma and coarser cromatin structure. Marrow biopsy revealed atypical lymphocyte infiltration with nodular pattern, immunohistochemistry staining of the biopsy found positive for CD 20, CD 25 and negative for CD 5, CD10, CD 23, CD 11 c, CD103, Cyclin D1. Trephine biopsy also demostrated grade 2 increase in reticuler fiber. PET-CT can of the whole body found increased FDG uptake multiple lymhpadenopathies localized servical, jugular, submandibular, supraclavicular, retroclaviculer, paratracheal, axillary, inguinal, external and interal iliac regions; a 178 mm splenomegaly and a diffuse uptake on the spleen. Becasue of the bone marrow fibrosis CALR gene examined and a exon 9 mutation discovered. Based on all of this data patient diagnosed with SMZL with bone marrow involvement.

CALR gene plays an important role immun regulation and apoptosis. In recent years CALR mutation added significant contribution to the knowledge of MPNs. Studies showed us CALR mutated MF patients has lower Hgb and platelet levels and higher lypmhocyte counts than compared with JAK-2 mutated MF patients. Although co-existence with CLL (Chronic Lymphocyic Leukemia) and JAK-2 or CALR positive MPNS are reported in the literature they ocur very rarely. In our patient we described SMZL with marrow involvement and marrow fibrosis. This stiuation may happen incidentally or co-existence of two rare hematologic conditions (MF and SMZL) in a same patient. Further studies are needed to evaluate CALR mutation status and lyphoma developmenta and B-Cell Lypmhocytosis.

Keywords: CALR, Splenic marginal zone lymphoma

Other

PS-82 **Abstract Referance: 105**

SEVERE REFRACTORY IMMUNE THROMBOCYTOPENIA SUCCESSFULLY TREATED WITH ELTROMBOPAG

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Introduction: Idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura (ITP) is a chronic disorder with thrombocytopenia that affects approximately 1 in 10.000 people. ITP is often a diagnosis of exclusion. Severe refractory ITP is clinically challenging and a variety of single or combination chemotherapies have been tried with limited out come. Wereport a case of ITP that was unresponsive to multiple agents including high-dose steroid, IVIG, Rho (D) immuneglobulin, rituximab, azathioprine and immune adsorption. However, it achieved remission with treatment of eltrombopag.

Case: A 18-year-old man was diagnosed with ITP 5 years ago, and had been treated with steroids succesfully. The patient was referred to the hospital with thrombocytopenia and epistaxis, 3 months ago and prednisone was started again. When the steroide response was received and the dose started to decrease, the patient reapplied with 3000 platelets and bleeding. The patient underwent IVIG treatment (2 days) and 5 days pulse steroid, followed by 1 mg/kg steroid. Hemogram was followed-daily. The platelet countd id not goabove 10.000. Than he underwent Rho (D) immuneglobulin but no response was obtained. On diagnosis of avascular necrosis in the patient with kneepain, steroid treatment was terminated. He was tried weekly rutu ximab (4 weeks) and azathioprine (35 days) treatments buttherewasnoresponse. There was also no response in the patient who received immunoadsorption afterwards. Splenectomy could not be performed because the patient had a platelet count <10.000. After these treatments, 50 mg eltrombopag was initiated and there was a rise in the patient's platelets after the 75 mg dose (25. days) was reached. The patient is still using eltrombopag and the platelet count is > 300.000.

Conclusion: We report our experience of a young patient with severe refractory ITP who succesfully treated with eltrombopag.

Keywords: Refractory Immune Thrombocytopenia, Eltrombopag

Stem Cell Transplantation

PS-83 Abstract Referance: 106

CHRONIC GRAFT-VERSUS-HOST DISEASE MANIFESTING AS POLYMYOSITIS AND HYPERCALCEMIA: AN UNCOMMON PRESENTATION

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Graft versus host disease (GVHD) is an immune-mediated disease resulting from a complex interaction between donor and recipient adaptive immunity, chronic GVHD describes more diverse syndrome developing after day 100 of allogeneic hematopoietic stem cell transplantation (HSCT). It occurs in 20–70% of patients with allogeneic HSCT, and frequently seen in patients with older age and history of acute GVHD. It may be an extension of acute GVHD, may occur de novo. Ocular, oral, gastrointestinal, pulmonary, liver, neuromuscular manifestations are mostly seen. Polymyositis is an idiopathic inflammatory myopathy characterized by symmetrical proximal mucle weakness and elevated skeletal muscle enzyme levels. It can be seen in 3.4–7.7% of patients with chronic GVHD also.

