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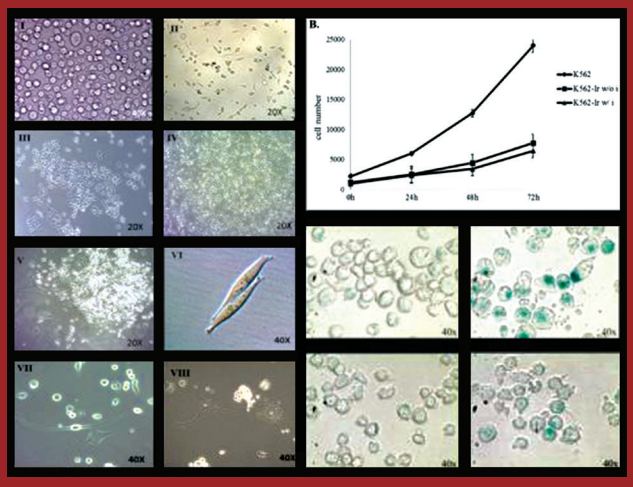
ABSTRACTS

ORAL PRESENTATIONS

POSTER PRESENTATIONS

7th International Congress on Leukemia Lymphoma Myeloma

May 2-4 2019, İstanbul



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An Adaptive Phenotypic Shift Leads to TKI Resistance by Acquisition of Leukemic Stem Cell-Like Properties in CML Cells

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Word Count: A word count for the manuscript, excluding abstract, acknowledgments, figure and table legends, and references, should be provided and should not exceed 2500 words. The word count for the abstract should not exceed 300 words.

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Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

Materials and Methods: Important methods should be written respectively.

Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

Other types of manuscripts, such as reviews, brief reports, and editorials, will be published according to uniform requirements. Provide 3-10 keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies a CONSORT abstract should be provided: http://www.consort-statement.org).

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text, tables, and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

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Cite references in the text, tables, and figures with numbers in square brackets. Number references consecutively according to the order in which they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus). Include among the references any paper accepted, but not yet published, designating the journal followed by "in press".

Examples of References:

1. List all authors

Deeg HJ, O'Donnel M, Tolar J. Optimization of conditioning for marrow transplantation from unrelated donors for patients with aplastic anemia after failure of immunosuppressive therapy. Blood 2006;108:1485-1491.

2. Organization as author

Royal Marsden Hospital Bone Marrow Transplantation Team. Failure of syngeneic bone marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2:742-744.

3. Book

Wintrobe MM. Clinical Hematology, 5th ed. Philadelphia, Lea & Febiger, 1961.

4. Book Chapter

Perutz MF. Molecular anatomy and physiology of hemoglobin. In: Steinberg MH, Forget BG, Higs DR, Nagel RI, (eds). Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management. New York, Cambridge University Press, 2000.

5. Abstract

Drachman JG, Griffin JH, Kaushansky K. The c-Mpl ligand (thrombopoietin) stimulates tyrosine phosphorylation. Blood 1994;84:390a (abstract).

6. Letter to the Editor

Rao PN, Hayworth HR, Carroll AJ, Bowden DW, Pettenati MJ. Further definition of 20q deletion in myeloid leukemia using fluorescence in situ hybridization. Blood 1994;84:2821-2823.

7. Supplement

Alter BP. Fanconi's anemia, transplantation, and cancer. Pediatr Transplant 2005;9(Suppl 7):81-86.

Brief Reports

Abstract length: Not to exceed 150 words.

Article length: Not to exceed 1200 words.

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Results: Present the findings/results in a logical sequence in the text, tables, and figures. Do not repeat all the findings/results in the tables and figures in the text; emphasize and/or summarize only those that are most important.

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COURSE PROGRAM

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AMGEN®

SATELLITE SYMPOSIUM

Scientific Chair: **Meral Beksaç (Ankara University, Turkey)**

Evolving Landscape of Relapsed Multiple Myeloma Treatment with Carfilzomib

Thierry Facon (Lille University Hospital, France)

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- Frontline Therapy of Chronic Lymphocytic Leukemia
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Sevgi Beşışık (İstanbul University, Turkey), Ant Uzay (Acıbadem University, Turkey)

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SCIENTIFIC PROGRAM

MAY 4, 2019

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- Molecular Subtypes of DLBCL and Clinical Implications
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PROCEEDINGS

Basic Immunology-Humoral

Safa BARIS

Marmara University, Istanbul, Turkey

Humoral immunity is accepted as a part of the adaptive immune system and includes B cells and antibody responses. The maturation of B lymphocytes occurs mainly in the bone marrow and continue in the peripheral lymphoid organs including spleen, lymph nodes, tonsils, Peyer patches, and mucosal tissues. Functionally, the humoral immune system protects the host form infections by neutralize and eliminate extracellular microbes and microbial toxins.

The activation of B lymphocytes results in the proliferation of antigen-specific cells, leading to clonal expansion, and in their differentiation into plasma cells, which actively secrete antibodies. In general, there are two types of antibody responses: 1) T-dependent and 2) T-independent. The classification of these responses is based on the requirement for T cell help during the process. In T-dependent immune responses, class-switched memory B cells and plasma cells were developed in germinal centers. The antibodies, which are produced in response to T-dependent antigens show more isotype switching and affinity maturation than antibodies against T-independent antigens. As a result, the most specific and longtime effective antibody productions are generated under the effect of helper T cells, whereas T-independent responses are comparatively naïve and includes predominantly IgM response with less affinity to antigens. Mutations affecting components of the class-switch and somatic hypermutation machinery prevent the formation of memory B and plasma cells expressing IgA, IgG, and IgE.

Currently, it is well known that defects in B-cell development, selection, and function lead to autoimmunity, malignancy, immunodeficiencies and allergy. The most common proportion of the primary immune deficiencies were consisted by humoral immune deficiencies including agammaglobulinemia and common variable immune deficiency (CVID). These diseases are characterized by early onset and predominantly susceptibility to bacterial infections. Up to 90% of patients who receive diagnoses of early-onset hypogammaglobulinemia carry mutations in the Bruton tyrosine kinase (BTK) gene located on the X chromosome, so called as X-linked agammaglobulinemia. The lack of peripheral blood B cells leads to severely reduced antibody titers of all isotypes. The CVID disorder is characterized by hypogammaglobulinemia, low class switched B cells and defective antibody responses. The long term favorable outcomes of these diseases are related to the early diagnosis and treatment.

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Regulatory Issues and Standards for CAR-T Cell Administration

Christian CHABANNON

European society for Blood and Marrow Transplantation (EBMT) Cellular Therapy & Immunobiology Working Party (CTIWP) Chair

CAR-T cells are human immune effectors that are equipped with a chimeric antigen receptor (CAR) targeting a membrane antigen regardless of HLA restriction. Although, evidences of in vivo reprogramming through the use of nanospheres have been published, all CAR-T cells that are currently approved or in development are manufactured in vivo, and mostly through viral transfer of the sequence coding for the CAR. As such they qualify as Gene Therapy Medicinal Products, a sub-category of Advanced Therapy Medicinal Products in the European regulatory framework. Although a small number of cases treated with off-the-shelf allogeneic CAR-T cells have been published, most available information describe the administration of autologous CAR-T cells that are paradigmatic of personalized medicines. The two approved products: tisgenlecleucel (Kymriah, Novartis) and axicabtagene ciloleucel (Yescarta, Kite Pharma/ Gilead) are autologous in nature, and uniquely manufactured for the intended recipient, through a complex supply chain where autologous mononuclear cells are collected by apheresis, shipped to a central manufacturing facility, and returned as a cryopreserved cell suspension following lymphocyte immuno-selection, genetic engineering and expansion. Hospitals or blood banks that provide the starting material act as critical suppliers to the marketing authorization holder (MAH). While rationally designed, CAR-T cells are also examples of targeted therapies that are associated with very significant and potentially lethal side effects. This unique combination of logistical and clinical issues is the reason why MAH must qualify hospitals before they are allowed to deliver the treatment to patients. In this context, there is a need for harmonization of the qualification process across various countries, hospitals and pharmaceutical companies. The Immune Effector Cells standards that have been developed by FACT in the USA, and are now adapted by JACIE in Europe represent a minimal set of essential requirements designed to ensure the quality of the drug product and the safety of the treated patient.

Cell procurement for CAR-T cell manufacturing.

Peripheral blood mononuclear cells (MNC) represent the starting material for autologous or allogeneic CAR-T Cell manufacturing. Allogeneic MNC are obtained from healthy donors, using a procedure that is very similar to the one used for the procurement of "donor lymphocyte infusions" (DLI), administered prophylactically or curatively after allogeneic hematopoietic stem cell transplantation. Since the two approved CAR-T cells are autologous, we will focus on procedural aspects in this situation. Autologous MNC are obtained through apheresis, using the same cell processors and same settings as the ones used in the context of hematopoietic cell transplants. Patients are screened for transmissible diseases in a similar manner to patients undergoing cell collection for autologous transplantation to support high-dose chemotherapy. Most patients are lymphopenic as the result of previous chemotherapy; however the collection and manufacturing process are robust enough that even severely lymphopenic patients can be collected and the DP can be engineered. However, since the Marketing Authorization Holder (MAH) must comply with good manufacturing practices, this includes evaluating and auditing the facilities that procure the staring material: a robust quality management system must thus be in place. The collected cell product is then shipped to the manufacturing facility, according to the MAH instructions; these in some instances include cryopreservation of autologous MNC before shipping. Cross-border shipment will usually require to comply with specific regulatory requirements, as defined by national and international health agencies.

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Treatment with CARTs in Malignant Hemopathies

Alvaro Urbano ISPIZUA

Josep Carreras Leukaemia Research Institue, Barcelona, Spain

The immune system defends the body against diseases. T cells are one of the key soldiers, eliminating infected or abnormal cells. Cancer cells can block those defenses. Now we are genetically modifying the patient's own T cells to make them more intelligent and powerful and to seek and destroy cancer. One version of these genetically modified T cells is called CART T cell therapy, or CART. The "CAR" procedure consists of four phases that can be summarized in a simplified manner: a) preparation of the CAR and integration in a viral vector, b) by leucoapheresis, mononuclear cells are extracted to the patient, b) the T lymphocytes are selected, activated and then they are cultivated with the CAR-viruses, and these cells are expanded ex vivo, c) the patient is administered a conditioning chemotherapy (in general, fludarabine and cyclophosphamide), before reinfusing the genetically modified T lymphocytes. Once CARs are administered, severe immunological reactions are triggered in 20-30% of cases. The success of the treatment with CARs is monitored by the analysis of the residual disease and the detection of blood CARs lymphocytes.

There is a marker, a target for these CARTs cells, called CD19. The CD19 molecule is expressed on the surface of the vast majority of lymphoid B cells, from the most immature stage to the intermediate stage and the mature stage. CD19 is only lost at the end of differentiation of B cells (plasma cells). Therefore, virtually all B lymphoid cells are CD19 +. CART cells are very effective against those diseases that express CD19 on the surface of malignant cells: the malignant transformation of Pro B or Pre B cells (acute lymphoblastic leukemia, or the malignant transformation of mature or activated B cells (diffuse cell lymphoma large, chronic lymphatic leukemia, mantle lymphoma, or follicular lymphoma). Thus, several American and Chinese groups have shown impressive results with the therapy of CART cells directed against CD19 in acute relapsed or refractory B-cell lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma (NHL), and in chronic lymphocytic leukemia. It was not a surprise to anyone that the US Food and Drug Administration (FDA) and the European Agency for Medicines (EMA) approved very quickly the use of these anti CD19 CART in pediatric patients and young adults with ALL R / R and in patients with NHL R / R. Other CARTs, which target BCMA, a molecule expressed almost exclusively in plasma cells, are also showing excellent results in patients with multiple myeloma (MM) previously treated with many anti-MM regimens. The use of a CART targeting the CD30 antigen in patients with Hodgkin's lymphoma and anaplastic lymphomas or T-lymphomas expressing this molecule, and the use of a CARTCD123 in acute myeloid leukemias is also being tested. The effectiveness of this treatment raises the question of whether CARTs will replace hematopoietic stem cell transplantation in a few years or CARTs will be used as a bridge treatment to achieve an excellent remission of the disease and thus bring the patient to optimal conditions. In order to answer this question, a longer follow-up of the clinical evolution of patients treated with CART is needed. Clinical trials are also lacking to see how CARTs behave in earlier phases of these diseases. Clinical trials are already being evaluated in this regard, and the results will be available in the near future. This procedure is marketed in some European countries. The cost of this treatment per patient also raises the concern that it is affordable for all European patients who need it. The production and distribution of academic CARTs could be part of the solution to this economic problem. Unfortunately, less than 10% of academic CARTs around the world are produced in Europe. In this regard, at the Hospital Clínic de Barcelona we have prepared a CAR-CD19 (ARI001) that, after the preclinical development and the authorization of the Spanish Agency for Medicines and Health Products, is already being administered to patients. The clinical trial began in July 2017, and 30 patients with ALL R / R or NHL R / R have already received the ARI001. The CART19 of the Clinical Hospital is showing efficacy and toxicity

results very similar to those published with commercial CARTs. In the coming months we will start a national multicenter clinical trial with a CARTBCMA for patients with MM who have already received at least the 3 families of most effective drugs in this disease.

Conclusions

1- The effectiveness of CARTs in ALL and NHL in relapse or resistant to treatment is extraordinary.
2- The preliminary clinical results of a BCMA CAR in multiple myeloma and a CARCD30 in Hodgkin's lymphoma are very encouraging.
3- It is possible to develop academic CART environments for clinical use in our environment.
4- The CAR CD19 (ARI001) produced at the Hospital Clínic seems safe and very effective.
5- More patients are needed and a longer follow-up to define the role of CARTs in early phases of the disease treatment with CARTs in malignant hemopathies.

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The Emerging Role of MRD in AML

Gert OSSENKOPPELE

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Prognostic factors determined at diagnosis are predictive for outcome while achievement of morphological complete remission (CR) is still an important endpoint during treatment. Residual disease after therapy may reflect the sum of all diagnosis and post-diagnosis resistance mechanisms/factors, its measurement could hypothetically be very instrumental for guiding treatment. The possibility of defining residual disease (measurable residual disease:MRD) far below the level of 5% blast cells is changing the landscape of risk classification.1,2 Currently the two methods mostly used are flowcytometry based immune MRD(MPFC) and molecular MRD assessed by RT-qPCR. Both have advantages and disadvantages. MPFC can be applied in most cases of AML but is less sensitive then RT-qPCR which can however only be applied in 40% of cases. Also new technologies are emerging like next generation sequencing and digital droplet PCR.

Although the concept of MRD negativity as an indicator for the quality of treatment response is the same in AML and other hematological diseases such as chronic myeloid leukemia (CML), multiple myeloma (MM), and acute lymphoblastic leukemia (ALL), application of MRD assessment in AML has lagged behind. Retrospective single center studies already demonstrated that MRD detection by MPFC provides strong prognostic information in AML after both induction and consolidation therapy. A couple of studies have now also been performed prospectively in a multicenter setting showing the independent predictive value mainly determined after 2 cycles of chemotherapy.2,3 An example indicative for the usage of molecular MRD was recently published by Ivey et al who showed in a large study by NCRI that the presence of MRD, assessed by Q-PCR of NPM1-mutated transcripts, provided powerful prognostic information independent of other risk factors. Persistence of NPM1-mutated transcripts in blood was present in 15% of the patients after the second chemotherapy cycle and was associated with a greater risk of relapse after 3 years of follow-up than was an absence of such transcripts (82% vs. 30%; hazard ratio, 4.80) and a lower rate of survival (24% vs. 75%; hazard ratio for death, 4.38. 4 Collectively, these studies showed that low levels of MRD were associated with improved survival and lower risk of relapse superior to other well-defined prognostic factors such as AML type, age, WBC count at diagnosis, and classification of cytogenetic risk.

Evidence is accumulating that the presence of MRD assessed by multi-color flow cytometry immediately prior to allogeneic HCT is a strong, independent predictor of post-transplant outcomes in AML.5 In a recent update, Araki et al showed that in 359 adults, the 3-year relapse rate was 67% in MRD positive patients, compared to 22% in MRD negative patients, resulting in OS of 26% vs 73%, respectively.6 Depth of response prior to transplant, as measured by level of MRD, has emerged as one of the most important predictors of transplant outcome. Randomized trials are warranted to determine if MRD-guided pre-emptive therapy is associated with improved outcome. MRD assessment in AML could be used

1) to provide an objective methodology to establish a deeper remission status, 2) to refine outcome prediction and inform post-remission treatment, 3) to identify impending relapse and enable early intervention, 4) to allow more robust posttransplant surveillance, and 5) to use as a surrogate endpoint to accelerate drug testing and approval.

Various major AML trial groups now use MRD status to guide further treatment. The question whether MRD could be used as a surrogate endpoint for survival which would be very helpful for faster dug approval is still unsolved. It is important that MRD assessment should be part of every clinical trial in order to achieve this important goal.

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Choosing First, and Second Line Therapies in the Era of Generic TKI

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Imatinib has become a mainstay of therapy in patients with CML. It induces high cumulative rates of complete cytogenetic responses (CCyR) and improved overall survival (OS), as it was demonstrated in the International Randomized Study of Interferon vs STI571 (imatinib) (the IRIS trial), the German CML-IV study as well as in other independent retrospective analysis performed on patients outside clinical trials. Patients who achieve and maintain CCyR for at least two years have the similar OS to that of a control population without leukemia. In contrary patients who do not achieve optimal cytogenetic or molecular responses to imatinib at defined time points have a worse outcome, characterized by an increased risk of relapse, of progression and of death. Based on this principle the European Leukemia Net (ELN) panel experts and members of the National Comprehensive Cancer Network (NCCN) have established treatment recommendations and the milestones to be achieved during CML therapy with TKIs to match the criteria for optimal response. It has been demonstrated that the achievement of CCyR is associated with the highest probability of long-term survival for CML patients. According to some reports further reduction of BCR-ABL IS level to ≤ 0.1% (MMR) did not improve OS relative to achieve CCyR without MMR, nevertheless a 4-year landmark analysis performed within the context of the German CML-study IV indicates that the achievement of a stable MR4.5 after 4 years is associated with a statistically significant better survival at 8 years with respect to those patients who have achieved CCyR only (without MMR). Stable MR4 or MR4.5 (Deep Molecular response; DMR) seems to be a new, attractive treatment goal for those CML patients who intend to stop TKI therapy. It has been shown in several discontinuation trials that the achievement of durable DMR is needed to obtain a long lasting TFR. The high cost of imatinib and second-generation TKI (2GTKI) therapy is an important concern for healthcare payers, not only in countries with restricted resources. Generic imatinib is already available in several countries. Poland was the first European country where generic drugs entered the market after the reimbursement of branded imatinib was stopped (on 1st July 2014). Some concerns about its efficacy and safety have been raised, causing anxiety among many patients in Poland. Therefore, the Polish Adult Leukemia Group (PALG) Imatinib Generics Registry was established in 2014 to provide clinical data on efficacy and safety in a large cohort of patients, who commenced CML therapy with generic drugs right after the diagnosis or were switched from branded imatinib to generic drug. The results of three years observation suggest that molecular and cytogenetic response rates and side – effect rates on imatinib generics and branded imatinib are alike when used in the upfront setting, as well as when used subsequently. The analysis of patients in the intention–to-treat population of the IRIS trial indicated, that after 10 years of follow-up the percentage of patients achieving DMR accounts for 23.3%, and 21,6% after 6 years of imatinib treatment within another study. Approximately 50% of those who achieve DMR and fulfil the criteria for imatinib discontinuation could achieve long-lasting treatment-free remission (TFR) as demonstrated by many discontinuation trials. The chance for durable TFR have therefore about 10% of patients treated initially and continuously with imatinib or imatinib generic. Patients receiving second generation TKIs (2GTKIs) as initial treatment achieve faster a cytogenetic and molecular responses, have a higher chance to reduce BCR-ABL transcript level to ≤10% at 3 months, and in higher rates achieve DMR. As demonstrated by ENESTnd and ENESTfreedom trials the rates of patients who met the criteria for attempting TFR during therapy with Nilotinib 300 mg BID, Nilotinib 400 mg BID were almost doubled when compared to Imatinib 400 mg QD (37.9%, 34.2% and 21.6%, respectively). The additional benefits for patients treated initially with 2GTKIs include a lower rate of transformation to more advanced phases of CML. It should be emphasized that approximately 15-20% of patients treated initially with imatinib are at high risk of progression

and death in a short time. Nevertheless, some reported long-term toxicity effects, like a higher rate of cardiovascular events, could raise concerns for second- and third-generation TKIs use, particularly in some categories of patients. The comorbidities (such as atherosclerosis and its complications, disorders in lipid and glucose metabolism, congestive heart failure, hypertension, etc.) appear in group of CML patients with increasing with age and with prolongation of TKI therapy incidences. Since many years some efforts are done to characterize and describe the risk profile of CML patients at diagnosis. Recently developed Eutos Long-Term Survival Score (ELTS) was established based on analysis of patients treated with TKIs. Italian observational study reported on ASH 2018 covered 1051 patients newly diagnosed with CML and treated between January 2012 and June 2016 in 66 Italian centers. Five hundred-ten (48.5%) and 541 (51.4%) patients were treated in first-line with imatinib (IMA) and with 2GTKI. The 2GTKI were able to obtain a higher, earlier and deeper molecular response at 3th, 6thand 12thmonth than Imatinib, additionally in the intermediate risk group of patients according to ELTS, administration of 2GTKI was associated with significantly better 4-year OS when compared to imatinib (99% vs 90,5%; p=0,0030). In another analysis presented during last ASH–Conference it was demonstrated that the ELTS can predict achievement of MR3 and MR4 and leukemia-free survival better than Sokal score in elderly (aged > 65 years) patients and is therefore recommended to assess the baseline disease-risk in this group of patients and to select candidates for frontline therapy with 2GTKI minimizing the risk for overtreatment. The prognostic significance of early monitoring of cytogenetics and of BCR-ABL transcript level decline have been suggested in many studies. The depth of cytogenetic and molecular responses within the first year of therapy represent very important prognostic parameters being the strongest predictors not only for OS, progression- free survival (PFS) or event- free survival (EFS), but also defining the chance to achieve deeper molecular responses required for attempting the trial of TKI discontinuation. The reduction of the BCR-ABL transcript level below 10% IS at 3 months is associated with a high statistically significant difference in OS and PFS therefore it represents the most clinically significant early target to be achieved during TKI therapy. The optimal choice of initial and subsequent TKI therapy should take into account the initial risk profile including the phase of CML, safety and tolerability of drug of choice, patient characteristics, particularly age and comorbidities, and last but not least the dynamics of initial and early response to TKI. The special attention should be paid on appropriate, and timely follow-up with cytogenetic and molecular methods, which should be performed in certified, reliable laboratories issuing the results of Real-Time Quantitative PCR (RQ PCR) using the international scale (IS).