A 35-year old male patient applied with polymyositis and hypercalcemia as an uncommon components of chronic GVHD was presented here for contribution to the literature.

He was transplanted from his sister HLA full-matched sibling donor due to acute myeloid leukemia with bad prognostic factors, 12 years ago. There were chronic skin GVHD findings and avascular necrosis of femur head due to steroid usage in his medical history. He applied to the hospital with fatigue, proximal muscle weakness and pain at the 15. years of transplantation. There were abduction limitations at left shoulder and left hip due to aseptic necrosis on physical examination. There were hypercalcemia (13 mg/dL), elevated creatine phosphokinase (CPK) (2826 u/L), SGPT and erytrocyte sedimentation rate (30 mm/hr) on laboratory Results: Because of hypercalcemia, PTH, OH-vitamin D levels also were examined. PTH and 1.25 (OH) 2 vitamin D levels were supressed. PET-CT evaluation to rule out secondary malignancy that may cause polymyositis and hypercalcemia revealed general muscle involvement. But muscle biopsy could't be made because of unwillingness of the patient. Electromyogram (EMG) confirmed the diagnosis.

The patient was accepted as polymyositis as a component of chronic GVHD. Treatment with cyclosporine and steroid resulted with complete remission. He is still under immunesupresive treatment on follow-up.

Keywords: polymyositis with chronic GVHD, hypercalcemia with GVHD

Non-Hodgkin's Lymphoma

PS-84 Abstract Referance: 107

PERIPHERAL T CELL LYMPHOMAS WITH COLONIC INVOLVEMENT: A RARE CASE

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Introduction: Peripheral T Cell Lymphomas (PTCL) is heterogenic group of lymphomas by the means of biological and clinical features and accounts for 10–15% of all lymphomas worldwide. Peripheral T Cell Lymphoma Unspecified (PTCL-U) is the most common type among PTCL and observed in 26% of cases. PTCL has an aggressive character and frequent relapses are common. Most common extranodal involvement can be observed in gastrointestinal tract and skin. In gastrointestinal tract, jejunum is the most common involved part and colonic involvement is rare. In this report we represent a case with PTCL with sigmoid colon involvement.

Case: A 72-years old male admitted to hospital with generalized edema, dyspnea, generalized pain, and weight loss. Physical examination revealed submandibular, submental, preauricular and anterior cervical lymphadenopathies, decreased pulmonary sounds at right lower hemithorax, abdominal distention and ascites. Massive ascites, splenomegaly and wall thickness at the ascending colon near to hepatic flexura and multiple omental and mesenteric lymphadenopathies near this colonic segment have been observed by abdominal ultrasound. Biochemical evaluation of ascitic fluid was consistent with exudative

Results: Whole body CT revealed patchy wall thicknesses at rectum, descending colon and ascending colon, peritoneal wall thickness and intraabdominal excess free water and the findings were consistent with peritoneal carcinomatosis. Colonoscopy for sampling the colonic lesions has been performed and lumen narrowing lesions at descending colon and sigmoid colon has been observed. Biopsy resulted as follicular T helper cell phenotype PTCL. Bone marrow biopsy was normal and the patient has been evaluated as Stage 4B lymphoma and received 2 cycles of CHOP chemotherapy. After those 2 cycles of chemotherapy, PET of patient revealed clinical progression and PESG (cisplatin, etoposide, methylprednisolone) protocol has been started. Because of the increase in pleural effusion of patient, patient has been concerned as chemotherapy resistant and Brentuximab vedotoin 1 therapy has been started. Patient is now clinically stable and has been following at the outpatient clinic.

Discussion: PTCL commonly presents with generalized lympadenopathy or extranodal involvement. Systemic B type symptoms are common and eosinophilia, pruritus and/or hemophagocytosis being observed in some cases. Thirtyeight percent of patients have only nodal involvement, 49% have nodal and extranodal

involvement and 13% of patients have only extranodal involvement. Skin and gastrointestinal tract are the most common extranodal involvement sites. Most common gastrointestinal involvement is seen at jejunum and weight loss and abdominal pain is common in patients at presentation. PTCL diagnosis is done by exclusion of the other subtypes of T cell lymphomas. Best method for the treatment of PTCL is not yet known, so "wait and see", steroid-only therapy, cytotoxic drugs and combined therapies are some options for disease treatment. A conventional therapy like CHOP chemotherapy regimen has limited effectiveness by the means of therapy. Autologous bone marrow transplantation can be first line therapy in high risk patients. Recurrent and patients those are not responsive to therapy can be treated with allogenic bone marrow transplantation. In this case report, we represent a patient with a rare presentation and successful treatment that has been diagnosed as PTCL.

Keywords: peripheral T Cell lymphomas, colonic involvement, non-hodgkin lymphoma

Acute Myeloid Leukemia

PS-85 **Abstract Referance: 108**

GRANULOCYTIC SARCOMA MANIFESTING WITH ATYPICAL LOCALISATION: 3 CASE REPORTS

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Granulocytic sarcoma is the extramedullary presentation of acute myeloid leukemia (AML), myelodisplastic syndrome (MDS) and myeloprolipherative neoplasms. It can also occur as isolated mass anywhere. Less than 1% of AML patients are dominantly presented with granulocytic sarcoma. Granulocytic sarcoma can be seen during any period of AML and MDS. Delay in diagnosis may cause increase in morbidity and mortality in these patients. We are presenting 3 case that are diagnosed with granulocytic sarcoma from appendix, gall-bladder and lip. In first case, granulocytic sarcoma was diagnosed during AML induction period. She had right lower abdominal pain and fever at the 14. th day of chmeothreapy. Because of the deep neutropenia, she was suspected to have typhlitis. She was consultated with general surgery and diagnosed appendicitis due severe abdominal pain localized to right lower quadrant, nausea and vomitting and findings at computed tomography. She had undergone appendectomy and diagnosed granulocytic sarcoma with pathological examination. Second case applied to another hospital with findings of the acute cholecystitis and undergone cholecystectomy. Her cholesistectomy material was revealed granulocytic sarcoma. Her peripheral smear and bone marrow aspiration were all normal. She was treated as AML. Third patient admitted to another hospital with a mass at lower lip. She was treated with topical acyclovir in terms of herpes labialis. But her lesion did not improve and she was referred to our clinic with pancytopenia. She was diagnosed as MDS RAEB-II and lesion was excised. Her biopsy revealed granulocytic sarcoma. These 3 patients are presented here to contribute the literature because of atypical localisation of granulocytic sarcoma and to raise the awareness.

Keywords: granulocytic sarcoma, leukemia, myelodisplastic syndrome

Chronic Lymphocytic Leukemia

PS-86 **Abstract Referance: 109**

SEVERE PNEUMONIA IN A TREATMENT-NAIVE PATIENT WITH CHRONIC LYMPHOCYTC LEUKEMIA.

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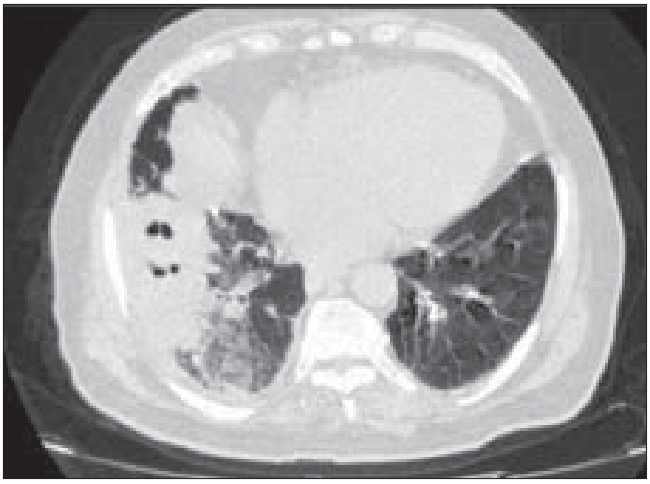
Introduction: Chronic lymphocytic leukaemia (CLL), even when severe, is not directly associated with opportunistic infections. Opportunistic infections that occur with CLL are almost exclusively related to immunosuppression caused by chemotherapeutic drugs used to treat CLL. We report a case of Acinetobacter baumannii pneumonia that occurred in a patient with untreated CLL. Acinetobacter baumannii is an opportunistic bacterial pathogen primarily associated with hospital-acquired infections. Infectious complications have been known for many years to be a major cause of morbidity and mortality in Chronic Lymphocytic Leukemia (CLL) patients. Patients with CLL are predisposed to infections because of both the humoral immunodepression related to stage and duration of CLL, and to a further immunosuppression related to therapy with steroids, cytotoxic drugs and monoclonal antibodies.