Clinical Applications of Prognostic Markers in Chronic Lymphocytic Leukemia

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CLL has an extremely variable natural history with survival from diagnosis ranging from months to decades. Some individuals require little or no therapeutic intervention and enjoy a normal life expectancy. Others require multiple courses of treatment and ultimately die from the disease. The desire to identify prognostic markers in CLL was originally sought to risk stratify these different groups of patients. More recently, prognostic markers have also been used to determine treatment choices and predict response. With the increasing number of new therapies available for CLL, including B-cell receptor (BCR) inhibitors such as Ibrutinib and Idelalisib, Bcl-2 antagonists such as Venetoclax and monoclonal antibodies such as Obinutuzumab, the overall clinical application of prognostic markers has broadened.

The range of prognostic markers is extremely extensive and some of the most traditional also remain the most robust. The clinical staging systems of Rai1 and Binet2 remain useful in predicting whether a patient is likely to progress and can be performed on any patient at time of presentation. However, for patients diagnosed with Rai Stage 0/ Binet Stage A disease, they are not capable of predicting progression: with increasing numbers diagnosed in this group (a result of early diagnosis through increased prevalence of blood testing) their utility is fairly limited for many. Another traditional measure, the lymphocyte doubling time (LDT- where a LDT of >12 months represents an excellent prognosis with <12 months indicating a poorer one), remains clinically robust and simple to perform, although by definition it cannot be measured at a single time point. LDT may actually be represented via serum markers such as beta2 microglobulin3, a marker of cell bulk/turnover, and a test that is readily measurable from blood testing. Flow cytometry based assays, for example measurement of CD38 and ZAP-70 on circulating peripheral blood CLL cells, have been extensively investigated and reported in clinical trials and retrospective series. Their clinical application, however, is limited by lack of standardisation in how these assays are performed and what cut off to use.

As genomic analyses have become more widely available and costs reduced, these have come to the fore. Chromosomal additions and deletions are common, including trisomy 12 and deletions of 6q, 11q, 13q14, and 17p. The pivotal study of Dohner defined specific genomic aberrations that determined prognosis in CLL. This led to standard FISH panels being used, with a hierarchical model for genomic aberration danger existing. Patients with del(17p) have the worse overall prognosis with the hierarchy then being del(11q) > tri(12) > del)13q4. Metaphase cytogenetics is difficult to perform in CLL and often fails, but the advent of array based technologies may supersede FISH allowing for more comprehensive analyses of gross genomic abnormalities in the disease5. There is increasing interest in the significance of the presence of a complex karyotype (usually defined as ≧3 abnormalities) and whether this should determine therapy choices especially after failure of BCR inhibitor therapy6. Importantly, however, no standard definition for complex karyotype exists and different platform usage makes comparisons between series difficult. Gene sequencing is becoming more common, and it is now becoming mandated to sequence the TP53 gene prior to initiation of therapy (especially in the absence of 17p deletion) as this is of vital importance in choosing appropriate licenced therapies: those patients with TP53 disruption (defined as the presence of TP53 mutation or 17p deletion) should not receive chemo-immunotherapy due to poor responses7,8 but be treated with newer agents9. Whole exome and whole genome studies are indicating a huge breadth of abnormalities present in CLL but are not yet suitable for routine clinical application.

The mutational status of the immunoglobulin heavy chain gene (IGHV) was reported twenty years ago as defining two groups

of CLL patients with different prognoses10,11: those patients with unmutated IGHV (as defined by 98% homology or more to the closest germline gene sequence) have significantly poorer outcomes than those with mutated genes. The ability to perform these assays has become easier and recent data suggests that this marker may also be used to guide choice of therapy for patients. Patients with mutated IGHV genes appear to respond extremely well to chemo-immunotherapy, with many obtaining long and durable remissions especially when minimal residual disease negativity is achieved12,13, whereas those patients with unmutated IGHV appear to universally relapse earlier and particularly benefit from newer therapies that target the B cell receptor pathway and anti-apoptotic machinery.

Combining prognostic factors has allowed streamlining of which ones to test for and provides useful clinical information. For example, the combined measurement of IGHV status, chromosomal losses and specific gene mutations allows for prediction of which patients require therapy within 3 years of presentation14. More recently, a CLL-IPI has been proposed using a 10 point weighted grading system assessing TP53 disruption (4), IGHV status (2), Beta2microglobulin (2), Clinical Stage and Age (1)15. This predicts at 5 years whether patients are likely to be alive or dead, will have received treatment or not, and it has also been proposed to be used for treatment recommendations.

In summary, prognostic marker assessment has been a major area of research in CLL for the past few decades. Indeed, many insights into the underlying biology of the disease have been identified through their study, for example linking CD38 expression with the disease microenvironment16. Their clinical application has, until recently, mainly been the ability to predict those progressing patients with overall poorer prognosis. With the advent of newer therapies, including the licensing of Ibrutinib, Idelalisib, Venetoclax and Obinutuzumab, their clinical application may become much more important in determining which therapies to use and what response to expect. Prognostic marker assessment in CLL will be part of the personalized medicine of the future.

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The Management of Chronic Lymphocyctic Leukaemia (CLL) is Undergoing Rapid Change

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In the last decade, chemo-immunotherapy has been the standard of care therapy for treatment naïve patients. Improvements in progression free survival (PFS) and overall survival (OS) of fit patients with CLL without comorbidities were first achieved by the addition of rituximab to the chemotherapy backbone combination consisting of fludarabine and cyclophosphamide (FCR) (1,2,3). Subsequently, it was shown that although bendamustine and rituximab (BR) was inferior to FCR with regards to PFS, it had a more favourable safety profile making it an attractive combination therapy for patients over the age of 65 (4). The German CLL11 study (5,6) and the UK COMPLEMENT study (7) demonstrated a significant PFS advantage in frail patients using chlorambucil & obinutuzumab or chlorambucil & ofatumumab, respectively, compared to chlorambucil alone. Patients treated with the chlorambucil & obinutuzumab combination also showed improved OS compared to those treated with chlorambucil alone.

Following on from the significant step change seen in the management of relapsed CLL using the small molecule B-cell receptor inhibitors (BCRi) ibrutinib and idelalisib or the BCL2 inhibitor venetoclax, these targeted agents are now being tested in the frontline setting.

Burger et al published the results of the RESONATE 2 trial (8) that directly compared chlorambucil against ibrutinib in frail patient with standard risk CLL. Not unexpectedly, this study showed clear superiority of the BCRi, however the study was critiqued for not having the right comparator.

At the 2018 American Society of Hematology meeting, three investigator-led trial provided further evidence for the superiority of ibrutinib with or without anti-CD20 antibody with respect to PFS and safety. These studies directly compared ibrutinib against either chlorambucil & obinutuzumab (9), BR (10) or FCR (11). Importantly, OS of patients treated with Ibrutinib and rituximab was also improved compared to FCR treated patients.

Long-term follow-up of these studies is awaited, especially to decide whether certain subgroups like patients with hypermutation of the immunoglobulin heavy chain still benefit preferentially from FCR treatment. It is likely that ibrutinib will become the new standard of care therapy for patients with therapy-naïve CLL.

However, many outstanding questions still remain. Ibrutinib does not induce minimal residual disease (MRD) negativity and does not cure. Second generation BCRi and combination therapies with antibodies and/or venetoclax and are under evaluation. The available data does not show any advantage of adding anti-CD20 antibodies to ibrutinib. The second question is that of fixed duration therapy or "drug holidays" that may be guided by MRD negativity. Finally, the significant improvements in outcomes of treatment-naïve patients with CLL will inevitably have knock-on effects on the management and long-term outcome of patients with relapsed CLL.

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Treatment of Relapsed Chronic Lymphocytic Leukemia

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Introduction

The development of targeted therapies has radically changed the management of CLL patients. These new agents such as ibrutinib, the first inhibitor of the Bruton tyrosine kinase (BTK), idelalisib, a PI3k delta inhibitor and more recently venetoclax, a bcl2 inhibitor have shown impressive results in the relapse setting. The place of chemoimmunotherapy (CIT) is sharply decreasing. Recent studies demonstrated interesting results with ibrutinib in frontline treatment of CLL, and some authors consider that ibrutinib should represent the standard of care for treatment naive patients, even in the absence of TP53 disruption [1–3]. Nevertheless, at the present time, most patients who relapse have received CIT as first line of treatment. Defining the best strategy in the relapse setting for these patients may differ from those treated with ibrutinib in front line, making the decision even more complicated. The aim of this lecture is to discuss the key questions concerning relapsed CLL.

Relpased CLL after CIT

Most of the early clinical trials of novel agents only included patients relapsing after CIT. The 5-years follow-up of the phase 1b-2 of ibrutinib in relapsed CLL has recently been published, with an overall response rate (ORR) of 89% and a median progression free survival of 51 months [4]. Even if the comparator is questionable, the phase 3 RESONATE study confirmed these results with a 3-years PFS of 59% in the ibrutinib arm, with substantial benefit in all subgroups [5]. The combination of idelalisib and rituximab also demonstrated high efficacy on relapsed CLL, but the toxicity profile of idelalisib has restricted its use [6,7]. Thus, unless limiting comorbidities or comedications, ibrutinib now represents the standard of care in CLL patients relapsing after CIT. Patients with low-risk CLL (ie IGHV-M without unfavorable cytogenetics) relapsing after a prolonged response to CIT could represent an exception. For this particular patients, both CIT and novel agents can be discussed [8,9].

The MURANO trial may challenge the primacy of ibrutinib as first novel agent in this setting. In this phase 3 randomized trial comparing 6 cycles of bendamustine + rituximab (BR) to a 24 months fixed-duration of venetoclax associated with 6 cycles of rituximab (VR), most patients had received one previous line of CIT [10]. With a median follow-up of 36 months, 3-years PFS was 71.4% in the VR arm vs 15.2% in the BR arm (HR 0.16 [95 CI, 0.12 to à.23], p<.001). Moreover, 64% of the patient who had completed the two years of venetoclax had blood minimal residual disease (MRD) < 10^{-4}. Even if the follow-up is still limited, for responding patients, 1-year PFS after venetoclax discontinuation was 87% [10]. This combination has been approved by the European Medicines Agency (EMA) and is an alternative to ibrutinib in patients relapsing after CIT. Medical history, comorbidities and concomitant therapies may be helpful to choose between these two options.

Relapsed CLL after BCR inhibitors

BCR inhibitors (BCRi) discontinuation is mainly due to three reasons: toxicity, Richter syndrome and CLL progression. Discontinuation of treatment because of toxicity often occurs early, during the first year of treatment, and CLL progressions usually occur much later [11,12]. Only very few data on the efficacy of ICT after BCR inhibitors are available, and two option seem valuable : alternative BCRi or venetoclax. Two retrospective studies demonstrated that the reason for first BCRi discontinuation is of great importance. The use of an alternative BCRi is a reasonable option only in case of intolerance to first BCRi. In case of CLL progression, the alternate KI seems unlikely to induce long-term control of CLL [13,14]. In the phase 2 M14-032 trial evaluating the efficacy of venetoclax for CLL patients relapsing after BCRi, median PFS was 24.7 months in the ibrutinib arm. The results of this trial led to venetoclax approval (FDA and EMA) for patients having received at least one BCRi. Nevertheless, relapses after both BCRi and venetoclax represent an unmet need.

Current indication of cellular therapies

In 2007, the European society for Blood and Marrow Transplantation (EBMT) proposed a definition of "high-risk" CLL to identify situations where allogenic stem cell transplantation (allo-SCT) might be a indicated for CLL patients. Patients with i) non-response or early relapse (within 12 months) after purine analogues, (ii) relapse within 24 months after having achieved a response with purine-analogue-based combination therapy, and (iii) patients with p53 abnormalities requiring treatment were considered as "high-risk" [15]. In CLL, because of the emergence of novel therapies, allo-SCT indications have decreased, and less than 20 allo-SCT have been performed in this indication in France in 2018. Moreover, the increasing availability of CAR-T cells may also give alternative options for "high risk" patients [16–18]. Both the EBMT and European Research Initiative on CLL (ERIC) recently proposed new definitions for "high-risk" CLL, along with indications for cellular therapies (ie, allo-SCT or CAR-T cells). CLL "high-risk I" (CIT-resistant) is defined by clinically CIT-resistant disease with TP53 aberrations, but fully responsive to novel agents. For these patients, cellular therapy remains an option only in selected patients with low individual procedure-related risk. For CLL "high-risk II" (CIT- and novel agent-resistant), characterized by increasing exhaustion of pharmacological treatment possibilities, cellular therapies must be considered in all eligible patients [19].

Conclusion and perspectives

Current sequencing of relapse therapies is primarily a consequence of their historical availability rather than an optimal prescription based on biological properties of the drugs. Moreover, the use of these molecules as single agents seems to facilitate the development of resistances [20,21]. Fixed-duration combinations of novel agents, with the goal of deep remission are currently being tested, but defining the best combinations is still challenging. Similarly, identifying the best populations who could profit from these new strategies seems mandatory.

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First-Line Treatment of Hodgkin Lymphoma

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Introduction

Hodgkin lymphoma has become one of the best curable cancers today[1]. Many patients affected with this disease are young and the median age at diagnosis is 34 years. On the other hand, patients aged over 50 years have a poor prognosis, which is even worse in those aged over 65 years. In part, this has to do with the poorer tolerability of aggressive chemotherapy such as BEACOPP escalated or high-dose chemotherapy in this setting. On the other hand, a substantial number of Hodgkin lymphoma patients who are cured from their original disease develop late side effects including secondary neoplasia, organ damage and others such as infertility or fatigue.

The German Hodgkin Study Group (GHSG) divides first-line diagnosed Hodgkin lymphoma patients into early favorable, early unfavorable and advanced stages.

Early favorable HL

Particularly in early favorable Hodgkin lymphoma, i.e. those patients in stages I-II without risk factors, are being treated with 2 cycles of ABVD followed by 20 Gy involved field radiotherapy (IFRT)[2]. Attempts to further reduce toxicity in early favorable Hodgkin lymphoma patients failed with poorer progression free survival (PFS) in those patients who had bleomycin, darcarbizine or both deleted from the original ABVD backbone[3].The more recent GHSG trial in early favorable stages demonstrated that 2 cycles of ABVD only result in significantly poorer outcome as compared to the standard of care, 2 x ABVD + 20 Gy IFRT. The difference in tumor control was 10% at 5 years[4].

Early unfavorable HL

In early unfavorable classical Hodgkin lymphoma (cHL), the HD11 trial by our group showed that there was little difference between 4 cycles of ABVD or 4 cycles of BEACOPP baseline[5]. However, patients receiving only 20 Gy involved field radiotherapy had a significantly poorer outcome as compared to those receiving 30 Gy IFRT after 4 cycles of ABVD and there was no improvement when patients were treated with 4 cycles of BEACOPP baseline. In our follow-up trial (HD14), we then introduced BEACOPP escalated into the treatment of early unfavorable Hodgkin lymphoma so that 2 cycles of BEACOPP escalated were followed by 2 cycles of ABVD plus additional radiotherapy[6]. Other groups in this setting such as the UK NCRI rapid trial showed similar results, i.e. those patients receiving combined modality treatment had significantly better outcomes as those who had ABVD chemotherapy only. The EORTC/GELA/IIL H10 trial showed that those patients in early unfavorable HL receiving 2 cycles of ABVD did much better if they were switched to BEACOPP escalated if PET-positive. Those who were PET-negative after 2 cycles of ABVD just needed 2 additional cycles of ABVD in early favorable and 4 cycles of ABVD in early unfavorable settings.

Advanced stages

For decades, the standard of care in advanced stage Hodgkin lymphoma was MOPP-ABVD or, more recently, 6-8 cycles of ABVD. With this treatment, a tumor control of about 60% at 5 years and an overall survival of 75% can be achieved.[7] This was the rationale by the GHSG to improve the outcome using COPP-ABVD as standard which was compared with 8 cycles of BEACOPP baseline and 8 cycles of BEACOPP escalated. The outcome was substantially improved with the use of 8 cycles of BEACOPP escalated giving an 80% difference between 8 cycles of BEACOPP escalated or 4 double-cycles of COPP-ABVD[8,9]. Follow-up trials then demonstrated that the reduction to 6 cycles of BEACOPP escalated gave significantly better outcomes as compared to 8 cycles of BEACOPP escalated or 8 cycles of BEACOPP baseline[10]. This was demonstrated by the GHSG HD15 trial that also included PET-driven radiotherapy for those patients who were PET-negative irrespective of the size of residual disease. More recently,

the GHSG HD18 trial demonstrated that Hodgkin lymphoma patients in advanced stages who were PET-negative after 2 cycles just needed 2 more cycles of BEACOPP escalated resulting in excellent outcomes of 94.8% at 3 years as compared to 92.3 % for those receiving 6 or 8 cycles of BEACOPP escalated[11]. Even more impressive was the overall survival for these patients with 98.7% of those receiving 4 cycles of BEACOPP escalated only as compared to 95.9% for those receiving 6 or 8 cycles of BEACOPP escalated. Thus, the PET-driven approach in advanced stage Hodgkin lymphoma has become standard of care, which was also demonstrated by our French colleagues[12]. Another trial by the UK RATHL group deleted bleomycin from the ABVD backbone after two cycles of ABVD demonstrating that bleomycin can safely be deleted from the ABVD regimen sparing substantial toxicity for most of these patients[13].

Perspectives

The antibody drug conjugate brentuximab vedotin targeting CD30 has been registered for relapsed and refractory Hodgkin lymphoma patients as well as those who are at high risk after second-line high-dose chemotherapy followed by autologous stem cell transplant[14]. More recently, a combination of brentuximab vedotin plus AVD was compared in a large prospectively randomized trial against 6 cycles of ABVD[15]. The GHSG is also currently evaluating a modified BEACOPP variant incorporating brentuximab vedotin in this setting. More interesting combinations include checkpoint inhibitors that had shown impressive activity in multiple relapsed Hodgkin lymphoma patients[16]. Here, a smaller phase II study with a total of 51 advanced stage Hodgkin lymphoma patients received a combination of AVD plus nivolumab[17]. A similar trial was conducted by the GHSG in a randomized fashion comparing AVD plus nivolumab with a modified regimen that includes 4 cycles of nivolumab alone followed a combination of AVD plus nivolumab (NIVAHL).

Particularly elderly patients with Hodgkin lymphoma have a rather poor prognosis so that new approaches for this very high-risk group are badly needed.

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Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity accounting for approximately 5% of all Hodgkin lymphoma (HL) cases. The disease is characterized by distinct pathological and clinical features. Of note, the malignant lymphocyte predominant cells consistently express CD20 but lack CD30. Clinically, NLPHL mostly has a rather indolent course and patients are usually diagnosed in early stages [1].

First-line treatment of NLPHL

Similarly to classical HL (cHL), treatment of NLPHL is stage-adapted. However, patients with stage IA NLPHL appear to be treated sufficiently with less aggressive approaches than their counterparts with cHL. A larger retrospective study from the German Hodgkin Study Group (GHSG) included patients with stage IA NLPHL who had received involved-field radiotherapy (IF-RT) alone (n=108), extended-field radiotherapy (EF-RT) alone (n=49) or combined-modality treatment (CMT) (n=72). The 8-year progression-free survival (PFS) rates for patients receiving IF-RT, EF-RT and CMT were 91.9%, 84.3% and 88.5% and did thus not differ. The excellent PFS rates translated into 8-year overall survival (OS) rates close to 100% (IF-RT: 99.0%; EF-RT: 95.7%; CMT: 98.6%) [2]. Based on these data and results from additional studies conducted by other groups, limited-field radiotherapy (limited-field RT) alone represents the accepted standard of care for patients with stage IA NLPHL.