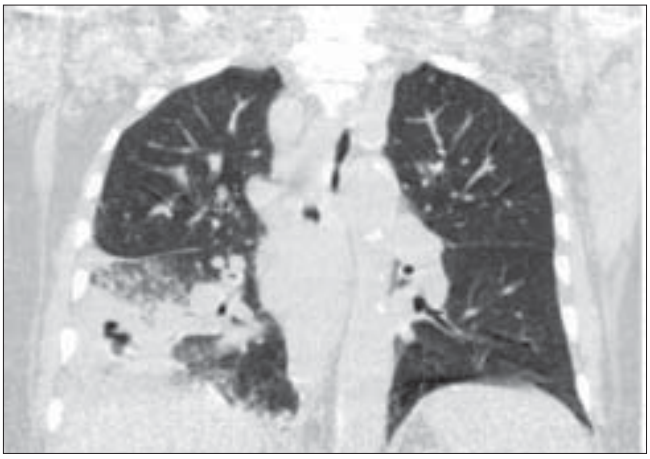
Case: An 80-year-old man, diagnosed 4 years previously with CLL, presented to our emergency department because of productive cough, dyspnea on exertion, sore throat and malaise. He denied fever but noted occasional night sweats. He had never received treatment for CLL. On presentation, the patient had a respiratory rate of 20 breaths/min and his oxygen saturation was %91 on room air. Auscultation revealed bilateral diminished vesicular breath sounds. Bronchial breath sounds, rhonchi and late inspiratory crackles were heard in the area of the right mid-anterior and right mid-lateral lung fields. Laboratory data revealed a white blood cell count of 70700 c/µL with %62 lymphocytes and %38 neutrophils, anemia (hematocrit 32.6% and hemoglobin 10.7 gr/dl), normal thrombocyt count (241000/µl), increased erythrocyte sedimentation rate (ESR = 129 mm/hr) and C-reactive protein (CRP = 380 mg/L), increased serum creatinin (2.03 mg/dL). Resorbtion areas in inferior lobe lateral basal, posterobasal segment of right lung, ground-glass parenchymal opacities and periferal consolidation with central necrosis and minimal pleural effusion on the right lung were detected via the high defination CT scan demonstrated (figure 1–2). As a result of the high defination CT scan findings the patient was treated with meropenem and linezolide. Due to insitability of vital parametres during the inpatient clinic monitorisation, patient was transferred to the intensive care unit. After

stabilasation of the vital parameteres patient retransferred to the inpatient clinic. Finally sputum cultures in three different samples revealed the presence of Acinetobacter baumannii. Inhaler colistin (2x75 mg) was added to the antibiotherapy during 21 days until the externation day. A significant clinical improvement in the patient's condition was noted only a few days later which was reflected in his laboratory investigation as well. The patient was discharged from the hospital after 35 days.

Conclusion: Patients with CLL require astute assessment of infectious symptoms, comprehensive nursing care and symptom management, and education about the disease and its effects. The challenges of caring for patients with CLL include patient management in the outpatient setting, quality-of-life issues, and ongoing support because of the chronicity of the disease.

Keywords: Chronic Lymphocytic Leukemia. pneumonia





Non-Hodgkin's Lymphoma

PS-87 **Abstract Referance: 110**

NON-HODGKIN LYMPHOMA DIAGNOSED IN THE FEMALE GENITAL TRACT: CLINICOPATHOLOGICAL CHARACTERIZATION OF 20 CASES

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Objective: Non-Hodgkin lymphoma (NHL) arising from the gynecologic tract is extremely rare. The incidence of primary extranodal lymphoma arising from the female genital tract is less than 1%. On the other hand, the incidence of involvement of the female genital tract secondary to disseminated lymphoma is about 7–30%. They are most commonly localized in the ovaries (49%), uterus (29%) and fallopian tubes (11%). However, once the disease is disseminated, the distinction between primary and secondary lymphoma is difficult. The aim of this study was to evaluate the presenting features, clinical, morphological and immunohistochemical characteristics of NHL in the female genital tract cases diagnosed in our institution, in view of the literature.

Methods: We searched the medical records of Ege University for the patients diagnosed as NHL in the female genital tract between 1999 and 2016. Twenty cases were reevaluated retrospectively.

Results: Median age was 48.2 years (range: 7–89 years). The most commonly involved sites were ovary, uterine cervix, uterine endometrium, and vagina. Four cases manifested in multiple sites. Bone marrow biopsies were examined in 9 cases and in 5 cases infiltration had been detected. In the ovary, Burkitt's lymphoma was the most common histologic type, followed by diffuse large B-cell lymphoma (DLBCL) and one case is of B lymphoblastic lymphoma. The histologic types of vaginal and vulvar lymphomas were DLBCL in all cases. One of our cases in cervix was of marginal zone lymphoma. The clinicopathologic, and histologic features for all cases are summarized in Table 1.

Conclusion: Primary and secondary lymphomas of the female genital tract are mostly NHL. The most frequent subtype affecting the female genital tract is DLBCL. The clinical presentation of hematologic malignancies of the female genital tract tends to be non-specific such as pelvic mass or vaginal bleeding and may easily be confused with other gynecological malignancies. The ovary is the most common site in the female genital tract to be involved with lymphoma. Most lymphomas arising from the ovary are DLBCL or Burkitt lymphomas. However, B lymphoblastic lymphoma arising from ovary is extremely rare and only few cases have been reported in the literature. Despite of the fact that chronic inflammation has an important role in the development of the thyroid, breast and stomach lymphomas, there are no reliable evidences about the role of chronic inflammation in the development of cervical lymphomas. NHL could be associated with a raised CA-125 level especially in cases of ovarian

involvement and is helpful when following up patients to detect relapse.

Uterine lymphoma must be differentiated from carcinoma because the latter requires surgery, radiotherapy, or chemotherapy depending on the stage, whereas lymphoma is treated with chemotherapy and radiotherapy. Even though hematological malignancies are rare, it is important to be aware of this disease, and to include pelvic lymphoma in the differential diagnosis of gynecologic cancer. Because of its rarity, NHL is often not considered in the differential diagnose of a female genital tract tumor and therefore frequently misdiagnosed as a benign process or confused with other types of tumors or other inflammatory reactive processes.

Keywords: Non-Hodgkin Lymphoma, Female Genital Tract

Table 1. Clinicopathologic Characteristics of Patients in the Female Genital Tract.

Distribution of Cases	n = 20	Mean Age (Range)	BM examined cases/infiltration detected cases
DLBCL	12	57.4 (23–89)	3 cases/none
Burkitt Lenfoma	3	21.7 (12–29)	2 cases/1 case
DLBCL + FL	1	47	1 case/1 case
ALK+ BCL	1	28	
B-ALL	1	7	1 case/1 case
SLL/CLL	1	76	1 case/1 case
MZL	1	52	1 case/1 case
Total	20	48.2 (7–89)	9 cases/5 cases

Multiple Myeloma

PS-88 **Abstract Referance: 111**

REAL-WORLD DATA IN RELAPSED REFRACTORY MYELOMA PATIENTS TREATED WITH CARFILZOMIB, A MULTICENTER TURKISH EXPERIENCE

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Carfilzomib is a potent and irreversible inhibitor of proteasome which exerts clinically significant anti-myeloma effect. Randomized phase 2 and 3 studies have validated carfilzomib as an effective therapy in relapsed or refractory myeloma setting.