The treatment of NLPHL in early stages other than stage IA and intermediate stages usually consists of CMT and is thus very similar to cHL. An analysis from the GHSG included 271 patients with early-stage NLPHL who had received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD-like protocols followed by limited-field RT within the HD7, HD10 and HD13 trials. At 8 years, PFS and OS rates after two or four cycles of chemotherapy plus RT were 83.2% and 95.1%, respectively [3]. A study using the British Columbia Cancer Agency (BCCA) database compared the outcome of early-stage patients treated with radiotherapy (RT) alone (n=32) and patients treated with two cycles of ABVD or ABVD-like chemotherapy followed by RT or ABVD chemotherapy alone (n=56). After a median follow-up of 6.4 years, the 10-year PFS estimate was significantly better for patients receiving chemotherapy-containing treatment than for patients treated with RT alone (91% vs 65%). The OS did not differ between the patient groups [4]. Thus, two cycles of ABVD followed by limited-field RT is the standard approach for early-stage NLPHL at most institutions.

Data on the treatment of intermediate-stage NLPHL are scarce. However, treatment with four cycles of ABVD or ABVD-like chemotherapy followed by limited-field RT results in excellent outcomes and should therefore be considered in this patient group [3].

In advanced NLPHL, cHL approaches such as ABVD or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and the B-cell non-Hodgkin lymphoma protocol R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) have been evaluated. A matched-control analysis using the BCCA database included 42 patients with advanced NLPHL and 84 patients with cHL. Treatment consisted of chemotherapy with ABVD or ABVD-like regimens. The 10-year freedom from treatment failure (FFTF) and OS rates were comparable for both patient groups. However, the definition of FFTF did not include cases of lymphoma recurrence with histological transformation. Those were taken into account in the time to progression (TTP) definition. As a result, the TTP was significantly impaired in

patients initially diagnosed with NLPHL histology as they had a cumulative 15-year transformation rate of 24% [5]. The more aggressive BEACOPP regimen resulted in better treatment results than ABVD. An analysis from the GHSG including 144 patients with advanced NLPHL who had received therapy within the HD9, HD12 and HD15 trials revealed 8-year PFS and OS rates of 76.2% and 87.4% [3]. The largest report on the use of the R-CHOP protocol so far came from the MD Anderson Cancer Center. Fourteen patients with advanced NLPHL who had been treated with R-CHOP optionally followed by RT were included in a retrospective analysis. All patients had responded to treatment. The 5-year PFS rate was 85.7% [6]. Taken together, BEACOPP and R-CHOP result in favorable outcomes in advanced NLPHL. However, no standard of care for this patient group has been established to date.

Treatment of relapsed NLPHL

Different approaches ranging from single-agent anti-CD20 antibody treatment to high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) represent options in relapsed NLPHL.

A phase II study by the Stanford group included 39 patients (18 patients with relapsed NLPHL and 21 patients with previously untreated NLPHL). Patients received four weekly doses of rituximab at 375 mg/m^2 either alone or followed by rituximab maintenance every six months for two years. All patients responded to treatment. After a median follow-up of 9.8 years for patients treated with rituximab alone and 5.0 years for patients receiving rituximab induction followed by rituximab maintenance, 5-year PFS estimates for previously treated patients were 36.4% and 71.4% whereas the 5-year OS estimates were 90.9% and 71.4% after rituximab alone and rituximab induction followed by rituximab maintenance, respectively [7]. More recently, the second-generation anti-CD20 antibody ofatumumab was evaluated in a prospective study including 28 patients with relapsed NLPHL. The overall response rate was 96%. After a median follow-up of 26 months, the 2-year PFS and OS estimates were 80% and 100%, respectively [8]. Thus, single-agent anti-CD20 antibody treatment results in high response rates and durable remissions in a relevant proportion of patients with relapsed NLPHL.

However, patients with NLPHL recurrence who present with high-risk features such as a short time interval between first-line treatment and the diagnosis of relapse are candidates for more aggressive salvage approaches, e.g. high-dose chemotherapy followed by ASCT. The largest analysis evaluating this treatment modality came from the European Society for Blood and Marrow Transplantation. A total of 60 patients were included. The patients had a median of two prior lines of therapy, the median time interval between NLPHL diagnosis and ASCT was 21 months. After a median follow-up of 56 months, the 5-year PFS and OS rates were 66% and 87%, respectively [9].

Risk factors

A prognostic score including the risk factors low serum albumin, male gender and variant NLPHL histology was developed using data from 413 NLPHL patients treated within nine prospective GHSG studies. On the basis of this score, three distinct risk groups with significant differences in terms of PFS and OS could be defined. 5-year PFS rates ranged between 68.7% and 95.2% and OS rates ranged between 88.3% and 98.7% [10].

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Follicular Lymphoma – Focus on Therapy

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Follicular lymphoma (FL) is a heterogenous disease both molecularly and clinically. The outcome has improved continuously during the last two decades, mainly due to the development of combinations based on rituximab (R) (Tan D, et al, 2013; Junlen HR, et al, 2014; Karmali R , et al, 2018). With immunochemotherapy most patients with disseminated disease achieve long-lasting remissions and have an excellent overall survival (OS). However, still most patients, also young ones, have a shorter life expectancy than that of an age-matched healthy population.

Diagnosis

Diagnostic tumor biopsies are required for an adequate diagnosis, preferentially an excisional lymphnode, but also core biopsies are used. Less-invasive sampling techniques, including small-caliber core biopsies or fine-needle aspiration (FNA) are mostly not diagnostic. FL is composed of centroblasts and centrocytes, both CD20+, growing in the follicles of lymph nodes, and is according to the World Health Organization (WHO) classification graded according to the number of centroblasts counted in 10 random neoplastic follicles. FL 1-3a is considered clinically indolent as opposed to grade 3b, which is an aggressive lymphoma. Most FLs harbor the t(14;18) translocation leading to over-expression of the anti-apoptotic gene BCL-2.

Staging

Initial staging includes physical examination; standard laboratory assessments including blood counts with differential, beta-2 microglobulin and LDH; computed tomography (CT) scans of the neck, chest, abdomen, and pelvis; and bone marrow biopsy.

PET-CT is required as a standard component of both the staging and response assessment of FDG-avid lymphoma histologies like FL according to the Lugano Classification, (Cheson BD et al, 2014).

Prognosis and predictive markers

Several risk classifications of FL have been used; the Follicular Lymphoma International Prognostic Index (FLIPI), the FLIPI 2 and PRIMA-PI. FLIPI was elaborated in the pre-rituximab era, and is well-established for predicting OS (Solal-Celigny P, et al, 2004). The FLIPI2 was developed for prediction of failure-free survival in mainly rituximab-treated patients (Federico M, et al, 2009). The computation of nodal areas, used in the FLIPI, is cumbersome and prone to error and the FLIPI2 is easier to calculate, but it is still not used as often as the FLIPI. The PRIMA-PI is based solely on two parameters, bone marrow involvement and serum beta2 microglobulin (ß2m), and is proposed for patients treated with immunochemotherapy (Bachy et al., 2018). The prognostic impact of the total metabolic tumor volume (TMTV) measured at baseline with [18F]fluorodeoxyglucose ([18F]FDG/PET-CT) scans has been shown to add value to FLIPI, especially in patients with high-tumor-burden FL (Meignan M et al, 2016).

More recently a "clinicogenetic" risk model, the m7-FLIPI, based on seven gene mutations, integrated into clinical risk models, has been used to stratify FL patients into "low-risk" and "high-risk" with respect to 5-year failure-free survival after first-line immunochemotherapy (R-CHOP or R-CVP) (Pastore A, et al, 2017). The prognostic significance of copy-number aberrations (CNAs) and copy-neutral loss of heterozygosity (cnLOH) identified by chromosome genomic-Array testing (CGAT) at FL diagnosis has been demonstrated in an US clinical trial. The TP53 and CDKN2A/B deletion was validated in the m-7-FLIPI cohort (Qu X, et al, 2019).

Identifying patients with high risk of progression to a specific therapy, before initial therapy, is unsatisfactory with the above prognostic models. Re-assessment of patient status 12 - 24 months after diagnosis/start of treatment, is another potential prognostic tool. With immunochemotherapy, R-CHOP, around

20% of patients showed progression of disease within 24 months (POD24) and this was related to a short OS (Casulo C et al, 2015). These observations were confirmed and extended in a study including a large dataset from FL patients (Maurer MJ, et al, 2017). Development of an event within or after 12/24 months after initial treatment (EFS12/EFS24) was evaluated. In patients treated initially with R-chemo, an event before 24 months was predictive for short OS. FL patients managed with different treatment strategies, also "wait and watch", and free of events at 12months (EFS 12) following initial management, showed survival rates comparable to rates in an age and sex matched general population.

Reliable predictive tools for patient stratification also before starting therapy are needed for avoiding overtreatment of low-risk patients and prioritizing alternative approaches in high-risk patients.

Efficacy endpoints

Response is valuated according to the Lugano criteria (Cheson BD et al, 2014). The term "indeterminate response" was introduced in the context of immunomodulatory therapy, to identify "unspecific" lesions until these were confirmed as flare/pseudo-progression or true progressive disease, by either biopsy or subsequent imaging (Cheson BD, et al 2016).

Progression-free survival (PFS) is often a primary efficacy endpoint in clinical trials, and is especially adequate if supported by objectively assessed improvement of life quality. Studies on life quality is however sparse.

Several surrogate endpoints have been proposed: One is "maintaining" complete response at 30 months (CCR30), which is an "intermediate" endpoint response (Shi Q et al, 2015). Another is end-of-induction PET (Trottman J, et al, 2018).

These surrogate endpoints have been used mainly for first line FL therapy in clinical trialds, and are not yet widely used in the clinic.

Treatment first-line

Early therapy with chlorambucil has not shown to prolong survival for asymptomatic low-burden patients (Ardeshna KM, et al, 2009). However, rituximab monotherapy in these patients results in delayed time to new treatment with minimum toxicity, but still without a survival benefit (Ardeshna KM, et al, 2014). This is why a "watch and wait" strategy" is still an option. The optimal timing, sequence and choice of therapy still remain matters of debate.

For symptomatic patients with advanced disease and in need of treatment, the combination of rituximab and chemotherapy, often followed by rituximab maintenance, has become standard (Salles G., et al, 2011; Rummel M , et al 2013), but for patients presenting with a slow progression of disease after an initial period of "watch and wait", rituximab single therapy remains a good choice. Results of the clinical studies by the Swiss Group for Clinical Cancer Research (SAKK) and the Nordic Lymphoma Group (NLG) were both positive (Martinello G, et al, 2010; Kimby E, et al 2015). The long-term follow-up of the FL patients from the two NLG trials, with rituximab monotherapy or rituximab in combination with interferon (IFN)-α2a, showed a 72% 10-years survival with no major safety issues and 38% of the patients had not needed any later chemotherapy (Lockmer S, et al. 2018).

Lenalidomide is an immunomodulary drug (IMiD), boosting natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity, thereby enhancing the activity of rituximab against CD20+ tumor cells in vivo (Wu L, et al, 2008). This synergism has been supported by promising results in clinical trials (Fowler N, et al, 2014; Leonard JP, et al, 2015). In the SAKK/3510 trial previously untreated patients were randomized to either R monotherapy (375 mg/m2 intravenously at day 1 of weeks 1 - 4, repeated in responding patients at day 1 of weeks 12-15) or to rituximab (given at the same schedule) in combination with lenalidomide (15 mg daily orally, starting 14 days before the first R administration and continuously given until 14 days after the last, up to a total 18 weeks). Results after a 3-year folow-up is promising (Kimby E. et al, 2017). In the large randomized Relevance trial the efficacy of rituximab plus lenalidomide was similar to that of rituximab plus chemotherapy; but differences were seen in safety profiles, with a higher incidence of grade 3/4 neutropenia and febrile neutropenia of any grade with rituximab plus chemotherapy and a higher incidence of grade 3/4 cutaneous reactions with rituximab plus lenalidomide (Morschauser F. et al, 2018).

Responses in most FL-trials with rituximab + lenalidomide were mostly irrespective of tumor bulk, stage and symptoms, why chemo-free approaches may be applied to both low and high tumor burden patients. However, for patients in need of rapid reduction of tumor burden, chemoimmmunotherapy, mostly R-CHOP, is still considered the best option. For the elderly bendamustine in combination with rituximab is an often used therapy (StiL study, Rummel M, et al 2014). A 5-year update of the BRIGHT study confirmed the findings of StiL, with a better PFS and a similar 5-year OS in BR versus R-CHOP/R-CVP groups (Flinn I, et al, 2014). CHOP or bendamustine in combination with the second generation anti-CD20 antibody obinotuzumab both in induction and maintenance, has favored the new antibody (Marcus R, et al, 2017).

Also with immunochemotherapy, like R-CHOP, around 20% of patients will show early progression of disease with short OS (Casulo C, et al, 2015).

Treatment att progress/relapse

Choice of treatment is often based on duration of response and type of prior therapies, and patient comorbidities. Rituximab monotherapy is a treatment option in patients with a previous response to rituximab, as frequent responses can occur with rituximab retreatment. The first approved indication for single-agent rituximab was for FL patients refractory to chemotherapy (Mc Laughlin P, et al, 1997). The immunomodulatory agent lenalidomide can increase the activity of rituximab (see above). In a phase III, multicenter, randomized trial (AUGMENT), lenalidomide plus rituximab was found more effective than placebo plus rituximab (Leonard et al, 2019). Rituximab was administered once per week for 4 weeks in cycle1 and then day1 of cycles 2 to 5 and lenalidomide or placebo was given orally for 12 cycles. The main endpoint, PFS, was significantly improved with lenalidomide plus rituximab versus placebo plus rituximab with a median duration of 39.4 months versus 14.1 months. Infections ocurred more often with the lenalidomide combination (63% v 49%) and also neutropenia and cutaneous reactions were more common.

In rituximab refractory patients phosphoinositide 3-kinase (PI3K) inhibitors have emerged as effective drugs. Both idelalsib and the newer agent copanlisib are now approved in this setting. These two agents differ in terms of specificity for PI3K isoforms and also in adverse effect profiles. Moreover, while idelalisib is an oral drug, copanlisib is administered intravenously.

Radioimmunotherapy with Zevalin® remains a therapy available for specialized centres. Fondazione Italiana Linfomi (FIL) has designed a response-adapted treatment based on an end-of-treatment PET scan by adding consolidation therapy with 90Y-ibritumomab tiuxetan in the PET-positive group and, at the same time, they study the effect of minimal residual disease in the PET-negative group.

The duration of response has been shown to shortens after each relapse, also after first-line immuno-chemotherapy (Rivas-Delgado A, et al, 2019).

Maintenance therapy

It was shown early that a prolonged treatment with rituximab significantly increases response duration and event-free survival(Ghielmini M, et al. 2004). Later, it was shown that 2-years rituximab maintenance lead to improvements in remission status and duration in both treatment-naïve and relapsed/refractory patients (Salles G, et al, 2011; von Oers, et al 2014). Maintenance also improved OS after a successful induction with R-CVP or R-CHOP, when compared with observation in a meta-analysis (Vidal L. et al 2017). If the good effect of maintenance is true for patients having received rituximab also in first induction is still unknown. Maintenance with binotuzumab has shown a positive effect both after first-line immunochemotherapy (Marcus R, et al, 2017) and in rituximab refractory patients (Sehn L et al, 2017). The effect of maintenance after bendamustine-rituximab/obinotuzumab induction is however questionable due to toxicity and should be further explored. Rituximab in combination with lenalidomide has been used as maintenance and will be further explored (Morschhauser F, et al 2018).

For low-tumour burden patients re-treatment with rituximab seems preferable to an extended schedule (Kahl BS, et al , 2014).

New Therapies

The BTK inhibitor, ibrutinib, and the bcl2 inhibitor venetoclax, have not been promising as single agents, in FL, but studies on combinations are ongoing, also with epigenetic modifiers and checkpoint inhibitors. Each drug is associated with unique, often surprising toxicity profiles. Recently, results from a trial with a triplet combination of rituximab, lenalidomide, and ibrutinib for untreated FL patients were reported. A high incidence of cutaneous toxicity was noticed and the efficacy was not superior to that of rituximab in combination with lenalidomide , why this regimen was eliminated from further study.

EZH2 is a mutation found in 25% of FL and can be targeted by tazemetostat. In relapsed or refractory FL single agent tazemetostat has resulted in an ORR of 82% in patients with EZH2-mutated and 35% in wild-type EZH2 FL (Morschhauser F , et al, 2018).

A new antibody Hu5F9-G4 is blocking the CD47 antigen, a "non-eat me" signal on monocytes/ macrophages, and has shown promising results in combination with rituximab (Advani R, et al, 2018).

Antibody–drug conjugates provide specific delivery of potent microtubule inhibitors or DNA-damaging agents to FL cells, while minimizing the systemic toxicities. Inotuzumab ozogamicin, an anti-CD22 IgG4 antibody linked to calicheamicin, has shown an ORR of 71% in refractory FL-patients. Polatuzumab vedotin, an anti-CD79b IgG conjugated to monomethyl auristatin E, a microtubule inhibitor, is evaluated in clinical trials (Palanca-Wessels MC, et al, 2015; Sehn L, et al, 2018).

Betalutin® is a first-in-class antibody radionuclide (Lutetium-177) conjugate which targets CD37, which is expressed on CD20+/ CD22+ B-cell subset. A cross-fire effect is seen, so that also tumor cells with less antigens or non-accessible tumor cells, are hit by the cytotoxic radiation. Good clinical results have been shown in early trials including rituximab refractory FL pts with ≥ 2 prior lines (ORR 62%, CR 19%) (Holte H, et a l, ASH 2018, abstract 2871).

Bi-specific T-cell engaging antibodies, like blinatumomab, joins CD19-positive B-cells to CD3ε-positive T-cells, resulting in

T-cell-mediated B-cell lysis along with T-cell activation. For FL several such bispecific antibodies are under development.

Therapy with chimeric antigen receptor (CAR) T-cells, autologous T-lymphocytes with engineered receptors for antigen-recognition moieties and T-cell signaling domains, has shown activity in DLBCL and transformed FL. Anti-CD19 CAR T-cells is also an appealing concept in the treatment of refractory FL.

Transformation to aggressive disease

During the course of the disease the lymphoma acquires additional genetic aberrations and may transform to a highly malignant lymphoma, most often diffuse large B-cell lymphoma (DLBCL). These transformed lymphomas tend to have a worse prognosis than their de novo counterparts. The risk of histological transformation as a first event can be significantly reduced by the use of rituximab (Link et al, 2015; Federico M, et al, 2018)

At any clinical suspicion of transformation a PET scan should be performed and if high SUV, especially if localized or a destructive bony lesion, a biopsy is required.

In summary

FL is a heterogenous disease both biologicaly and clinically, but mostly with a long survival. Rituximab in combination with lenalidomide is one alternative to standard immunochemotherapy as first or second line therapy and more toxic immunochemotherapy can be deferred in many patients without compromising outcomes. All therapies, both the type of 1 st-line induction and maintenance, as well as relapse treatment, are of importance for disease-free survival, long-term toxicity and quality of life. Early events following immunochemotherapy identifies a subset of patients who are at high risk for early mortality. There is a great need of new concepts for curative treatment.

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Cellular Therapy for Follicular Lymphoma

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Despite major advances in the treatment of follicular lymphoma, the disease generally remains incurable. Novel targeted agents often require prolonged or continuous administration with issues of cost, compliance and cumulative toxicity. Autologous stem cell transplantation results in very prolonged remissions and cure in up to 50% of patients with chemotherapy-sensitive recurrence. Recent data indicate that salvage autologous transplantation leads to improved survival for patients with early treatment failure, i.e. recurrence within 2 years after appropriate initial treatment. It may be the preferred treatment for such patients. Autologous transplantation has also been extensively investigated in the consolidation treatment of younger patients with high-risk features, but has largely been abandoned in that setting because of concerns over late therapy-related MDS/AML. Purging techniques to reduce graft contamination have been associated with decreased rates of disease recurrence after autologous transplantation, as has post-transplant rituximab maintenance. Allogeneic transplantation has low rates of disease recurrence but a higher rate of complications, despite widespread use of reduced-intensity conditioning. Haplo-transplant, umbilical cord blood transplant or haplo-cord transplants are excellent graft sources for those lacking HLA-identical donors. For transformed lymphoma, autologous transplant improves survival. Novel cellular therapies including CAR T therapy is playing an increasing role in the management of transformed B-cell lymphoma and will likely also find a role follicular lymphoma.

Autologous Transplantation

Follicular lymphoma is an exquisitely chemosensitive disorder, with a high response rate, but upon treatment with conventional chemotherapy also a very high recurrence rate. Dose intensification with autologous stem cell rescue was one of the earliest methods available to overcome inherent resistance of residual lymphoma cells and has proven remarkably effective. With a length of follow up of a minimum of 12 years, 48% of patients with follicular lymphoma, transplanted in second or subsequent remissions, were free from disease progression and 54% were alive at 10 years.[1] But these initial studies also found a high rate of therapy related MDS. The risk for MDS persisted for up to ten years after transplant and its cumulative rate was approximately 10% may have been in part related to use of TBI and, in some patients, to prior chemotherapy exposure. Efforts to further improve on the efficacy of autologous transplant have mostly relied on intensification of the conditioning regimen, but have largely failed. Radio-immunotherapy using tositumomab (Bexxar ®) or ibritumomab (Zevalin®) in combination with BEAM has been extensively tested in recurrent B cell lymphoma, including follicular lymphoma and were not superior to Rituximab BEAM [2,3] Autologous stem cell transplantation has been extensively studied as consolidation of first remission, with most studies conducted in the pre-rituximab era and all comparing high dose chemotherapy to CHOP-like regimens. Most studies found an improvement in progression-free survival but due to transplant associated toxicities, no definitive overall survival advantage was ever established.[4-9] The lack of convincing survival data has led to a consensus statement by the EBMT-Lymphoma working party supporting autologous transplant after relapse, but not as consolidation of first remission [10]. Most recently however, the Spanish group found – with a median follow up of 12 years (interquartile range 8-15 years) - a projected 12 year PFS of 74% for patients transplanted in first remission. They argue that previous studies lacked sufficient follow-up,and that autologous transplant remains a superior treatment. Several recent report provide strong evidence for a benefit of autologous transplantation in patients with unfavorable features, i.e. early treatment failure after appropriate initial therapy.[11]

Allogeneic Transplantation

Allogeneic transplantation was initially investigated as a treatment of last resort in patients with very advanced low grade lymphoma [12]. The rates of disease recurrence after allogeneic transplantation have been remarkably low, establishing it as a highly curative therapy that can often be effective in patients with considerable amounts of residual disease. The advantage of an assuredly lymphoma free graft – exemplified by the low recurrence rates after syngeneic transplant[13]- acting synergistically with graft versus lymphoma (GVL) effect – demonstrated through observations of disease regression after donor lymphocyte infusion [14,15] all contribute to these low rates of disease recurrence.

CAR-T Cells

CAR- T cell technology (Chimeric antigen receptor) has revolutionized the management of B-cell ALL and of refractory diffuse large B cell lymphoma. CAR-T cells are patient-derived-lymphocytes that are transduced in-vitro with a chimeric receptor, part antibody, part co-signaling domain, part T-cell signaling domain. Anti CD19 CAR T have resulted in impressive and durable responses in patients with refractory ALL and large cell lymphoma [16] The CAR T cell field is developing rapidly with studies of modified CARs, and new targets being reported daily. Most of the studies have been conducted in aggressive and transformed lymphoma, where approximately 50% of treated patients obtain durable remissions- a rate of response that is unheard of with other therapies. Experience in untransformed follicular lymphoma remains at present limited although some of the initial observations were made in this setting [17] The toxicity of CAR-T cell therapy is considerable and includes severe cytokine release syndrome and neurological toxicity [18] Commercial products have only recently been approved and the use of CAR T cells is – for now- restricted to experienced centers [19]

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ABSTRACTS

■ Non-Hodgkin's Lymphoma

OP-001 Abstract Referance: 88

EXOSOMAL DNA FROM PLASMA OF PATIENTS WITH DLBCL: COMPARISON DNA METHYLATION PATTERNS OF EZH2-TARGET GENES OF EXOSOMES AND MATCHING PRIMARY TUMOR TISSUE

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Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of aggressive lymphoma, and accounts for approximately 30-40% of non-Hodgkin's lymphomas. The pathogenesis of DLBCL is a highly complex multistep process which is not fully understood. It is well known that exosomes derived from cancer cells are able to transfer important modulators for tumor formation, progression and spread. The current study was designed to assess whether the tumor specific epigenetic alterations detected in the primary tumor may be found in plasma exosomes of patients with DLBCL. In this respect, we focused on *EZH2*-target genes including *CDKN1A*, *CDKN1B*, *CDKN2A*, and *CDKN2B*.

This study included 21 DLBCL patients who did not recieve chemotherapy and 21 age-matched healthy controls. Exosomes were isolated from blood plasma by ultracentrifuge-based protocol and verified by electron microscopy, total protein concentration and western blot. After DNA isolation from the exosomes and primary tumor tissue samples, methylation-specific PCR was used to determine methylation status of the target genes. DNA sequencing was used to determine the presence of mutation in *EZH2*.

In concordance with the primary tumors, unmethylated *CDKN1A* and *CDKN1B* DNAs and methylated *CDKN2A* and *CDKN2B* DNAs were determined in the exosomes isolated from DLBCL patients. In addition to, *EZH2*Y641 mutation was not detected in both exosome samples and primary tumor samples counterparts.

To our best knowledge, this is the first study to show that plasma exosomes include DNA fragments which is in concordance with primary tumors in DLBCL. We thought that plasma exosomes preferentially packed both methylated *CDKN2A* and *CDKN2B* DNAs in accordance with primary tumor tissues and may be a suitable source to investigate the presence of this dual methylation marker.

Keywords: Diffuse Large B-Cell Lymphoma, exosome, DNA methylationn, EZH2-target genes

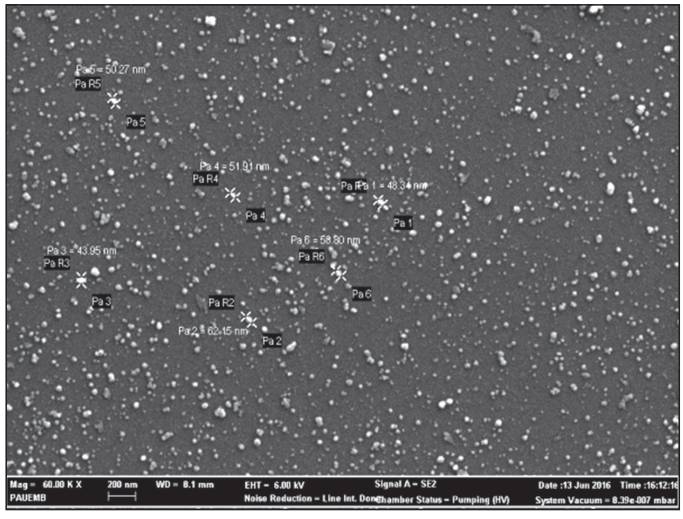

Figure 1. Scanning electron microscopy of plasma exosomes isolated from DLBCL patient.

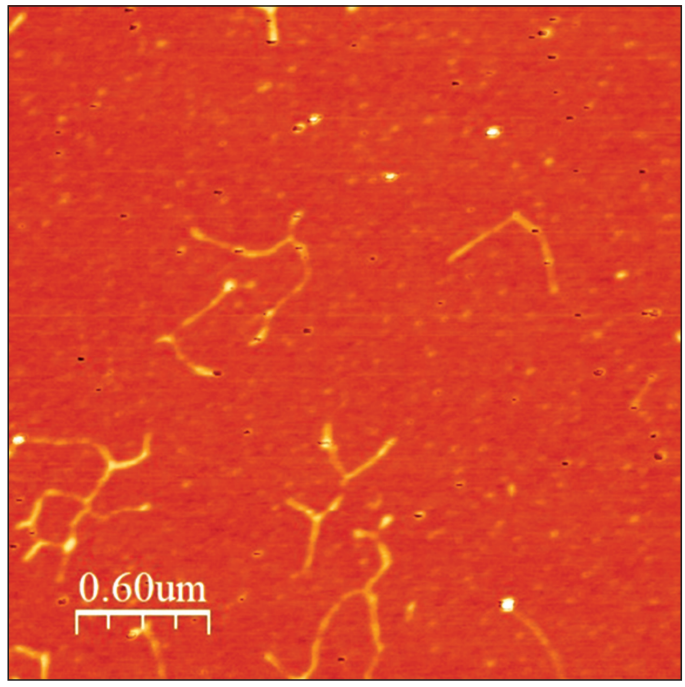

Figure 2. Atomic Force Microscopy image of exosomal DNA. Exosomal DNA was absorbed on a mica surface in the presence of 5 mM Mg2+.

■ Chronic Myeloid Leukemia

OP-002 Abstract Referance : 62

AN ADAPTIVE PHENOTYPIC SHIFT LEADS TO TKI RESISTANCE BY ACQUISITION OF LEUKEMIC STEM CELL-LIKE PROPERTIES IN CML CELLS

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Tyrosine kinase inhibitor (TKI) resistance is a major problem in chronic myeloid leukemia. Phenotype switching has been identified as an escape route for cancer cells. A reversible phenotypic plasticity in tumor cells renders a proportion of cells to be more aggressive and resistant to therapy. To understand the role of cellular plasticity in TKI resistant CML cells, we generated a high dose imatinib-resistant K562 subclone, K562-IR. We've shown that K562-IR cells are not only resistant to imatinib but also to 2nd, 3rd generation TKIs and cytotoxic drugs. Sequencing data revealed that no kinase domain mutations were present. Both K562 and K562-IR showed extensive oncogene amplification, albeit there was no difference between the two. In addition, no difference in BCR-ABL mRNA expression levels was observed. No difference in the inhibition of p-BCR-ABL, p-STAT5, p-CrkL and PDGF signaling between K562 and K562-IR cells, following imatinib treatment was observed; indicating imatinib is sufficiently active and functional in both cell lines. K562-IR cells are capable in growing in monolayers, proliferate slower than their parental counterparts and are resistant to doxorubicin-induced senescence. Unlike its parental cell line, TKI resistant K562-IR cells form tumor spheroids, express high levels of E-cadherin, caveolin-1, CD44 and decreased β-catenin.

Expression of CD45 is significantly reduced in resistant cells; suggesting that K562-IR cells are gradually drifting away from their hematological origin. Cell surface expression of CD33, CD146, and CD65 were also decreased.

CD34 and CD38 are markers for both HSC and LSCs. K562 and K562-IR cells are negative for CD38 in repeated experiments. CD34 expression was either negative or displayed low positivity (1-4%) and comparable in both cell line. Their CD34-/CD38- and decreased β-catenin expression deviates from the accepted LSC phenotype, albeit high CD44 expression.

In CML, we propose that cells undergone "adaptive phenotypic shift" will display different transcriptional frameworks; some partially, others fully compatible with the LSC/CSCs phenotype. Neoplastic cells have the potential of phenotype switching, however only a minority succeeds at any given time. Subset of cells defined as LSC/CSCs may be transient states rather than entities. Recognizing APS has great clinical importance. With LSC/CSC targeted therapies underway, the difference between treating an entity and a spectrum of dynamic reversible states will have conclusive effects on the outcome. APS also needs to be investigated in the context of leukemic cell dormancy and recurrence after withdrawal of TKI treatment in CML. The achievement of long-term clinical responses in targeted therapy will depend on successful targeting of these adaptive phenotypic modulations in cancer cells.

Keywords: Chronic myeloid leukemia, drug resistance, cancer stem cell, transcriptional instability, adaptive phenotypic shift

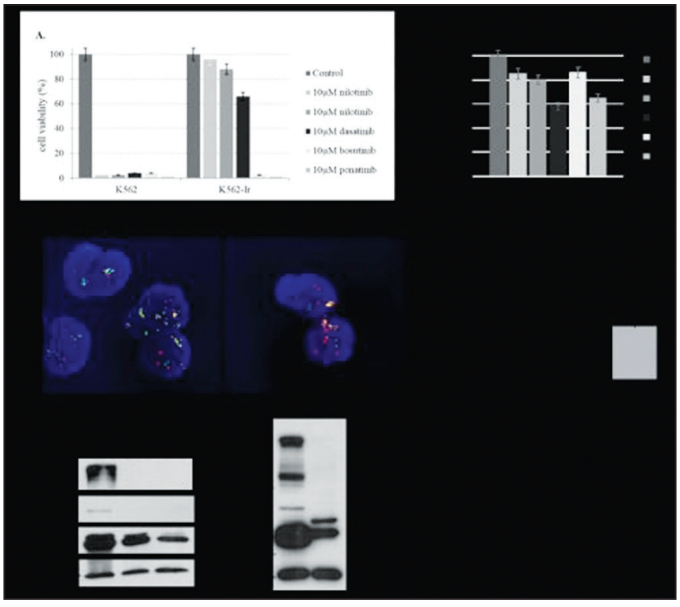

Figure 1. K562-IR cells are resistant to TKIs and do not conform to known TKI resistance mechanisms. A. Cell viability of K562 and K562-Ir cell treated with 10μM TKIs B. Cell viability of K562-IR cells treated with Cmax (daily clinical dose) concentrations. Flow cy

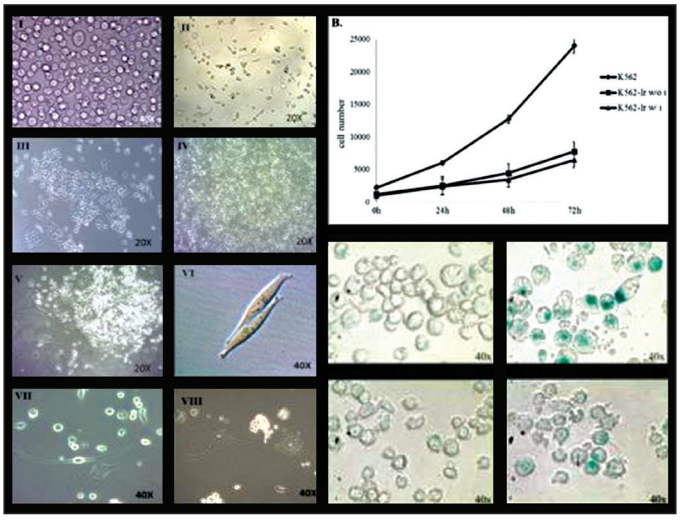

Figure 2. Cellular morphology and proliferative properties of K562-IR cells. A. K562 parental cells (I). K562-IR cells 24h day after of a new passage. A few adherent cells are observed. (II). Proliferation of adherent K562-IR cells (III). Monolayer of K562-IR cell

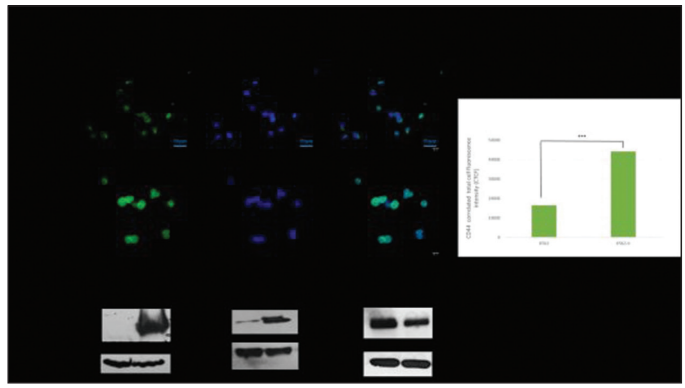

Figure 3. Protein expressions of CD44, Caveolin-1, and B-catenin in K562 and K562-IR cells. A. CD44 immunofluorescence staining. DAPI was used for nuclear visualization. Total corrected cellular fluorescence (TCCF) intensity of CD44 immunofluorescence images (righ)

■ Chronic Myeloid Leukemia

OP-003 Abstract Referance : 98

LONG NONCODING RNA HOTAIR IS A NEW POTENTIAL BIOMARKER FOR CHRONIC MYELOID LEUKEMIA (CML) NOT FOR ACUTE MYELOID LEUKEMIA (AML) IN TURKISH PATIENTS

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Homeobox Transcript Antisense Intergenic RNA (HOTAIR) is a long non-coding RNA that is reported to be more expressed in various cancers in humans compared to non-cancerous adjacent tissues in recent studies. However, little is known about the role of *HOTAIR* in acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). In this study, we aimed to investigate the relationship of *HOTAIR* and *HOXD* genes with leukemia such as AML and CML. Expression levels of *HOXD8, HOXD9* and *HOXD11* genes from *HOXD* genes and *HOTAIR* were determined from peripheral blood samples of 30 AML and 30 CML patients and 20 healthy controls as control group by Real Time PCR method. The expression levels of *HOXD9* gene in the AML patients was significantly lower than the control group ($p < 0.05$). There was no statistically significant difference in the expression levels of *HOTAIR* and *HOXD11* and *HOXD8* genes in the AML patients when compared to the control group ($p > 0.05$). In the newly diagnosed CML patient group; there was a statistically significant increase in the expression level of the *HOTAIR* gene compared to the control group ($p<0.05$). The expression levels of *HOXD9* and *HOXD11* genes in CML patient groups were found to be statistically significantly lower than control group ($p<0.05$).

This study was supported by Erciyes University Scientific Research Projects Unit as TYL-2016-6245 project and Erciyes University Ethics Committee received approval.

Our study showed that *HOTAIR* is not a biomarker in the diagnosis of AML and *HOTAIR* expression is not significantly correlated with the clinicopathological prognostic characteristics of AML. There is still a need for more extensive studies on the level of *HOTAIR* expression in patients with AML.

As a result; It can be said that the *HOTAIR* gene is oncogenic by suppressing the expression of *HOXD9* and *HOXD11* genes in CML patients. In addition, our study, clinical route and drug use of CML patients were followed. Expression level of *HOXD11* and *HOXD8* genes were found to be significantly lower in patients with drug exchange ($p > 0.05$). No significant difference was observed when the expression levels of the other genes measured at the time of diagnosis of CML patients were compared between patients who responded to treatment and those who did not and were resistant to

imatinib. *HOTAIR* may be a potential biomarker in the diagnosis of CML and its prognostic effects in CML patients should contine to be investigated.

HOTAIR gene expression of the CML group was higher than the AML group (p <0.05). The *HOTAIR* gene expression level in the patient group (AML-CML) was found to be significantly higher than the control group (p = 0.032). According to our findings, the increase in *HOTAIR* expression may be play an important role in the development of leukemia. This study provides a new insight into the relationship of *HOTAIR* with HOXD genes in leukemia; however, the molecular mechanisms of *HOTAIR* and HOXD genes should continue to be elucidated in the development and prognostic significance of CML and AML.

Keywords: HOTAIR. lncRNA. HOXD. AML. CML

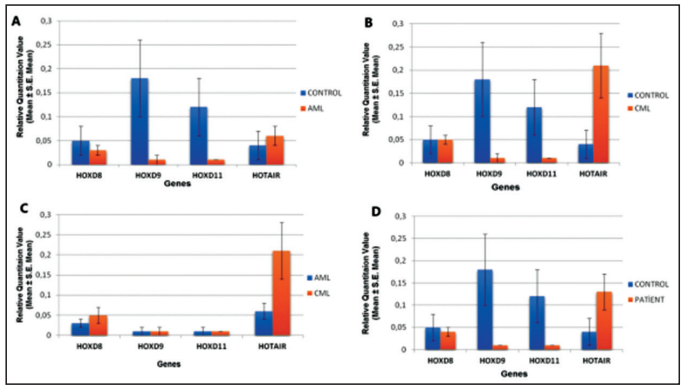

Figure 1. Comparison of Mean Values of Expression Levels of Target Genes Among Control, CML and AML Patient Groups

■ Acute Lymphoblastic Leukemia

OP-004 Abstract Referance : 145

WHOLE GENOME EXPRESSION PROFILING AT DIAGNOSIS PREDICTS RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Acute lymphoblastic leukemia (ALL) is the most common malignancy seen among children accounting for 30% of pediatric cancers. Despite the overall favorable treatment outcome, relapse remains the major clinical challenge in childhood ALL.

In our study, we aimed to identify relapse specific gene expression profile in diagnostic ALL. Raw microarray data (Affymetrix HG-U133_Plus_2) of 351 childhoods ALL samples obtained at diagnoses were retrieved from public databases; four cohorts from GEO database (GSE13576, GSE18497, GSE28460, GSE46170) and one cohort from ArrayExpress database (E-MTAB-2305). Diagnostic samples were labeled either as early relapse or non-relapse feature. Raw CEL. files were used for background correction and RMA normalization. ArrayQualityMetrics was used for QC analyses. ComBat and Harman packages were separately used for batch effect removal and gPCA and pvca packages were used for batch extent and the efficacy of its removal. *Limma* package was used for differential gene expression analysis.

Out of total 351 samples 40 were excluded due to the quality issues. Using an adjusted *p value <0.05* we defined a signature 243 probes that were differentially expressed between diagnosis with non relapse future and diagnosis with relapse feature. This list of significant probes were submitted to DAVID database and Hematopoietic cell lineage (Benjamini corrected *p value 2e-6*), Cell adhesion molecules (*2.6e-6*), B cell receptor signaling pathway (*2.3e-5*), Primary immunodeficiency (*3.6e-5*), Antigen processing and presentation (*4e-5*) and T cell receptor signaling pathway (*2.4e-4*) were seen among others as significantly enriched pathways. Same filter were applied only for B-ALL subtype and 44 genes were found significant. Functional annotation revealed enrichment in genes related to translation initiation (*p value = 7.3e-4*), focal adhesion (*2.1e-3*), extracellular exosome (*3.7e-3*), ribosome (*2.2e-2*) and rRNA processing (*3.2e-2*) in B-ALL samples. In total 95 probes have been found differentially expressed in T-ALL (p*<0.01*) and functional annotation revealed genes related to RNA splicing (*p value = 1.8e-2*), mRNA processing (*2.2e-2*), transcription regulation (3.5e-2), cell cycle (4.1e-2).