In our country, Carfilzomib has recently gained approval in relapsed refractory setting in patients who were both refractory to a proteasome inhibitor and an immunomodulatory drug (imid). Before this approval we were able to use carfilzomib as a single agent or as part of a combination approach via off-label approval of health authority. Here we present our retrospective, multicenter, real life experience among patients with relapsed refractory myeloma and treated with carfilzomib.

95 heavily pre-treated patients from 10 centers were retrospectively evaluated and the data among the use of carfilzomib, its efficacy and safety were collected.

Median age of the patients included in the study was 64 (48–74). All of the patients were refractory to at least one proteasome inhibitor and one imid. Only a small amount of patients has used carfilzomib with one other immunomodulatory drug and remaining majority used as a single agent approach. All patients have received concomitant corticosteroids. Median number of prior therapy line was 4 (3–7). Overall response rate, complete response + Very good partial remission rate and Partial remission rates were 44%, 16% and 28% respectively.

Median duration of response was 5.6 months and median progression free survival was 4.8 months. Hematological toxicity was the major toxicity which were reported at 59% of patients. Other major toxicities were as follows: combined cardiovascular toxicity (heart failure, pulmonary hypertension, systemic hypertension) 25%, renal toxicity 7%.

Carfilzomib based treatment is efficient in advanced multiple myeloma. Even in a heavily pretreated real-life patient group carfilzomib led to a significant response rate. Most important side effects are hematologic and cardiovascular. Patients should be closely monitored for a potential cardiac adverse effect.

Keywords: Relapsed, Refractory, Multiple, Myeloma, Carfilzomib, Turkey

Myeloprofilerative Disorders

PS-89 **Abstract Referance: 112**

A CASE REPORT: CHRONIC EOSINOPHILIC LEUKEMIA ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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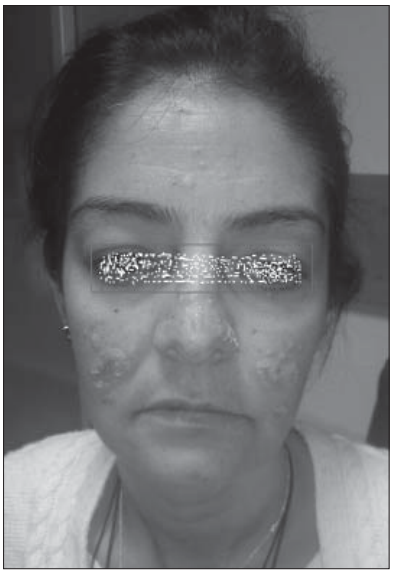
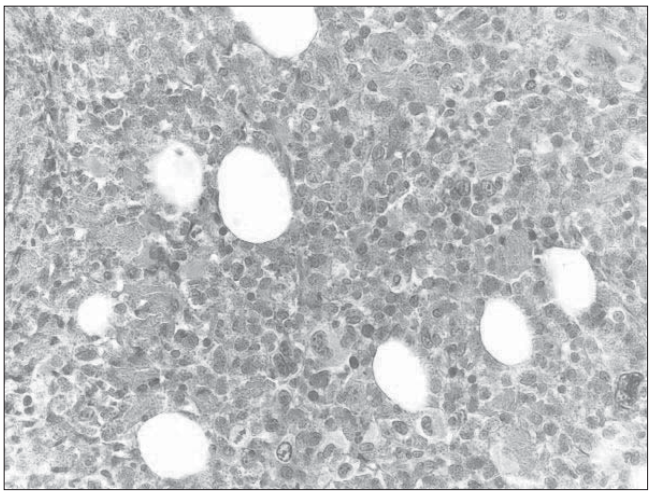
A 40-year-old female patient was admitted to the hospital due to fatigue, arthralgia and weight loss for six months. She was using azathioprine for SLE since two years. She had hepatosplenomegaly and hyperemic, squamous skin lesions on the face. Laboratory evaluation revealed leukocyte and eosinophil counts of 32 and 6.7 x 10 (3)/µL, 70% eosinophils and 2% blasts in bone marrow. Cytogenetic evaluation was normal. She has not BCR/ABL ve FIP1L1/PDGFRA fusion genes. She first received hydroxyurea and then methylprednisolone and imatinib. Now, splenomegaly and skin lesions were regressed. Eosinophil count is 0.1 x 10 (3)/µL. We report this case that chronic eosinophilic leukemia associated with systemic lupus erythematosus.