Microarray data gives us great opportunity to get high throughput data in a single experiment. But microarray data usually contain inherent technical challenges, which should be handled carefully during normalization and batch removal steps. Herein, we have analyzed an ALL cohort consisting of data obtained from 5 different study groups. Four out of five cohorts had significant variation stemming from scan data (year) of samples, which shows that batch effect may present itself not only when conducted in different centers but also within a single center. Differential gene expression analysis of good and poor therapy responded ALL patients provides an opportunity to discover the biological pathways that may contribute to drug resistance. Our results examining confirm many of earlier findings, but also offer new insight into the relapse.

Keywords: Acute lymphoblastic leukemia, expression array, relapse

■ Acute Lymphoblastic Leukemia

OP-005 Abstract Referance : 97

A NOVEL MARKER CD317 IN PATIENTS WITH CD34 NEGATIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: CD317 was identified in normal B-cells and B-cell malignancies like multiple myeloma and chronic lymphocytic leukemia. However, CD317 is barely detectable in B-cell acute lymphoblastic leukemia. In this study, we investigated the relationship between the presence of CD317 and other markers in flowcytometry in newly diagnosed B- cell acute lymphoblastic leukemia (B-ALL) patients.

Methods: 69 patients age of between 0 and 93 years were included in the study diagnosed with B-ALL betweenJanuary 2017 and December 2018. Demographic features and flow cytometric data of patients were retrospectively evaluated. CD317 and other markers used in diagnosis investigated in bone marrow and peripheral blood samples with ten-color flow cytometry. For comparison, chi square and fisher exact test were used for the nominal data and Mann Whitney U test for the non-nominal data in SPSS 15.0 statistics program. 20% was the cut off for CD34 and CD317 to be considered positive in blastic cells.

Results: In 75% of patients (n=52) ALL blast were CD34 positive and in 25% of patients (n=17) blast were CD34 negative. No statistical difference was found in terms of gender, sample type, leukocyte count, lymphocyte count, hemoglobin and platelet count between CD34 positive and negative groups. However, $CD34^{negative}$ patients tended to be younger. Median age of $CD34^{positive}$ patients and $CD34^{negative}$ patients were 29 years (range: 2-93 years) and 15 years (range: 0-65, respectively (p = 0.08), (table 1). In patients with $CD34^{negative}$ blast, these cells were also found to have a higher rate of CD45 expression, in which the association of TDT, CD19, CD10 and CD19 expression and the rate of CD79a expression were lower (Table 2). CD317 expression rate was 26% in ALL blast. Moreover, when expression of CD34 and CD317 in ALL blast were evaluated together, $CD34^{-}/CD317^{+}$ cells were obtained in more than half of patients and $CD34^{+}/CD317^{+}$ cells in only 17% of patients. The result was statistically significant (p=0,009), (Table 3).

Discussion: In our study CD317 expression of blast was observed in ¼ of B-ALL patients However, when $CD34^{negative}$ blasts were examined in detail, CD317 expression was found in more than half. Our results suggest that CD317 expression might be of diagnostic significance for B-ALL particularly

in CD34 negative blastic cells. CD317 could be used as a new marker for minimal residual disease detection in B-ALL and our study on the prognostic significance of CD317 for B-ALL is ongoing.

Keywords: CD317, B-Cell Acute Lymphoblastic Leukemia

All tables of the study

Table 1 Demographic features of patients at the time of diagnosis

	CD34+	CD34-	P value
Gender, n (%)			
• female	28 (54)	9 (53)	1.0
• male	24 (46)	8 (47)	
Sampletype, n (%)			
• peripheralblood	22 (42)	4 (24)	0.25
bone marrow	30 (58)	13 (76)	
Count of leukocytes	23.2X10³/µl (14.4X10³/µl -774 X10³/µl	15.9 X10³/µl (28 X10³/µl–258 X10³/µl)	0.75
Count of lymphocyte	15 X10³/µl (0.97 X10³/µl -647 X10³/µl)	7.5 X10³/µl (2.4 X10³/µ-117.66X10³/µl)	0.38
Hemoglobin	8,8 g/dl (2,4-13,2)	8,0 g/dl (3,6-11,1)	0.27
Count of thrombocyte	62 X10³/µl (8 X10³/µl -284 X10³/µl)	37X10³/µl (17X10³/µl -181X10³/µl)	0.18
Age, median (range)	29 years (2-93)	15 years (0-65)	0.08

Table 2 Flowcytometry data of patients at the time of diagnosis

	CD34+	CD34-	P değeri
CD 45 ratio, median (range)	9 (0-99)	93 (0-100)	0.03*
CD 38 ratio, median (range)	81 (0-98)	86 (3-96)	0.55
TDT ratio, median (range)	91 (0-98)	49 (0-99)	0.006*
CD10 with CD19 ratio, median (range)	88 (0-98)	57 (0-99)	0.02*
CD19 ratiomedian (range)	93 (0-99)	85 (14-99)	0.02*
CD20 ratio, median (range)	2 (2-95)	7 (0-98)	0.16
CD22 ratio, median (range)	63 (0-97)	58 (0-98)	0.64
CD79a ratio, median (range)	94 (0-99)	81 (39-99)	0.005*
CD9 ratio, median (range)	95 (56-99)	83 (40-90)	0.15
MPO ratio, median (range)	0 (0-3)	0 (0-59)	0.17
CD15 ratio, median (range)	0 (0-93)	7 (0-86)	0.006*
CD33 ratio, median (range)	0 (0-91)	0 (0-92)	0.67
CD13 ratio, median (range)	0 (0-94)	0 (0-50)	0.75
CD58 ratio, median (range)	99 (80-100)	95 (3-99)	0.15

Table 3 The relationshipbetween CD317 and CD34

	CD34+	CD34-	P value
CD317, n (%)			0.009*
• positive	9 (17)	9 (53)	
• negative	43 (83)	8 (47)	

■ Chronic Myeloid Leukemia

OP-006 Abstract Referance : 59

EPIDEMIOLOGY OF CHRONIC MYELOID LEUKEMIA IN AZERBAIJAN

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Institute of Hematology and Transfuziology

Background: Chronic myeloid leukemias (CML) widespread throughout the world, with certain differences in climatic and geographical zones, among different social and ethnic groups of the population. The study of epidemiological data is necessary to assess patients morbidity, mortality and survival, to monitor and determine factors affecting them. Epidemiological studies can be used to organize and improve the hematology service in the country.

Aim: The purpose of this study is to study the epidemiological features of CML in Azerbaijan.

Materials and methods: 766 CML patients diagnosed between 2008 and 2017 were researched. The distribution of CML patients by sex, the age groups at the time of diagnosis, economic-geographical and administrative regions of Azerbaijan were calculated. The incidence, prevalence, mortality and overall survival rates of CML patients were analyzed. Additionally, seasonality in the diagnosis of CML was evaluated. P values calculated from chi square using the software IBM SPSS.

Results: As results of our study it was determined that CML is more common in women than in men (respectively 54% and 46%). Median age is 49. Diagnose frequency is highest among the age group 50-59 (1.96 per 100,000), 40-49 (1.65), 30-39 (1.26). The analysis of epidemiological indicators over the period of 2008–2017 showed that the incidence of the disease in the Azerbaijan was increasing. The lowest incidence of CML was noted in 2008 (0.31), the highest was recorded in 2016 (1.01).

Mortality increased from 0.57 (per 100,000) in 2008 to 0.163 in 2017. However, in recent years, there has been not only a stabilization of this indicator and its decrease in 2017 compared to 2016. In connection with the latest advances in the treatment of CML, the response to therapy has changed dramatically. The overall survival in our patients receiving tyrosine kinase inhibitors (TKI) after 10 years was 64%, while the survival of patients who did not receive TKI after 6 years was only 4%. Distribution of CML patients by economic-geographical regions of Azerbaijan, the highest incidence is detected in east side, precisely in Absheron peninsula (10.6 per 100,000) and the lowest is shown in west side, Ganja-Gazakh (5,57). The result of seasonal characteristic of CML shoved that 23.5% of patients diagnosed in autumn, 21.5% in winter, 29.6% in summer and 25.4% in spring. However, seasonal differences were not statistically significant (χ^2=5.3463, p=0.1481).

Conclusion: Although there has been an increase in incidence rates over the study period (2008-2017), it is encouraging that as a result of the use of TKI in the treatment of patients, the survival rate of patients has significantly increased. The results obtained can be used for comparative studies and improvement of specialized medical care for CML patients.

Keywords: Leukemia, Chronic Myeloid, epidemiology.

■ Non-Hodgkin's Lymphoma

OP-007 Abstract Referance: 155

RETROSPECTIVE ANALYSIS OF 149 UNSELECTED PATIENTS WITH MANTLE CELL LYMPHOMA CONFIRMS PROGNOSTIC RELEVANCE OF MIPI: SINGLE CENTER EXPERIENCE

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Introduction: Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma with distinguished clinical, biologic, and molecular characteristics. The MCL-International Prognostic Index (MIPI) incorporates age, EGOC performance status, normalized LDH level and WBC and has improved discriminatory power. The aim of this retrospective single-center study was to evaluate the clinical characteristics and response to treatment of patients with MCL.

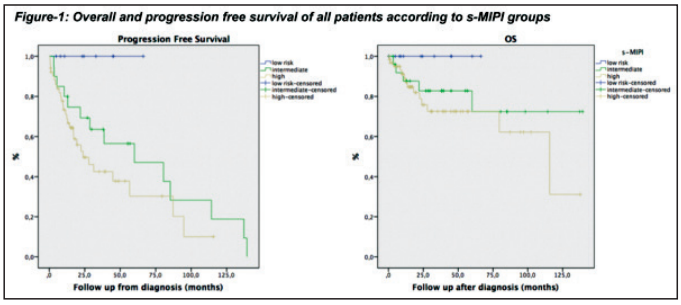
Methods: This single center retrospective study included 297 adult patients diagnosed with MCL between December 2005 and May 2018. The diagnosis of MCL was rendered in accordance with the later World Health Organization (WHO) classification. Outcome was determined as response to treatment, progression free survival (PFS) and overall survival (OS) by Kaplan-Meier analysis using SPSS (IBM SPSS Statistics 21; IBM Corp., Chicago, IL) statistical tool kit. We also compared the PFS and OS according to simplified MIPI (s-MIPI) index.

Results: All clinical data were available in 149 cases. There were 38 (26%) female and 208 (74%) male patients. The median age at diagnosis was 66 years (range, 31-93 years). The median time of follow-up was 14.5 months (range, 3-139.3 months). Bone marrow and extra-nodal involvements was observed in 64 patients (43.8%) and 23 patients (15.7%), respectively. The median s-MIPI was 6 points (range 2-11). Most patients were in the high-risk group (62.2%). Induction chemotherapy was administered in 128/146 patients. Two patients deceased after diagnosis. One hundred and fifteen out of 146 patients (78.8%) were treated with a combination of chemotherapy and anti-CD20 monoclonal antibody rituximab. One elderly patient received Rituximab immunotherapy only. The majority (56.5%) of the patients received CHOP with rituximab as induction chemotherapy. Thirty-one patients underwent ASCT. In total 40 patients achieved complete remission (CR) with an overall response rate of 63.9% after the induction therapy. During follow up, 20 relapses and 28 deaths were noted. Infection was thesss most common cause of death (50%). Following ASCT, OS was significantly

improved; estimated median OS in transplant cohort was 115.7 months vs. 60 months compare with non-transplant group (p=0.013). According to the long-rank test, estimated 5-year OS was not significantly different between intermediate-risk and high-risk s-MIPI categories (72.4%±1.2% vs. 72.6%±0.7%; p=0,202). Estimated 5-year PFS was significantly different between intermediate-risk and high-risk s-MIPI cohorts (47.1%±1.3% vs. 33%±10.3%; p=0,05). Among the transplanted patients, there is no differences between the OS of s-MIPI groups (p=0.952). No patient died or progressed in the low-risk group.**Conclusion:** We have confirmed the validity of the MIPI and simplified MIPI for the prognosis of patients with MCL even in the era of rituximab. The general results of both indexes are fully comparable, facilitating the broad application of s-MIPI as a simple bedside prognostic tool.

Keywords: Mantle cell lymphoma, The MCL-International Prognostic Index (MIPI)

Figure-1: Overall and progression free survival of all patients according to s-MIPI groups



■ Other

OP-008 Abstract Referance: 69

VANCOMYCIN RESISTANT ENTEROCOCCI COLONIZATION, PREDISPOSING FACTORS FOR INFECTION AND PROGNOSTIC FACTORS IN PATIENTS WITH FEBRILE NEUTROPENIA

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Introduction: Vancomycin resistant enterococci (VRE) colonization is mostly found in high risk units like haemato-oncology units. Vancomycin resistant enterococci colonization has an increasing risk of VRE infections, mortality and longer hospitalization. In the studies VRE infection rate changes between 0-45% in colonized patients. Some risk factors were determined such as advanced age, severity of disease, prolonged hospitalization, gastrointestinal surgery, transplantation, exposure to medical devices and broad spectrum antimicrobial agents for VRE infection.

The aim of this study is to analyse epidemiological data and to evalute possible risk factors associated with VRE infection and mortality in colonized acute leukemia patients with febrile neutropenia.

Methods: Two hundred and forty adult acute leukemia patients with febrile neutropenia (FN) who colonized with VRE were included to the study between January 2010-January 2016 in Uludag University Medical Faculty Hematology Clinic. We used open source software R 3.4.4, revision number 74408 for statistical analysis. For continuous variables, we provide the mean and standard variation. For comparing continuous variables, we used Mann-Whitney-Wilcoxon and t tests. For comparing categorical variables, we used the χ^2 test or Fisher exact test, as seen appropriate.

Results: Two hundred and seventeen patients were in colonized group while 23 were in infected group. *Enterococcus faecium* was isolated in all patients. Mean age was 47 years (median 54) in infected group and 43 years (median 45) in colonized group (p= 0.155). Female/male ratio were 1,55 and 0,63 in infected and colonized groups respectively (p= 0.066).Active disease was present in 82.1% in colonized group while 86.9% in infected group (p= 0.774). Demographic, epidemiological and clinical characteristics of the patients were shown in Table 1. The infection rate was found 9,58%. The distrubition of infections were 15 (65.2%) blood stream, 3 (13%) skin and soft tissue, 2 (8.7%) urinary infections and others (13.1%). In the multivariate logistic regression analysis, advanced age, previous colonization, exposure to invasive procedures, coinfection and duration of VRE positivity were found as independent risk factors for VRE infection in VRE colonized patients. Among all patients 86.25% survived and 13.75% died. In the infected patients 47.9% survived and 52.1% died while 90.3% survived and 9.7% died in colonized patients. The all cause of mortality rate between groups is statistically significant (p= <0.001).

Discussion: Vancomycin resistant *enterococcus*is considered as a pathogen bacteria causing an infection which result in subsequently morbidity and mortality especially in high risk patients such as neutropenic from haematology and oncology departments. The VRE colonized cancer patients who had FN tend to VRE infection much more than the general hospitalized patients. In the studies, infection rate in colonized patients seem higher than ours. Some risk factors were revealed about transition from colonization to infection similar to our study. Worth et al. demonstrated all cause of mortality 21.4% in patients with VRE infected while 52.1% in our study. The clinical approach to VRE infected patients should be revised due to higher mortality rates. We need risk assessment models which defining high risk patient groups for VRE colonization and infection and empirical or treatment options to avoid morbidity and mortality.

Keywords: Vancomycin-Resistant Enterococci, Leukemia, Febrile Neutropenia

Table 1. Demographic, epidemiological and clinical characteristics of the patients and risk factors

	Infected (n = 23)	*Colonized (n = 217)*	*P Value Mann-Whitney-Wilcoxon*	*P Value t-test*	*P Value χ2 or Fisher exact*
Age	Mean = 47.13 St. Dev. = 14.86 Median = 54	Mean = 43.92 St. Dev. = 14.01 Median = 45	0.155	0.331	
Gender (M/F)	M= 9 (39.2%) F = 14 (60.8%)	M = 133 (61.3%) F = 84 (38.7%)			0.066
Diagnosis	ALL = 5 (21.7%) AML = 18(78.26%)	ALL = 51(23.5%) AML = 166(76.5%)			0.999
Active/Remission	Active = 20(86.9%) Remission = 3 (13.1%)	Active = 178 (82.1%) Remission = 39 (17.9%)			0.774
Previous hospitalization	0 = 13 (56.5%) 1 = 3 (13%) 2 = 2 (8.75%) 3 = 3 (13%) ≥4 = 2 (8.75%)	0 = 104 (47.9%) 1 = 51 (23.5%) 2 = 29 (13.3%) 3 = 23 (10.7%) ≥4 = 10 (4.6%)			0.574
Previous colonization status	Negative = 21 (91.3%) Positive = 2 (8.7%)	Negative= 175 (80.6%) Positive = 42 (9.4%)			0.267
Number of days colonized	Mean = 17.96 St. Dev. = 10.76 Median = 17	Mean = 21.51 St. Dev. = 12.85 Median = 19	0.183	0.151	
Empirical antibiotics for FN (in the last week before evaluation of the colonization)	Yes = 21 (91.3%) No = 2 (8.7%)	Yes = 194 (89.4%) No = 23 (10.6%)			0.999
Exposure to vancomycin/ daptomycin/ linezolid duringcolonization	None =13 (56.5%) D = 0 V =10 (43.5%) D & L = 0 V & L = 0	None = 128 (59%) D= 3 (1.4%) V = 82 (37.8%) D& L = 2 (0.9%) V & L= 2 (0.9%)			0.913
Exposure to broad spectrum antibiotics after colonization (modification of treatment after colonization)	Yes = 19 (82.6%) No = 4 (17.4%)	Yes = 113 (52%) No = 104 (48%)			0.007
Mucositis (oral mucositis or diarrhea)	No = 13 (56.5%) Yes = 10 (43.5%)	No = 128 (59%) Yes = 89 (41%)			0.995
Central venous catheter	Yes = 13 (56.5%) No = 10 (43.5%)	Yes = 143 (65.9%) No = 74 (34.1%)			0.505
Invasive procedures	No = 17 (74%) Yes = 6 (26%)	No = 212 (97.7%) Yes = 5 (2.3%)			0.0001
Acute kidney injury	No = 22 (95.7%) Yes= 1 (4.3%)	No = 179 (82.5%) Yes = 38 (13.5%)			0.138
Duration of neutropenia (days until colonization)	Mean = 14.96 St. Dev. = 16.52 Median = 11	Mean = 20.86 St. Dev. = 13.98 Median = 19	0.005	0.110	
Coinfection	Yes = 15 (65.2%) No = 8 (34.8%)	Yes = 199 (91.7%) No = 18 (8.3%)			0.001
Neutrophil counts while VRE(+)	<0,5x 109 /L = 22 (95.7%) 0,5-1x 109 /L =0 1-1,5x 109 /L = 0 >1,5x 109 /L = 1 (4.3%)	<0,5x 109 /L = 135 (62.2%) 0,5-1x 109 /L = 7 (3.2%) 1-1,5x 109 /L = 17 (7.8%) >1,5x 109 /L = 58 (26.8%)			0.0001
VRE (+) days	Mean = 34.74 St. Dev. = 32.34 Median = 21	Mean = 16.81 St. Dev. = 14.96 Median = 14	0.001	0.015	
≥3 Weeks VRE (-)	No = 23 (100%) Yes = 0	No = 208 (95.9%) Yes = 9 (4.1%)			0.0001
Time between arrival to hospital and colonization	Mean = 17.96 St. Dev. = 10.76 Median = 17	Mean = 21.51 St. Dev. = 12.85 Median = 19	0.183	0.151	

M: male, F: female, AML: acute myeloid leukemia, ALL: acute lymphoid leukemia, FN: febrile neutropenia, VRE: vancomycin-resistant enterococcus, D: daptomycin, V: vancomycin, L: linezolid

■ Acute Myeloid Leukemia

OP-009 Abstract Referance: 157

LEUKAPHERESIS REDUCES 4-WEEK MORTALITY IN ACUTE MYELOID LEUKEMIA PATIENTS WITH HYPERLEUKOCYTOSIS - A RETROSPECTIVE STUDY FROM A TERTIARY CENTER

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Introduction: Hyperleukocytosis (HL) is defined as the clinical condition when the white blood cell (WBC) count is above 100 000/mm^3 in peripheral blood and the reported incidence of HL is between 5 and 20% in acute myeloid leukemia (AML). The effect of leukapheresis on early mortality data is scarce. The aim of this study was to investigate the effect of leukapheresis on early mortality of AML patients with HL.

Patients &Methods: From January 2005 through October 2017, data from 70 patients with AML who were eligible for leukapheresis were evaluated. All these data were obtained from the Ankara University Faculty of Medicine Center for Therapeutic Apheresis and written informed consent was signed according to our institution regulations. All leukapheresis procedures were performed according to the institutional standard operating procedures after informed consent. Leukapheresis was performed with a continuous-flow blood cell separator (COBE Spectra; TerumoBCT, software version 7.0) via central venous access. The leukapheresis procedures were continued on a daily basis until clinical improvement was determined. Early mortality was defined as death within the first 15 days of leukapheresis.

Results: The study cohort consisted of 70 (36 male/33 female) newly diagnosed AML patients who had presented with HL and/or symptoms of leukostasis and underwent leukapheresis. The median age was 52 years (range, 4–86 years). The median WBC counts at diagnosis was 179.2x10^9/L (range, 56.5-558.0x10^9/L). The majority of patients, 88.6% (n=62) had WBC count ≥100x10^9/L. The majority of patients had symptoms of pulmonary leukostasis. A total of 140 leukapheresis cycles were performed among the 70 AML patients. The median number of leukapheresis cycles was 2 (range, 1–7). The median initial WBC was 179.2×10^9/L, which reduced to 121.7x10^9/L after the first leukapheresis. Eleven of the seventy patients had died by the time of analysis. Seven patients (10%) died within two weeks after leukapheresis commenced. Among the 7 patients, one patient was treated with induction chemotherapy and the remaining received palliative and supportive care. The main cause of early death was respiratory failure. The mean overall survival for all patients was 112±17 months (95% CI 78–145 months) (Figure). The median overall survival for patients who achieved complete all-cause 2-week mortality rate was 10% (7/70 patients) and the all-cause 4-week mortality rate was 12.8% (9/70 patients).

Conclusion: Leukapheresis is effective and safe procedure in reducing the peripheral blood leukocytes and leukemia blasts. Furthermore, high initial response rates in a subgroup of newly diagnosedAML patients fit to receive intensive chemotherapy suggest that leukapheresis could be beneficial in reducing the complications associated with hyperleukocytosis until systemic intensive chemotherapy commences.

Keywords: acute myeloid leukemia, hyperleukocytosis, leukapheresis

■ Other

OP-010 Abstract Referance: 133

HODGKIN LYMPHOMA IN THE ELDERLY: A RETROSPECTIVE MULTICENTER STUDY BY TURKISH SOCIETY OF HEMATOLOGY, LYMPHOMA ACADEMY

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Introduction: Hodgkin Lymphoma in elderly is described as the disease of patients over the age of 60. Treatment response of this population has been shown as being worse than the young population, due to both disease characteristics and patient related factors. In this study, data from elderly population was analyzed retrospectively.

Methods and Results: 52 patients from 4 centers were identified and reviewed. Table 1 shows the characteristics of these patients. The mean age was 69.4 years (range: 60-91 years). 37% of the patients had at least one comorbidity including COPD, DM, hypertension and chronic ischemic cardiovascular disease. 51 of 52 patients had received chemotherapy; 43 of them had ABVD regimen. Overall response (complete +partial) was 73.1%. Eight patients died during treatment (Table 2). Hematologic, neurologic or pulmonary side effects were observed in 57.6% of treated patients. Seventeen of them had therapy modifications while 31% of patients had bleomycin toxicity. The use of G-CSF (11 of 13 patients) was more common in patients who had pulmonary toxicity compared to patients without pulmonary toxicity (p: 0,01). Median survival was not reached, and two-year overall survival was 72.6% (Figure 1).

Discussion: Treatment response and survival of Hodgkin Lymphoma in elderly was lower than expected for this patient group. These results can be explained by the patients being late stage, higher rates of histologically aggressive types, having comorbidities affecting the therapy and the need of treatment modification in most of the patients. Although we had small number of patients, the higher rates of pulmonary toxicity in the G-CSF receivers suggested that the use of G-CSF in elderly population should be with caution. The use of monoclonal antibodies such as Brentuximab can become widespread sooner.

Keywords: Lymphoma, Hodgkin, elder

■ Non-Hodgkin's Lymphoma

OP-011 Abstract Referance: 10

CIRCULATING MICRORNA-125A AS A POTENTIAL SERUM BIOMARKER FOR DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive disease, and it is the most frequent form of non-Hodgkin's lymphoma. MicroRNAs (miRNAs) are short, non-coding RNA molecules that average 18-22 nucleotides long and act as important posttranscriptional regulators. This presents an opportunity for specific miRNAs to serve as diagnostic and prognostic biomarkers for several malignancies.

Method: Serum samples were collected from DLBCL patients and healthy individuals. We extract total RNA from serum collected from 24 DLBCL patients and 23 healthy individuals and performed reverse transcription. In order to quantify miR-125a levels, Realtime quantitative polymerase chain reaction was used to measure miR-125a levels in serum samples from 24 patients and healthy individuals. The relative expression of serum miRNA in CLL cases was analyzed with the $2^{-\Delta\Delta Ct}$ method, using pooled miRNA from normal controls as the reference.

Results: We found that serum miR-125a expression was significantly over-expressed in DLBCL patients (median expression value 3.71, range: 1.31-231.43) to compare healthy individuals (median expression value 1.921, range: 0.29- 8.53; P< 0.001). Moreover, significant correlations were found between miR-125a overexpression and DLBCL patients' clinical characteristics, including staging and International Prognostic Index (IPI). In addition, DLBCL patients with elevated level of miR-125a have shown significantly shorter overall survival (p<0026) than those with lower miR-125a expression. **Conclusion**: This finding suggests that miR-125a in peripheral blood serum could potentially be used as a clinical biomarker for DLBCL.

Keywords: miR-125a, diffuse large B-cell lymphoma, Prognosis

■ Acute Myeloid Leukemia

OP-012 Abstract Referance: 51

COMPARISON OF CONSOLIDATION STRATEGIES IN ACUTE MYELOID LEUKEMIA: STANDARD CHEMOTHERAPY VS AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Treatment of acute myeloid leukemia (AML) is based on remission induction therapy and several consolidation approaches including standard consolidation regimens such as high dose/intermediate dose Ara-C (HIDAC/IDAC) and allogeneic hematopoietic stem cell transplantation (HSCT) based on risk assessment models, particularly cytogenetics. Autologous HSCT is considered as a feasible option for patients without adverse cytogenetics and HLA-compatible donors. The aim of this study is to compare the efficacy of HIDAC/IDAC regimens and autologous HSCT as consolidation modalities in terms of relapse and overall survival (OS) in AML patients.

Methods: A total of 101 patients [median age: 47(19-79) years; M/F: 51/50] who were diagnosed as AML between in 2002 and 2019 were reviewed in this retrospective study.

Results: After standard 7+3 remission induction therapy, 70 patients (69.3%) continued with consolidation chemotherapy including 3 to 4 courses of HIDAC/IDAC, while autologous HSCT was performed in 31 patients (30.7%) after the first consolidation course. Patient characteristics are summarized in Table 1. All patients were in complete remission before HSCT. G-CSF was used for median 8(1-16) days during stem cell mobilization. Median infused $CD34^+$ cell count was 4.47(2.2-5.86)x10^6/kg. Neutrophil and platelet engraftments were achieved on day 12(9-27) and 13(10-202), respectively. Grade 1(1-3) mucositis was observed during peri-engraftment period. A total of 16 patients (51.6%) had neutropenic fever and 1patient (3.2%) had sinusoidal obstruction syndrome. In chemotherapy group, 22 patients (31.4%) experienced hematological relapse at median 330(60-2190) days after the first remission, 4 of these patients (18.2%) underwent allogeneic HSCT for salvage treatment. A total of 14 patients (45.2%) relapsed at median 225(60-395) days after autologous HSCT and 12 patients (85.7%) underwent allogeneic HSCT in this group. At a median follow-up of 915(30-4470) days, OS was found to be better in autologous HSCT group compared to chemotherapy group without statistical significance [79.2% vs 38.8%, p=0.054] (Figure 1). Leukemia risk status at diagnosis was considered as the only prognostic parameter for OS in Cox regression analysis (p=0.002).

Conclusions: In this study, the superiority of consolidative autologous HSCT was demonstrated in AML patients compared to standard chemotherapy arm, without statistical significance. This favourable issue, despite high and early relapse rates after autologous HSCT, may be explained by the additive positive impact of high percentage of salvage allogeneic HSCT in this group of patients. Furthermore, patients in the chemotherapy arm were relatively older and had more comorbidities compared to HSCT group. As leukemia risk status at diagnosis was indicated to be the only statistically significant factor for OS, the importance of patient-based treatment decisions in newly-diagnosed AML patients should be underlined. Small sample size may be another explanation for statistical inconvenience. Further studies are required in order to standardize consolidation strategies in AML patients.

Keywords: Acute Myeloid Leukemia; Autologous Stem Cell Transplantation; Consolidation Therapy; Prognosis

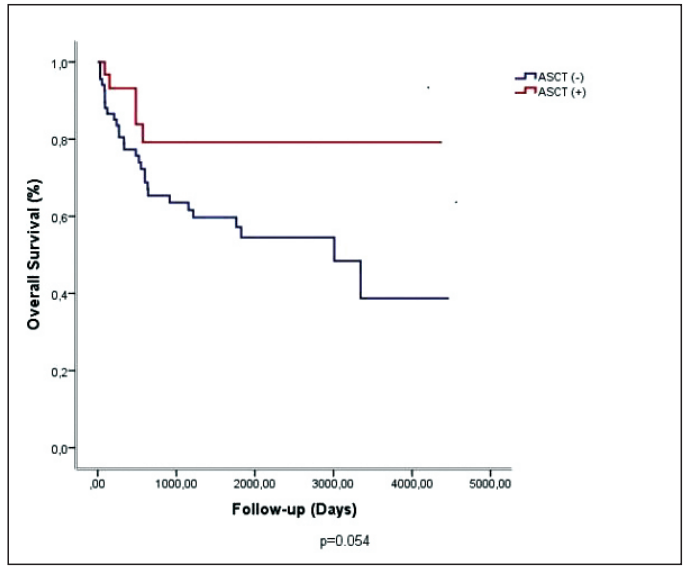

Figure 1. Impact of Autologous HSCT and Standard Chemotherapy on Overall Survival (p=0.054)

Table 1. Patient Characteristics

Age [median(range)] (years)	47(19-79)
Gender [n] (male/female)	51/50
AML Subtype (FAB Classification) [n(%)]	
AML-M0	8(7.9)
AML-M1	13(12.9)
AML-M2	18(17.8)
AML-M4	31(30.7)
AML-M5	9(8.9)
Unclassified	22(21.8)
Risk Status [n(%)]	
Low-risk	12(12.9)
Intermediate-risk	37(39.8)
High-risk	44(47.3)
Extramedullary disease [n(%)]	5(4.9)
CNS involvement [n(%)]	3(2.9)
Time to transplant [median(range)] (months)	95(57-187)
ECOG Performance Status [median(range)]	0(0-1)
Sorror Comorbidity Index [median(range)]	0(0-2)
Mobilization regimen [n(%)]	
HDAC	22(71)
IDAC	7(22.6)
Cy-Etoposid	1(3.2)
G-CSF	1(3.2)
Conditioning regimen [n(%)]	
Cy Bu	30(96.8)
TEAM	1(3.2)
Infused CD34+ Cells [median(range)] (106/kg)	4.47(2.2-5.86)
Neutrophil Engraftment [median(range)] (days)	12(9-27)
Platelet Engraftment [median(range)] (days)	13(10-202)
Sinusoidal obstruction syndrome [n(%)]	1(3.2)
Mucositis Grade [median(range)]	1(1-3)

AML, Acute myeloid leukemia; FAB, French-American-British; CNS, Central nervous system; ECOG, Eastern Cooperative Oncology Group; HDAC, High dose ARA-C; IDAC, Intermediate dose ARA-C; Cy, Cyclophosphamide; G-CSF, Granulocyte colony stimulating factor; Bu, Busulfan; TEAM, Thiotepa, etoposide, cytarabine, melphalan; CD, Cluster of differentiation)

■ Acute Myeloid Leukemia

OP-013 Abstract Referance: 24

POST REMISSION TREATMENT SCORE FOR PREDICTING THE SURVIVAL IN ACUTE MYELOID LEUKEMIA : SINGLE CENTRE EXPERIENCE

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Objective: Post-remission treatment (PRT) in acute myeloid leukaemia (AML) is still a matter of debate. Treatments after first remission may be chemotherapy or allogenic stem cell transplantation (AHSCT) or autologous stem cell transplantation (autoHSCT). The decision to is generally given based on the cytogenetic risk group, but there are also others ,such as age, comorbidity and molecular factors that may affect the outcome of the treatment. A PRT scoring system that included independent prognostic factors such as cytogenetic risk, age, percentage of CD34-positive blasts, *FLT3-ITD* mutant-to-wild-type ratio, and de-novo or secondary AML , has been reported by Priffman et al.

Method: In this single centre trial, 231 patients with AML who were in their first complete remission, treated with AHSCT or chemotherapy were included. Patients were retrospectively classified according to the PRT score. We investigated whether survival after treatment can be predicted by PRT scoring system. The PRT scoring system separated the patients into three groups, such as favourable, intermediate and unfavourable groups.

Results: Overall survival rate after treatment in three groups were significantly different. While there was no difference between transplantation and chemotherapy in the favorable group, our data suggested that stem cell transplantation improved survival in the intermediate and high risk groups.

Conclusion: All risk classification models were only prognostic and could not be used to predict optimum treatments for the different risk categories but the PRT score groups might help physicians to individualise treatment in patient with AML after achieving complete remission. Longer confirmational studies may further elucidate the role of PRT score in patients.

Keywords: transplantation, post,remission,treatment,score

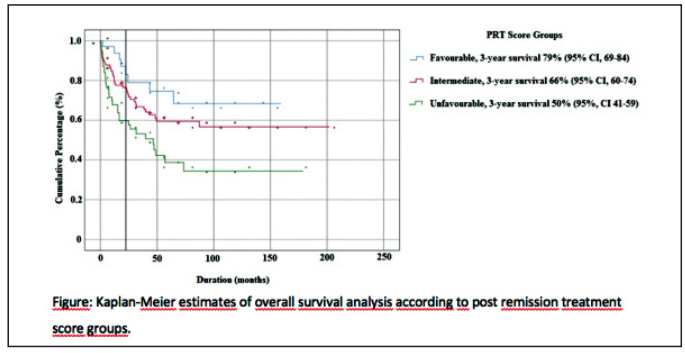

Figure: Kaplan-Meier estimates of overall survival analysis according to post remission treatment score groups.

■ Acute Myeloid Leukemia

OP-014 Abstract Referance: 94

LONG TERM FOLLOW UP OF IDIOPATHIC CYTOPENIA OF UNDETERMINED SIGNIFICANCE (ICUS), CLONAL CYTOPENIA OF UNDETERMINED SIGNIFICANCE (CCUS) TOWARDS MYELODYSPLASTIC SYNDROME (MDS)

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Introduction: Myelodysplastic syndrome (MDS) is defined by World Health Organization (WHO) and International Working Group (IWG)-MDS as not a single but a group of disorders characterized as persistent cytopenia or cytopenias and dysplasia of significant percentage of (≥10%) single or multiple lines in the bone marrow with support of clonal cytogenetic abnormalities. The pre-lesions of MDS, as assimilated with the pre-lesions of multiple myeloma, monoclonal gammopathy of undetermined significance and smoldering myeloma; were defined by pioneers of morphology and persistence of cytopenia (s), persistence of dysplasia, adequate evaluation of clonality are suggested. In this perspective, there are significant number of patients who do not fulfill the diagnostic criteria of MDS, but still, has solely cytopenia or cytopenia and clonality but not MDS. These patients are categorized as Idiopathic Cytopenia of Undetermined Significance (ICUS) who just have persistent cytopenia; Clonal Cytopenia of Undetermined Significance (CCUS) who has persistent cytopenia and a clonality, but this clonality is not suggestive of MDS and Idiopathic Cytopenia of Undetermined Significance (IDUS) who have just dysplasia without cytopenia and no definitive cytogenetics for MDS. In this study, we retrospectively evaluated the data of our patients who have been followed up as MDS but in fact, was either ICUS or CCUS; re-evaluated their cytopenia(s), bone marrow morphology and clonality; combined with a follow up data regarding the potential concern of evolution to MDS and/or AML.

Methods: Data of 300 patients who have been evaluated and regarded as MDS in Trakya University Faculty of Medicine, Department of Hematology were evaluated in a retrospective manner.

Baseline features, including whole blood count, and follow ups, clonal evaluation by conventional cytogenetics are recorded from files. All bone marrow aspirations were re-evaluated by two hematologists and dysplasia observations are recorded and photographed individually.

Results:166 patients were female (55,3%) while 134 were male (44,7%). Mean age was 66,11 years (23-89). Regarding initial presentation, 246 patients were anemic (82%), while 165 patients had leucopenia (55%), 104 patients neutropenia (34,7%) and 161 had thrombocytopenia (53,7%). Morphologic dysplasia was observed in 82 patients (27,3%). 152 patients had no cytogenetical abnormality (50,7%) while 71 patients had MDS related cytogenetical abnormality (23,7%) and 77 patients had clonality but not related with MDS (25,7%). According to initial presentation and findings, 59 patients were regarded as MDS (19,7%), 147 as ICUS (49%), 77 as CCUS (25,7%) and 17 patients (5,7%) were categorized as not MDS-not ICUS-not CCUS, including patients who had dysplasia and not MDS related cytogenetical abnormalities or cytopenia with not MDS related cytogenetical abnormality without dysplasia. Mean follow up duration was 3,04 years (1-11 years). Results regarding follow up were summarized in Table 1.

Discussion: Though regarded as pre-lesions of MDS, ICUS/CCUS/CHIP and all other not-MDS definitive diagnoses should be regarded as distinctive yet, worth to be followed entities.

Keywords: Myelodysplastic sydrome, Cytogenetic

Table 1.

	Initial Evaluation	*First Year*	*Third Year*	*Fifth Year*	*Tenth Year*
CCUS (Anemia)	n=77 62 (80,5%)	n=77 33 (42,9)	n=40 9 (11,7%)	n=25 3 (3,9%)	n=2 none
ICUS (Anemia)	n=147 119 (81%)	n=147 92 (62,6%)	n=47 7 (4,8%)	n=28 4 (2,7%)	n=3 1 (0,7%)
Not-MDS (Anemia)	n=17 12 (70,6%)	n=17 14 (82,4%)	n=6 1 (5,9%)	n=3 none	none none
MDS (Anemia)	n=59 53 (89,8%)	n=59 49(83,1%)	n=30 24 (40,7%)	n=16 4(6,8%)	n=1 none
	Initial Evaluation	First Year	Third Year	Fifth Year	Tenth Year
CCUS (Leucopenia)	n=77 41 (53,2%)	n=77 40 (51,9%)	n=40 16 (20,8%)	n=25 3 (3,9%)	n=2 none
ICUS (Leucopenia)	n=147 88 (59,9%)	n=147 88 (59,9%)	n=47 14 (9,5%)	n=28 4 (2,7%)	n=3 1 (0,7)
Not-MDS (Leucopenia)	n=17 10 (58,8%)	n=17 13 (76,5%)	n=6 4 (23,5%)	n=3 none	none none
MDS (Leucopenia)	n=59 26 (44,1%)	n=59 26 (44,1%)	n=30 8 (13,6%)	n=16 4 (6,8%)	n=1 none
	Initial Evaluation	First Year	Third Year	Fifth Year	Tenth Year
CCUS (Thrombocytopenia)	n=77 37 (48,1%)	n=77 37 (48,1%)	n=40 14 (18,2%)	n=3 none	n=2 none
ICUS (Thrombocytopenia)	n=147 74 (50,3%)	n=147 74 (50,3%)	n=47 17 (11,6%)	n=28 none	n=3 none
Not-MDS (Thrombocytopenia)	n=17 13 (76,5%)	n=17 13 (76,5%)	n=6 4 (23,5%)	n=0 none	n=0 none
MDS (Thrombocytopenia)	n=59 37 (62,7%)	n=59 37 (62,7%)	n=30 12 (20,3%)	n=1 none	n=1 none

■ Acute Lymphoblastic Leukemia

OP-015 Abstract Referance: 57

DETERMINATION OF THERAPEUTIC POTENTIAL OF LUTEOLIN FOR ACUTE LYMPHOBLASTIC LEUKEMIA CELLS

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Acute lymphoblastic leukemia (ALL) which is a malign hematologic cancer is characterized with increased number of lymphocytes whose developments are genetically and/or epigenetically inhibited in bone marrow. Reciprocal translocations of BCR (chromosome 22) and ABL genes (chromosome 9) lead to Philadelphia (Ph) chromosome which has tyrosine kinase activity in ALL that called as Ph+ ALL. Although tyrosine kinase inhibitors (Imatinib and Dasatinib) are used in addition to classical chemotherapy, current therapies only help to prolong lives of Ph+ ALL patients. Due to complete cure could not be succeeded novel strategies are needed for Ph+ ALL. Luteolin which has antioxidant, pro-oxidant, anti-inflammatuar and anticancer activity is a member of flavones family of flavanoids and found in many vegetables and medical herbs. According to several studies, luteolin decreases cell proliferation, tumor growth and induces apoptosis, cell cycle arrest; inhibits migration, invasion, angiogenesis and metastasis in many cancers including breast, lung, colon, prostate, gastric, chronic myeloid leukemia and acute myeloid leukemia. Bioactive sphingolipids have crucial roles in many cellular processes including proliferation, growth, apoptosis, senescence, invasion, metastasis, and drug resistance. In the literature, only one study showed that luteolin induced apoptosis through regulating sphingolipid levels in colon cancer cells.