Keywords: chronic eosinophilic leukemia





Chronic Lymphocytic Leukemia

PS-90 **Abstract Referance: 113**

EFFECT OF DIFFERENT TREATMENT PATTERNS TO COST EFFECTIVENESS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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First and 2nd line treatments were recorded retrospectively in 8 centers (n= 115) from hospital medical records of patients diagnosed with chronic lymphocytic leukemia (CLL) and data collected was analyzed for main cost parameters of duration of hospitalization, total number of specialist visits and G-CSF use. Treatments were classified as fludarabine (FCR-fludarabine, cyclophosphamide, rituximab), bendamustine (benda) and chlorambucil (clb) based. Benda and clb chemotherapy consisted of anti CD20 treatment or not. Median treatment durations were 6 cycles for FCR, 6 cycles for benda and 7.4 months for clb arm. Hospitalization days and G-CSF administration rate was significantly higher in FCR arm compared to benda and clb arms altough mean age in FCR arm was lower. There was a slight significance in terms of specialist visits between FCR and benda arms. No statistical significance was noted between benda and clb regarding age and other cost related parameters (table).

This study confirms that the costs for FCR therapy is higher due to its toxicity. Lack of statistical significance between FCR and clb regarding hospitalization duration and specialist visits might be related with older age of clb arm. Cost related information in CLL treatment is becoming more important for reimbursement decisions of new generation expensive drugs. Cost effectiveness ratios should be calculated both in daily practice and clinical trial settings using data from prospective patient registries.

Keywords: CLL, Cost, Effectiveness, FCR, Clb, Bendamustine

Table 1. Comparison of Cost Parameters Among Different Treatment Groups

	Chlorambucil (n= 38)	FCR (n= 54)	Bendamustine (n= 23)	Clb vs FCR vs Benda	Clb vs FCR	FCR vs Benda	Clb vs Benda
Age**	74 (51–89)	59 (42–82)	70 (49–81)	<0.001	<0.001	0.001	0.058
GCSF Use*	7.9%	33.3%	4.3%	0.001	0.004	0.007	0.558
Duration of Hospitalization (days per admission)**	5 (1–28.5)	5.2 (1–62)	3 (1.5–25)	0.037	0.285	0.011	0.199
Total Number of Visits by a Specialist	11 (2–26)	13 (1–28)	8 (2–25)	0.157	0.628	0.047	0.185
* Percentage	** Median (Min-Max)	comparisons: as p values					

Other

PS-91 **Abstract Referance: 114**

TESTIS LYMPHOMAS, EVALUATION OF 35 CASES, SINGLE CENTER EXPERIENCE

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Testicular lymphoma is rare; accounting for 5% among all testicular malignancies, and 1–2% of all Non Hodgkin lymphomas (NHL), but in the elderly, after sixth decade, it is the most common testicular malignancy. Among the lymphomas diagnosed in testis, diffuse large B-cell lymphoma (DLBCL) is the most common histhological type, though rare, many other types can involve testis. In this study we aimed to evaluate the subtypes of NHL, their clinical, morphological and immunohistochemical characteristics, diagnosed in testicular biopsies or orchidectomy materials in our institution, in view of the literature. We searched the medical records of Ege University Faculty of Medicine Hospital for the patients diagnosed as NHL in testis, between 1999 and 2017. Thirty five cases were reevaluated retrospectively.

Results: Among the 35 cases, DLBCL was the most common type; accounting for 71.4% of all (25 cases), followed by B lymphoblastic lymphoma cases (7/35; 20%); and others were 1 case for each; Burkitt Lymphoma, Extranodal NK/T Cell Lymphoma, nasal type; and Plasmablastic Lymphoma. The age range was 3–84; the median age was 50.2. With respect to histhological subtypes; B lymphoblastic lymphoma cases were all young patients with a median age of 15.2 (range 3–29); where DLBCL patients were all adult age group; the median 61.2 (range 41–84). Among the 23 bone marrow examined cases; 7 patients had bone marrow involvement; four of them were B-lymphoblastic lymphoma, three DLBCL patients. The distribution of cases with type, age and bone marrow involvement are summarized in Table 1.3 of the B lymphoblastic lymphoma cases and 1 of DLBCL cases had central nervous system (CNS) involvement. DLBCL cases were examined based on immunohisthochemical features according to Hans algorithm and classified as activated B cell (ABC) subtype with a higher incidence of 64%, (16/25); and germinal center B cell (GCB) subtype for 36% (9/25).