In this study, therapeutic effects of luteolin on Ph+ ALL cells have been determined for the first time as well as the roles of bioactive sphingolipids genes on possible therapeutic potential of luteolin on Ph+ ALL cells comparing with healthy cell line. Dose and time dependent cytotoxic and cytostatic effects of luteolin were determined by MTT assay and cell cycle analysis while dose and time dependent apoptotic effect of luteolin was determined by AnnexinV-Propidium Iodide Double Staining Assay and JC-1 Mitochondrial Membrane Potential Assay through flow cytometry. Our ongoing studies will determine the effects of luteolin on expression levels of BCR/ABL and bioactive sphingolipid genes as well as human telomerase activity by both qPCR and western blotting in Ph+ ALL cells.

Therefore, the therapeutic potential a new herbal product-derived drug candidate for ALL patients with short life and low quality of life will be determined for the first time by our study.

Keywords: acute lymphoblastic leukemia, luteolin, bioactive sphingolipids

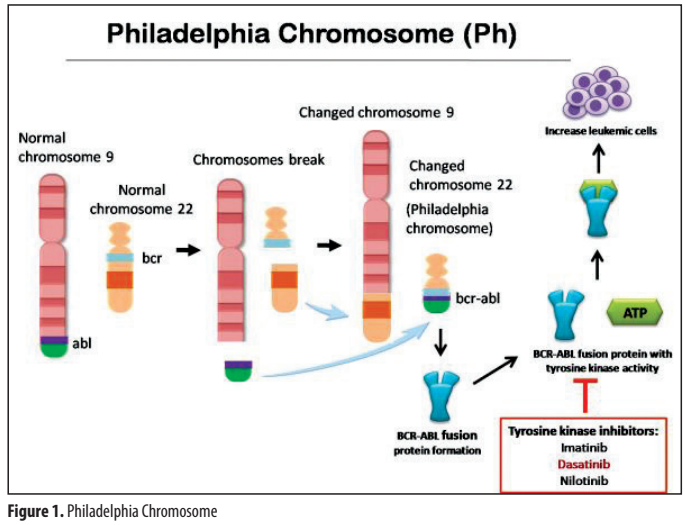

Figure 1. Philadelphia Chromosome

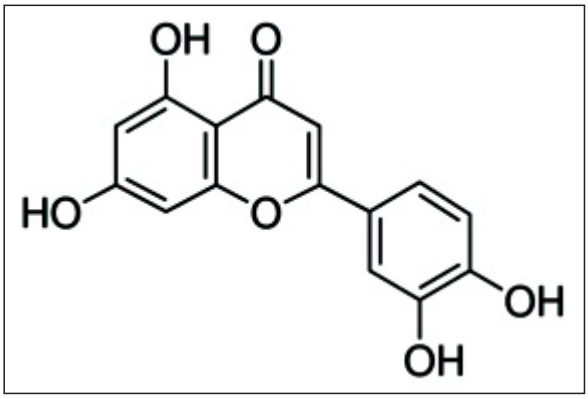

Figure 2.

■ Multiple Myeloma

OP-016 Abstract Referance: 46

MYTH OR REALITY? THE FREQUENCY AND SIGNIFICANCE OF DOUBLE HIT OR TRIPLE HIT MULTIPLE MYELOMA AT A SINGLE CENTER IN NORTHWESTERN TURKEY

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Introduciton: Risk stratification of Multiple Myeloma (MM) is based on Floresence in Situ Hybridization (FISH) method. High risk MM is defined as having at least one of the mutations related with poor prognosis including; t(4;14) t(14;16), t(14;20), del 17p, p53 mutation, gain 1q and del 1p. Mayo clinic's recent M-Smart MM risk stratification guidelines proposed a fresh point of view as having two of the high risk genetic abnormalities should be named as double hit MM and having any three as triple hit MM. From this perspective, double or triple hit MM might be related with poorer outcome. As more risk stratification tools are developed with sophisticated tools including genetical evaluation, the initial and consecutive treatment approaches for patients in these poor risk groups are not established. In this study, we aimed to evaluate the frequency and the significance double hit, triple hit myelomas in newly diagnosed patients.

Patients and Methods: Data of 163 patients diagnosed with MM between May 2014 and December 2018 at Trakya University Medical School of Faculty were evaluated retrospectively. FISH analyses for TP53/CEN17, D13S319 for 13q14, 13q34 (LSI13q34), t(4;14) (p16;q32) (LSI FGFR3/IGH Dual Color, Dual Fusion Translocation Probe Set), t(11;14) (q13;q32) (LSI CCND1/ IGH Dual Color, Dual Fusion Translocation Probe Set), t(14;16)(q32;q23) (LSI IGH/ MAF Dual Color, Dual Fusion Translocation Probe Set), CKS1B/CDKN2C (P18) Amplification/Deletion Probe (CytoCell, Cambridge, UK) were performed on bone marrow samples. A total of two hundred nuclei were enumerated for each FISH Panel probe and cut off for detection of deletion/ fusion signal in normal individuals was taken as 3%. The first line treatment agents, ISS stages, demographic and clinical characteristics and overall survival were recorded from files.

Results: Mean age at diagnosis was 64,62 ± 11,07 years. 76 patients were male and 83 were female. 24 patients were with one high risk, 7 patients with two high risk and 2 patients with three high risk determiners. 61,6% of the patients have received a triple regimen with bortezomib, cyclophosphamide, dexamethasone (CyBorD) in the first line setting. % 17,6 of the patients received bortezomib, dexamethasone and % 1,9 of the patients received bortezomib, thalidomide, dexamethasone. 47 of the 159 patients (% 29,6 of the study) proceeded with ASCT in the upfront setting. (Detailed information were given in Table 1). Overall survival of the patients with two high risk abnormality was 6 ± 4,2 months, patients with one high risk abnormality was 32,0 ± 25,6 months and patients with no high risk abnormality was 57,0 ± 9,6 months.

Discussion: Novel drugs have changed the outcome and dramatically prolonged the survival of MM risk patients. However, challenges regarding treatment of high risk MM patients still remain an unsettled issue. As double hit or triple hit lymphomas need more intensive treatment compared to standard first line treatment, it may be attributed to MM as a concern that double hit or triple hit MM patients should also be treated more intensively. In our study, patients with one or two high risk abnormalities had lower overall survival than patients with no high risk abnormality.

The evolution of MGUS to overt MM with addition of extra genetic evolution and instability step by step show us a great example of cancer stem cell theory. Double or tiriple hit MM may find their place as the last ring in this theory.

Keywords: Multiple Myelome, Double Hit, Triple Hit , FISH

Table 1. Demographic and Clinical Characteristics of the Patients

	No high risk Cytogenetic abnormality (n=126)	*One high Risk Cytogenetic Abnormality (n=24)*	*Two High Risk Cytogenetic Abnormality (n=7)*	*Three High Risk Cytogenetic Abnormality (n=2)*	*Total (n=159)*
Age (years)	64,5±11,5	65,4±9,4	61,6±9,9	71,0±4,2	64,6±11,1
Gender (male/ female)	60/66	12/12	2/5	2/0	76/83
ISS Stage at Dignosis					
Stage 1	70 (%58,8)	1 (%4,3)	0	0	71(%47,0)
Stage 2	44 (%37,0)	8 (%34,8)	1 (%14,3)	0	53(%35,1)
Stage 3	5 (%4,2)	14 (%60,9)	6 (%85,7)	2 (%100,0)	27(%17,9)
First Line Treatment					
VCD	75 (%59,5)	14(%58,3)	7 (%100,0)	2(%100,0)	98(%61,6)
VD	25 (%19,8)	3 (%12,5)	0	0	28(%17,6)
VTD-PACE	0	3 (%12,5)	0	0	3(%1,9)
Others	26 (%20,7)	4 (%16,7)	0	0	30(%18,9)
Upfront ASCT	39 (%31,0)	7 (%29,2)	1 (%14,3)	0	47(%29,6)
Overall Survival (months)	57,0 ± 9,6	32,0 ± 25,6	6 ± 4,2	-	50,0±11,0

■ Multiple Myeloma

OP-017 Abstract Referance: 68

THE COMPARISON OF THE RELATIONSHIP BETWEEN POLYNEUROPATHY FREQUENCY AND CLINICAL AND LABORATORY FINDINGS IN MULTIPLE MYELOMA CASES

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Aim: Multiple myeloma (MM) patients compose approximately 10% of patients with hematological malignancies. Polyneuropathy (PN) is one of the most important complications related to the disease and treatmentc.

Materials and Methods: A total of 121 MM cases followed in the Hematology Clinic of Atatürk Training and Research Hospital between 2010-2018 were included in the study. Electromyography results were evaluated retrospectively and clinical and laboratory findings were compared. Five cases with diabetes mellitus were excluded from the study. Chi-square method was accepted as statistically significant p <0.05.

Results: The median age of the patients was 64.5 (min 39 max: 88), and Female / Male ratio was 51/65 (44% / 65%). Demographic data of 28 (24.3%) patients with PN and 87 (75.7%) patients without PN were presented in Table 1. Renal function tests were normal in 64 (55.7%) of 87 patients without polyneuropathy (p = 0.005). There were 28 (23%) cases with extramedullary plasmacytoma larger than 1.5 cm which were detected by MR imaging at the time of diagnosis. In cases with extramedullary plasmacytoma, the prevalence of polyneuropathy was higher at the initial diagnosis (p = 0.012).

Discussion: There are publications in the literature showing that PN is associated with perineural and perivascular monoclonal immunoglobulin accumulation in MM. In our cases, there was no correlation between the presence of PN during diagnosis and the immunoglobulin subtype, but it was found to be related to the presence of renal dysfunction and the presence of extramedullary plasmacytoma. And we think that this result is the considerable.

Keywords: Multiple myeloma, Extramedullary Plasmacytoma, Polyneuropathy, Renal failure

Table 1. Comparison of the data of MM cases with and without Polyneuropathy

	Patients with Polyneuropathy n(n%): 28 (24.3%)	*Patients without Polyneuropathy n(n%): 87 (75.7%)*	*P Value*
≥ 65 years old	11 (39.3%)	48 (%55.2)	>0.05
Gender (F/M)	14/14 (50%/50%)	37/50 (42.5%/ 57.5%)	>0.05
Light chain / Heavy chain	4 (3.5%)/16 (13.9%)	24 (20.9%)/71 (61.7%)	>0.05
Immunoglobulin Subtype: IgG kappa / IgG lambda / IgA kappa / IgA lambda / Lambda light chain / Kappa light chain	11 (39.3%)/ 6 (21.4%)/ 3 (10.7%)/ 4 (14.3%)/ 4 (14.3%)/ 0 (0%)	33 (37.9%)/ 17 (19.5%)/ 15 (17.2%)/ 6 (6.9%)/ 9 (10.3%)/ 7 (8%)	
ISS: I/ II/ III	9 (32.1%)/ 6 (21.4%)/ 13 (46.4%)	25 (28.7%)/ 25 (28.7%)/ 37 (42.5%)	
Beta 2 microglobulin ≥3.5 mg/L	14 (50%)	34 (39.1%)	>0.05
Albumin ≤3.5 g/dL	12 (42.9%)	32 (36.8%)	>0.05
Hemoglobin ≤10 g/dL	20(71.4%)	51 (58.6%)	>0.05
Calcium ≥12 mg/dL	6 (21.4%)	16 (18.4%)	>0.05
Creatinine ≥2 g/dL	16 (57.1%)	23 (26.4%)	0.005
Extramedullary plasmacytomas	12 (42.9%)	16 (18.4%)	0.012
Lytic bone lesions	18 (64.3%)	52 (59.8%)	>0.05
Pathologic fracture	9 (32.1%)	24 (27.6%)	>0.05

■ Multiple Myeloma

OP-018 Abstract Referance: 149

PRE-TRANSPLANT HEMOGLOBIN AND SERUM CREATININE LEVELS CORRELATE WITH PROGRESSION FREE SURVIVAL IN MYELOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: High dose melphalan and autologous stem cell transplantation (ASCT) significantly prolong survival for patients with multiple myeloma (MM). However, prognostic biomarkers in ASCT are needed to improve risk assessment and help guide therapeutic and surveillance strategies to alleviate the risk of death from the procedure. The purpose of this study is to assess the effects of hemoglobin (Hgb) and serum creatinine (Crea) values at the time of transplantation on the overall outcome of patients with multiple myeloma treated at our transplant center.

Material & Methods: This analysis included 247 consecutive patients who underwent ASCT for MM between 2010-2016. Hemoglobin was grouped as low or high relative to their sample median. Patients were also stratified according to serum Crea value at the time of transplantation (<2 or ≥2 mg/dl).

Results: The median age was 57 (29-75) years and most patients were male (n=151, 61.1%), IgG subtype (n=124, 50.2%), and ISS stage 3 (n=122, 49.4%). The interval from the time of diagnosis to ASCT was median 7 months and median follow-up from ASCT was 49 months (range, 3-198 months). The most commonly induction regimens included VAD (vincristine, doxorubicin and dexamethasone) and VCD (bortezomib, cyclophosphamide, dexamethasone), respectively. Since maintenance was not an approved treatment in myeloma most patients did not receive any. For the entire cohort, the median Hgb and Crea were 11.5 g/dL and 0.9 mg/dL respectively. No difference in progression free survival (PFS) was observed between a lower and higher Hgb (82 vs. 81 months, p=0.96). However, the median PFS was significantly longer in patients with a lower Crea compared to those with a higher Crea (83 vs. 48 months, p=0.01). Patients with both a lower hemoglobin and higher Crea experienced shorter PFS compared to those with a higher hemoglobin and lower Crea (45 vs. 82 months, p<0.001). We failed to demonstrate the impact of creatinin levels on time to neutrophil and platelet engraftment. There were no differences in OS according to lower vs. higher Hgb (58 vs. 52 months; p=0.29, respectively) but in higher crea cohort worse OS was observed (41 months vs. 57 months; p=0.02, respectively).

Conclusions: We demonstrate that hemoglobin and creatinine represent important determinants of clinical outcomes after ASCT. A lower hemoglobin and higher creatinine, individually and when combined, were associated with shorter PFS. Therefore, further studies of larger randomized cohorts are required to clarify the impact of pre-transplant Hgb and Crea levels on ASCT outcomes.

Keywords: Multiple myeloma, Autologous Stem Cell Transplantation, Hemoglobin, Serum Creatinine

■ Other

OP-019 Abstract Referance: 50

THE CORRELATION BETWEEN INTERIM IMAGING RESULTS AND DISEASE PROGNOSIS OF PATİENTS WİTH HODGKIN AND DIFFUSE LARGE B CELL LYMPHOMA: SINGLE CENTER EXPERIENCE

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Objective: In our study, we aimed to investigate the relationship between the interim imaging response and disease prognosis in patients with Hodgkin (HL) and Diffuse Large B-Cell Lymphoma (DLBCL).

Materials and Methods: The study included 90 DLBCL and 67 HL patients observed in Dokuz Eylul University (DEU) Hospital Department of Hematology. The pre-treatment and interim PET / CT (I-PET/CT) images of 121 patients who underwent imaging with PET/CT were evaluated by two nuclear medicine physicians as a blind experiment. The first and interim CT (I-CT) images of 53 patients who underwent imaging with contrast-enhanced CT were evaluated by a two radiology physicians as a blind experiment. Patients' interim responses and end-treatment responses were compared using the SPSS 22.0 statistical analysis program.

Results: According to I-PET / CT positivity or negativity and post-treatment disease status; the positive (PPV) and negative predictive value (NPV) of the method were calculated separately for both HL and DLBCL patient groups. I-PET / CT PPV was 36% for HL, 61.9% for DLBCL; NPV was 95.4% for HL and 93.1% for DLBCL. The 7-year progression-free survival rate was 54% for I-PET / CT + patients and 83% for I-PET / CT - patients in HL; DLBCL was also 20% for

I-PET / CT + patients and 79% for I-PET / CT - patients. I-CT response was negative despite I-PET / CT positivity for 2 of 8 patients who were evaluated with both of PET / CT and contrast-enhanced CT in the DBBHL group. I-CT response was positive despite I-PET / CT negativity for 3 of 9 patients who were evaluated with both of PET / CT and contrast-enhanced CT in the HL group. In a group of 157 patients, when assessed based on the kappa analysis it was found that there was no agreement between Lugano I-PET / CT related response and Lugano and RECIST 1.1 I-CT related responses. On the other hand, a higher agreement was determined between the end-of-treatment response and the I-PET / CT-related response group compared to the I-CT groups.

Conclusion: PET / CT scans significantly improved the assesment of treatment responses. Compared with CT, PET/CT prevented some early-stage patients' being treated with unnecessary intensive therapies and some advance stage patients' being treated with less intensive therapies. I-PET/CT negativity has a high prognostic value in terms of progression-free survival, and this may be helpful for clinicians to reduce the number of cures and the intensity of treatment. Treatment intensification based only on I-PET/CT positivity may cause patients to be exposed to unnecessary drug toxicity.

Keywords: lymphoma, interim assesment, PET/CT

■ Chronic Lymphocytic Leukemia

OP-020 Abstract Referance: 66

WHICH MARKERS SHOULD BE USED FOR CHRONIC LYMPHOCYTIC LEUKEMIA SCORING SYSTEM BY IMMUNOPHENOTYPING ?

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CLL is one of the most common diagnoses made by flow cytometry laboratories. As there is no pathognomic molecular anomaly in CLL, flow cytometry is almost the gold standard for diagnosis. The scoring system used for diagnosing CLL has some limitations. Not every laboratory can consistently and reproducibly determine weak expressions of sIg, CD22/CD79b. In the present study we assessed the importance of the expressions of CD43, CD81, CD20, and ROR1, which are not present in the scoring system for CLL, for the differential diagnosis of CLL, and their expressions in non-CLL cases

Methods: We performed immunophenotyping from peripheral blood or bone marrowaspiration samples of 165 cases using 8 color flow cytometry. We retrospectively evaluatedall cases' diagnoses, immunophenotypic features, and morphological, histopathological, andmolecular data.

Results: CD43 positivity was sensitive but of lower specificity. It had a high diagnostic power (sensitivity 100% , specificity 88.5% AUC 98.0%)CD200 was a sensitive marker for CLL (sensitivity 98% and specificity 90%, AUC: 96%) CD81 negativity for CLL had a sensitivity of 95%, specificity of 82% , and AUC of 92%. ROR1 was positive in all CLL and MCL cases. CD79b was a highly specific and sensitivemarker for MCL.

Discussion: CD43, CD81, CD200, and ROR1 should be definitely inlcuded in diagnostoc algorithms for the differential diagnosis of CLL especially from MCL.

Keywords: CD43,CD81, CD200, ROR1; chronic lymphocytic leukemia; B-cell lymphoproliferative disorder

Table 1.

CD name	*AUC%*	*Sensitivity%*	*Specifity%*
CD43	98	100	88
CD81	92	95	82
ROR1	95	94	90
CD200	96	98	90
CD22	90	92	80
CD23	97	99	92
CD79b	77	70	95
sIg	50	51	64

■ Other

OP-021 Abstract Referance: 159

MERSIN UNIVERSITY LAST DECADE EXPERIENCE WITH MYELOFIBROSIS

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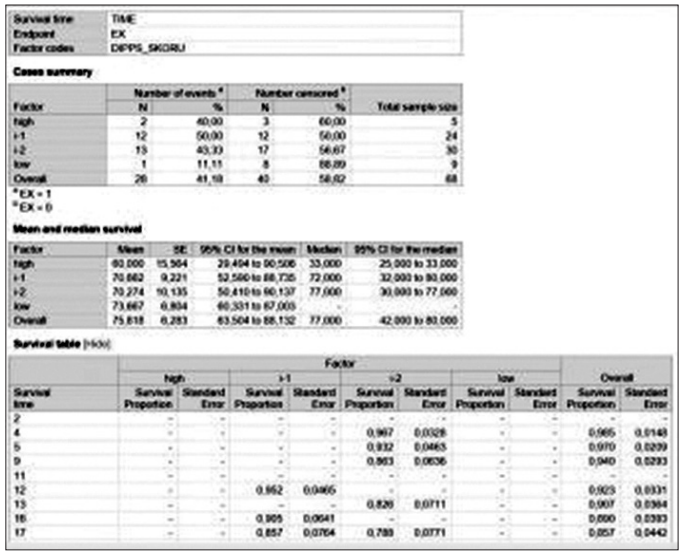
Objective: To document the Mersin University last decade experience with primary myelofibrosis and provide mature risk-stratified survival data and disease complication estimates

Patients and Methods: Mersin University patients with World Health Organization–defined primary myelofibrosis diagnosed between 2009-2019 constituted the core study group. Clinical and laboratory data were abstracted from medical records. Risk-stratification used conventional risk models considering age, leukocytes, and thrombosis, dynamic international prognostic scoring system. Statistical analyses were based on parameters obtained at the time of referral to MU which, in the majority of cases, coincided with or was within 1 month of diagnosis. All patients were followed from diagnosis until death or date of last follow-up/contact. .