Conclusions: Some extranodal lymphomas in some different primary sites can behave different from their nodal counterparts. DLBCL is the most common lymphoma in elderly, behave aggressively, and when relapsed, may involve some other extranodal sites; with the propensity to involve immune privileged organs; CNS and contralateral testis involvements are reported to be the common sites, other sites are skin and pleura. Testicular DLBCLs are mostly classified as ABC subtype. Understanding the pathogenesis, immunphenotypic and genetic charactheristics of testicular lymphomas may lead to potential improvements in treatment of these rare but aggressive extranodal lymphomas.

Keywords: Lymphomas, Testis

Table 1.

Distribution of Cases	n =35	Mean Age (Range)	BM examined cases/infiltration detected cases
DLBCL	25	61.2 (41–84)	16/3
B-ALL	7	15.2 (3–29)	5/4
Burkitt Lenfoma	1	26	1/0
Extranodal NK/T-CL	1	34	-
Plasmablasic Lymphoma Total	1	60	1/0
Total	35	50.2 (3–84)	23/7

Multiple Myeloma

PS-92 **Abstract Referance: 115**

EVALUATION OF CYTOKINE LEVELS, TREGS AND MYELOMA CELLS IN DIFFERENT MICROENVIRONMENTS

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Multiple Myeloma (MM) is a genetically heterogeneous hematological cancer in which malignant plasma cells accumulate in and destroy the bone marrow (BM). The complex interactions between MM cells and components of the microenvironment is crucial for developing new therapies. Based on this fact, we aimed to evaluate alterations of cytokine levels, regulatory T cells and MM cells levels in various microenvironment conditions.

Whole BM cells were freshly obtained from healthy donors and RBCs were removed by lysis. BM cells were added to 8 wells in 12 well plate. αMEM medium were supported with 10% FBS and 10% healthy donor's serum (Ns) or MM patient's serum (Ps) depending on the test group. Patient serum was obtained from a serum pool of MM patients which were mostly new diagnosed. CD138+ MM cells of two patients (one with low rish and one with high risk) were sorted with FACS and added to related wells on the 2nd day of BM incubation. CD4+CD25+Foxp3+ Treg cells and CD38+CD45-MM cells were detected on day 1 and 7. Also multi-analyte elisarray was used to analyze IL2, IL4, IL5, IL6, IL10, IL12, IL13, IL17A, IFNY, TNFα, G-CSF and TGFβ1 levels in the supernatant on day 7.

MM cells were 8.7% and 8.2% in Ns and Ps supported cultures of high risk patient and 7.03% and 7.37% in low risk patient's test groups. After 7 days CD38+CD45-MM cell levels did not show a significant increase in high risk patient while increased to 10.55% and 9.74% in low risk patient's co-culture test groups. Treg levels were low at BM+Ns conditions in both low and high risk patients (0.19%, 0.41%) and did not show a significant increase in addition of MM cells (0.23% and 0.75%). In BM+Ps test groups Tregs were 0.16% low risk patient and 0.10% high risk patient and also did not show an increase in BM+Ps+MM groups (0.10% low risk patient and 0.07% high risk patient). However, according to cytokine levels IL-6, IL-10 and TGFβ1 showed a significant increase in both patients, especially in Ps+MM groups.

The serum contains various soluble factors leading to specific interactions of cells in the microenvironment. IL6 (an antagonist of Tregs), IL10 and TGFb1 (immunesuppresive cytokines) levels showed increase based on the serum in co-culture conditions. Although Treg cells and MM cells did not show difference among these groups, other components of microenvironment and IL6, IL10 and TGFb1 levels should be studied in a wide series of patients according to our test groups.

Keywords: Multiple Myeloma, Microenvironments, Tregs, Cytokine

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