Results: A total of 74 patients (median age, 60,5 years; range, 30-85 years) were considered; 3 PV, 5 ET, 1 CML and 8 MDS 57 PMF. Number of males 35(47,3%) and females 39 (52,7%) From October , 2009, through , October 2019, 34 deaths (45,9%), 3 leukemic transformations (4%), and 3 thrombotic events (4,2%) were recorded. Median overall survival (OS) was 6 years. PMF cases were attributed low (12,2%), intermediate-1 (32,4%) -2 (40,5%) and high (6,8%) risk. Documented median hemoglobin levels were 9,75 g/dL (range, 3.8-20 g/dL). Furthermore, 20 of 74 evaluable patients (27%) overall were transfusion dependent. Platelet counts were 510109 /L (range, 4-2228000 /L). Median leukocyte counts were 9.140 /L (range, 1420-290000 /L) . the median peripheral blood blast percentage was 2% (range, 0%- 10%; 17%). 30 of 74 evaluable patients abnormal karyotype was documented 4,1%. Constitutional symptoms and palpable splenomegaly were documented in 23% (n=17) and 92% (n=47) of 74 and 51 evaluable patients. A history of hemorrhage at or before diagnosis was present in 3 patient 4,2%. Overall, 2 patients (2%) with PMF underwent allogeneic stem cell transplant.

Conclusion: This study provides mature survival and outcomes data in myelofibrosis. One of the results is statistically that the life curves do not differ significantly or the factor (underlying disease type) has no significant effect on the survival time.(chi square statistic 1,9945 and p:0,7368 >0,05). In the literature Survival was significantly different among the 4 risk categories ($P < .001$).(1) median survival was 14.6 years in low-risk patients, 7.4 years in intermediate-1, 4 years in intermediate-2, and 2.3 years in high risk. In our study Dipps Scores has no effect until the time to exitus.(chi square value 3,1392 and p:0,3707 >0,05).and median survival was 72 months in intermediate-1, 77 months in intermediate-2, and 33 months in high risk. Comparison of Ruxolitinib and the other medications has no prominent difference on life expectancy. .(chi square value 3,5149 and p:0,0608 >0,05). Hereby miyelofibrosis is a serious disease with high mortality and there is need for effective disease treating agents

Keywords: myelofibrosis



Survival time	TIME
Endpoint	EX
Factor codes	DIPPS_SKORU

Cases summary

Factor	Number of events * N	Number of events * %	Number censored * N	Number censored * %	Total sample size
high	2	40,00	3	60,00	5
i-1	12	50,00	12	50,00	24
i-2	13	43,33	17	56,67	30
low	1	11,11	8	88,89	9
Overall	28	41,18	40	58,82	68

* EX = 1
* EX = 0

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
high	60,000	15,564	29,494 to 90,506	33,000	25,000 to 33,000
i-1	70,662	9,221	52,590 to 88,735	72,000	32,000 to 80,000
i-2	70,274	10,135	50,410 to 90,137	77,000	30,000 to 77,000
low	73,667	6,804	60,331 to 87,003	-	-
Overall	75,818	6,283	63,504 to 88,132	77,000	42,000 to 80,000

Survival table [Hide]

	Factor									
	high		i-1		i-2		low		Overall	
Survival time	Survival Proportion	Standard Error	Survival Proportion	Standard Error	Survival Proportion	Standard Error	Survival Proportion	Standard Error	Survival Proportion	Standard Error
2	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	0,967	0,0328	-	-	0,985	0,0148
5	-	-	-	-	0,932	0,0463	-	-	0,970	0,0209
9	-	-	-	-	0,863	0,0636	-	-	0,940	0,0293
11	-	-	-	-	-	-	-	-	-	-
12	-	-	0,952	0,0465	-	-	-	-	0,923	0,0331
13	-	-	-	-	0,826	0,0711	-	-	0,907	0,0364
16	-	-	0,905	0,0641	-	-	-	-	0,880	0,0393
17	-	-	0,857	0,0764	0,788	0,0771	-	-	0,857	0,0442

Figure 1. Passamonti F, Cervantes F, Vannucchi AM, et al. Blood. 2010;115:1703-1708.

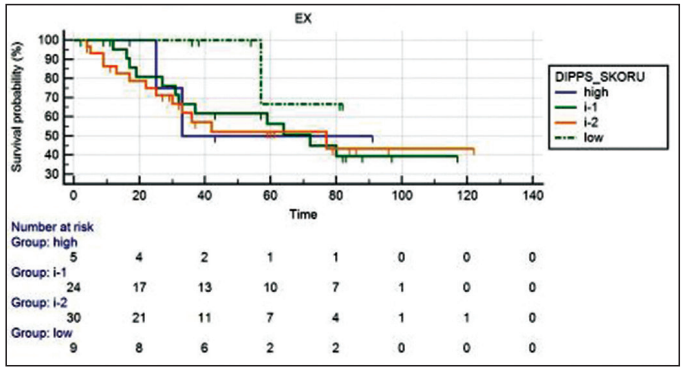


Figure 2.

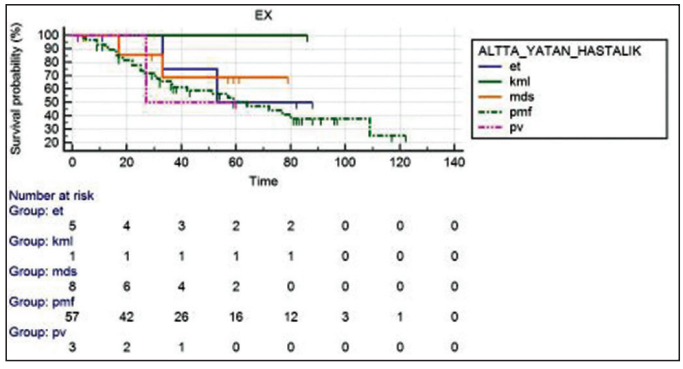


Figure 3.

■ Multiple Myeloma

OP-022 Abstract Referance: 138

RETROSPECTIVE EVALUATION OF IMMUNOMUDULATORY AGENTS RESPONSE AND SIDE EFFECTS IN RELAPSED REFRACTOY MYELOMA PATIENTS: REAL LIFE EXPERIENCE

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Objective: Multiple Myeloma is a clonal plasma cell disease leading to renal failure, hypercalcemia, anemia and destructive bone lesions. The overall survival (OS) has significantly improved with the usage of immunomodulatory drugs (IMIDs) and proteosome inhibitors. But there are various side effects that can affect the effective usage of these drugs. In this study, we aimed to review management of side effects of IMIDs in our daily practice and reveal their treatment responses.

Method and Results: Demographic data, survival and response conditions of eighty-five patients who were treated with IMIDs in Dokuz Eylul University between 2001-2018 were evaluated retrospectively.

Results: Median age was 62 (38-83). Median follow-up time was 57 months (5-177). At the end of follow-up time, 34.7% of the patients were dead. Median overall survival was 77 months (61.4-92.6). IMIDs were used in relapsed/refractory myeloma for all patients. After the first line treatment, very good partial remission (VGPR) was obtained in the 87.1% of the patients. Others had stabil diseases. Autologous transplantation was made in the 57.6% of the patients. IMIDs usage at relapsed disease was as follows: 12.9% thalidomide (27.2% 2. line,36.4% 3.line, 36.4% other), 91.8% lenalidomide (12.8% 2.line, 82.1% 3.line, 5.1% other), 17.6% pomalidomide (all after 3.line). Pomalidomide had used after lenalidomide generally. The most common side effect during thalidomide was neuropathy (63.6% grade 2-3 neuropathy). VTE was not observed. VTE prophylaxis like acetylsalicylic acid had been used 54.5% of the patients during thalidomide therapy. None of the patients left thalidomide due to side effects. Median lenalidomide use was 12 months (1-46). Response rates were as follows: 39.7%PR, 34.6%VGPR, 14.1% CR. 62.8% of the patients had received antibiotic prophylaxis. All patients had been taken VTE prophylaxis (75.7% ASA, 24.3% ASA+ LMWH). Grade 1-2 neutropenia was seen at the 69.2% of the patients, grade 1-2 thrombocytopenia was 33.3%, grade 2 anemia was 10.3%. G-CSF was used in 23.1% of the patients. DVT was found in 5.1% of the patients, pulmonary thrombosis was found in 5.1% of the patients in prophylaxis group. The most common side effect was infection (mostly pneumonia). Hepatotoxycity rate was 7.7%. Lenalidomide was interrupted at 32.1% of the patients mostly due to infection for median 7 days. Infection rate was 14.2% at the antibiotic prophylaxis group while 58.8% at other group. During pomalidomide therapy, antibiotic prophylaxis were given for 73.3% of the patients, DVT prophylaxis were given for all patients. Neutropenia was seen as 73.3% of the patients. Infection rate was 73.3%. 2/11 patients died due to sepsis. These patients were refractory for all anti-myeloma therapy also.

Conclusion: IMIDs are frequently used at relapsed/refractory setting in Turkey. Infections, DVT can cause drug interruptions or dose reductions in some cases. These may affect the effectiveness of therapy. To be able to use these drugs effectively, we should take care to use prophylactic approaches.

Keywords: Keywords: IMIDs, immunomudulatory drugs, side effects, multiple myeloma

■ Multiple Myeloma

OP-023 Abstract Referance: 150

CAN AUTOLOGOUS STEM CELL TRANSPLANTATION ABROGATE THE POOR PROGNOSIS ASSOCIATED WITH HIGH LDH?

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Background: Multiple myeloma (MM) is a plasma cell neoplasia characterized by a diffuse clonal plasma cell infiltration of the bone marrow. Serum lactate dehydrogenase (LDH) is a relevant biomarker in MM and in the era of novel agents, LDH confirmed its negative impact on survival in newly diagnosed setting (Bal et al., presented at ASH2018).

Methods: This single center retrospective study included 208 patients with a diagnosis of MM who underwent ASCT at our center between January 2008 - Mart 2018 were prospectively analyzed. We identified patients with baseline serum LDH values (ULN=247 U/L). We compare baseline characteristics and outcomes of ASCT according to LDH values.

Results: All clinical data were available in 208 cases (High LDH: 92 (44.2%), Normal LDH: 116 (55.8%)). There were 87 (41.8 %) female and 87 (41.8 %) male patients. The median age at diagnosis of MM was 63 years (range, 37-77 years). The median time of follow-up was 48 months (range, 2.8-197.5 months). Of the 92 patients with high LDH who underwent ASCT, median age was 65 years and ECOG performans status was 1 and 58.6 % were male. Induction therapy consisted of ≥ 3 drugs in 5.4 % and 2 drugs in 35.9 %. Forty-eight (53.3%) patients with high LDH received a bortezomib-based induction and 35 patients (40.2 %) achieved ≥ very good partial remission (VGPR) after the induction therapy. During follow up, 45 relapses were occurred and all relapsed patients died. According to the long-rank test, estimated 5-year OS was not significantly different between normal and high LDH categories (63.3 %±0.6 % vs. 64.6 %±0.5 %; p=0.99) (Figure-1). Median PFS was 101.4 months (95% CI: 73.7-129) in high LDH group and 92.1 months (95% CI: 71.1-113.1) in normal LDH group (p=0.99).

Conclusion: Elevated LDH was confirmed as a poor prognostic factor in previous reports. In our transplanted patients with high LDH cohort, clinical outcomes are favorable and similar those have normal LDH. Therefore, further studies of larger randomized cohorts are required to clarify the impact of pre-transplant LDH levels on ASCT outcomes.

Keywords: Multiple myeloma, Serum lactate dehydrogenase Autologous Stem Cell Transplantation

■ Stem Cell Transplantation

OP-024 Abstract Referance: 90

COLLECTION OF STEM CELLS ≥ 5.0 X 106/Of BODY WEIGHT IN ONE DAY IN MULTIPLE MYELOMA IN THE PROCESS of AUTOLOGOUS STEM CELL TRANSPLANTATION

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Introduction: Autologous hematopoietic stem cell transplantation (ASCT) is an established treatment for patients with hematologic malignancies. Requested $CD34^+$ cell dose needed to ensure hematopoietic recovery following ASCT is 2.5 cells $x10^6$/of body weight, and 5.0 cells $x10^6$/of body weight (BW) for two ASCT in patients with multiple myeloma.

The aim of study was to analyse absolute number of cells (ANC) CD34+ ≥40.01 $x10^6$ /L in peripheral blood as guarantor of successful apheresis for two ASCT in patients with multiple myeloma (MM).

Patients and methods: The study was conducted in a retrospective-prospective manner. In the Clinic of Hematology, Clinical Center University of Sarajevo, during period April 2013-March 2019, treatment with high-dose therapy and ASCT was performed 94 patients who underwent 145 apheresis: 33pts (35%) with MM; 22pts (23%) with Hodgkin lymphoma; and 39pts (42%) with non-Hodgkin lymphoma. Collection performed in one day were characterized by the number collected CD34+ cells into two groups: collection of CD34+ cells <5.0 $x10^6$/BW; and ≥5.00 $x10^6$/BW. We examined correlation of CD34+ cells collection according to ANC CD34+ in peripheral blood by apheresis per day. Independent analyzed variables were: CD34+ cell dose, age, gender, disease.

Results: The average age of patients was 45 years, youngest was 18 and the oldest was 68 years. The group consisted of 17 males (51,52%) and 16 (48,48%) female patients. Collection of CD34+ < 5.0 $x10^6$/BW occurred in 27 (62,79%) cases; while collection of CD34+≥ 5.0 $x10^6$/BW was achieved in 16pts (37.21%). All the patients that achieved collection of CD34+ ≥ 5.0$x10^6$/BW in one day had 100% ANC CD34+ ≥40.01 $x10^6$/L in peripheral. Displayed difference was statistically significant p=0.0001. For statistical analysis, we used the c^2 test, Kolmogorov Smirnov and Mann-Whitney U test. P<0.05 was considered significant.

In conclusion: the guarantor of collection≥5.0 cells $x10^6$/BW is ANC CD34+ ≥40.01 x 10^6/L in peripheral blood on the day of apheresis.

Keywords: Myeloma multiplex, ANC in peripheral blood, collection

■ Stem Cell Transplantation

P-001 Abstract Referance: 79

EFFICACY OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Gazi University School of Medicine, Department of Hematology and Stem Cell Transplantation Unit

Background: Primary central nervous system lymphoma (PCNSL) is a rare type of lymphoma with poor responses to chemotherapy, which is mainly based on less penetrance of chemotherapeutic agents through blood brain barrier. Consolidation approaches including high dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT) have been developed to overcome this obstacle . The aim of this study is to evaluate the efficacy of AHSCT in PCNSL patients in terms of progression free and overall survival.

Methods: A total of 11 patients [median age: 43(28-62) years; male/female: 6/5] who had undergone AHSCT for a diagnosis of PCNSL were evaluated retrospectively.

Results: First-line chemotherapy regimen was BONN protocol [A: methotrexate 5 g/m^2 (day 1), vincristine 2 mg (day 1), ifosfamide 800 mg/m^2/day (days 2-5), dexamethasone 10 mg/m^2/day (days 2-5); B: methotrexate 5 g/m^2 (day 1), vincristine 2 mg (day 1), cyclophosphamide 200 mg/m^2/day (days 2-5), dexamethasone 10 mg/m^2/day (days 2-5); C: Ara-C 3 g/m^2/day (days 1,2), vincristine 2 mg (day 1), dexamethasone 10 mg/m^2/day (days 2-5)] in 9 patients (81.8%), Rituximab-BONN in one patient (9.1%) and high dose methotrexate in one patient (9.1%). Complete response was achieved in 4 patients (36.4%), partial response in 6 patients (%54.5), and refractory disease was observed in one patient (%9.1). Intrathecal prophylaxis was administered to all patients during the induction therapy. Hematopoietic stem cell mobilization was performed after BONN C protocol with granulocyte colony stimulating factor (G-CSF) at a dose of 10 mgr/kg/day in 10 patients (90.9%) and G-CSF-Plerixafor in one patient (9.1%). Median time from diagnosis to AHSCT was 123(94-668) days. Pre-transplant disease status was complete response in 5 patients (45.4%), partial response in 5 patients (45.4%) and refractory disease in one patient (9.1%). Pre-transplant Sorror comorbidity index score was 0(0-3). Conditioning regimen consisted of thiotepa [300 mg/m^2/day (2 days), cyclophosphamide 2 gr/ m^2/day (2 days) and busulfan 3,2 mg/kg/day (3 days)]. Median infused CD34$^+$ cell count was 5(3,35-6,95)x10^6/kg. Grade 2(1-4) mucositis was observed in 7 patients (63.6%). All patients experienced grade 4 hematological toxicity and peri-engraftment infection. Median neutrophil and platelet engraftment days were 11(10-17) and 11(8-17) days respectively. Complete response was demonstrated in 9 patients (81.8%) at median 75(60-90) days after AHSCT. Relapse was observed in 5 patients (45.4%) at median 4(2-30) months after AHSCT. Median progression free survival and overall survival were found to be 33.9% and 48.5% respectively at 12(1-104) months of follow-up (Figure 1, Figure 2).

Conclusions: Autologous HSCT is considered as a feasible treatment modality in patients with PCNSL with complete response rates reaching up to 90%. Thiotepa based conditioning should be preferred considering high CNS penetrance of the drug. Furthermore, addition of rituximab to induction regimens may help to improve response rates. Our results seem to be concordant with the previous reports which confirm the efficacy of AHSCT in PCNSL treatment.

Keywords: Primary Central Nervous System Lymphoma, Hematopoietic Stem Cell Transplantation

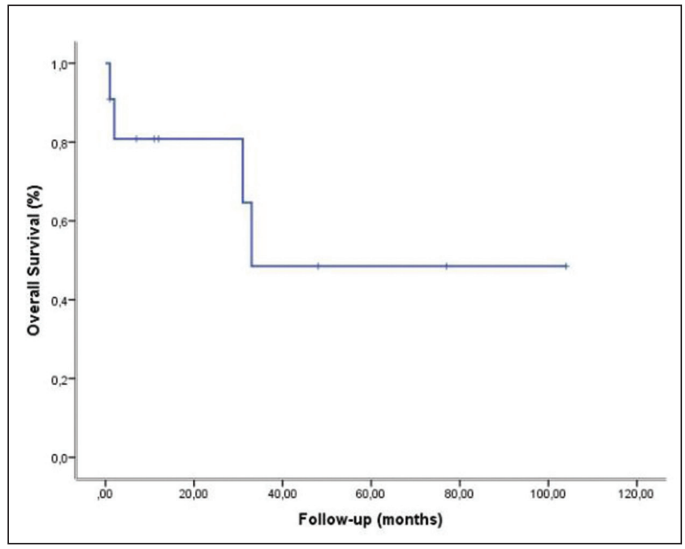

Figure 1. Overall survival was 48.5% at 12(1-104) months of follow-up

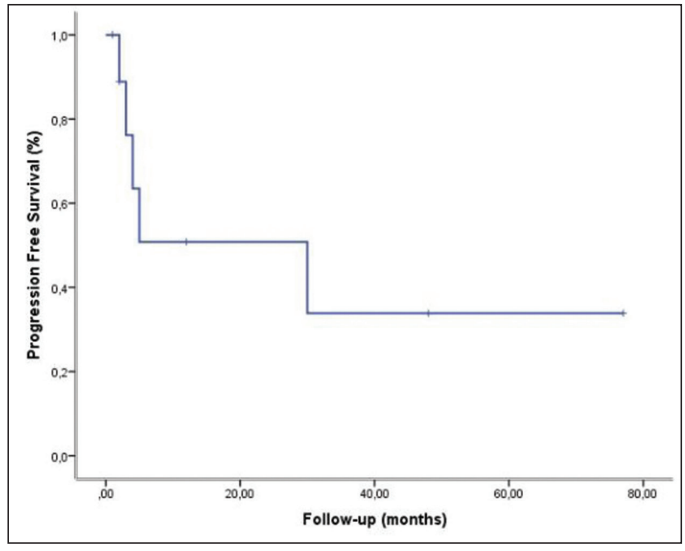

Figure 2. Progression free survival was 33.9% at 12(1-104) months of follow-up

■ Non-Hodgkin's Lymphoma

P-002 Abstract Referance: 154

IS AGE AN IMPORTANT FACTOR FOR AUTOLOGOUS PERIPHERAL HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS WITH NON-HODGKIN LYMPHOMA?

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Introduction: High-dose chemotherapy followed by autologous hematopoietic cell transplantation (auto HSCT) may provide survival benefit in patients with non-hodgkin lymphoma (NHL). Retrospective analyses suggest that the benefit of HDT extends to elderly patients with NHL, which is an important finding considering that the median age at diagnosis is 67 years (range: 65-74) for NHL in United States, using 2010-2014 US SEER data. We

aimed to define the efficacy and toxicity of auto HSCT in patients >60 years with NHL compared with younger patients.

Patients and Methods: From January 2005 through August 2017, data from 102 chemosensitive aggressive NHL patients below the age of 60 were compared to 26 lymphoma patients above 60 years of age who were eligible for auto HSCT according to geriatric assessment (GA). All these data were obtained from the Ankara University Faculty of Medicine, Department of Hematology and Bone Marrow Transplant Unit. Patients were excluded if they had an indolent lymphoma, chemo refractory disease, or underwent a second autologous or allogeneic HSCT. We compared the toxicity profile and outcome between the research group: patient aged 60 years and above and the control group: patient <60 years.

Results: Median age of research group was 47.5 (range, 18-74) years, and 2 patients were 70 years and older. The majority of patients (n=55, 43%) underwent an autologous HCT due to relapsed DLBCL. Median follow up of surviving patients was 20.5 (range, 1-60 mos) months at the time of data collection, 82 patients (64.6%) were alive. Patients' characteristics were similar between the two age cohorts. All of the patients were stage III or IV at diagnosis; ten out of 26 elderly patients had active disease at the time of auto HSCT. The median follow-up was 20.5 months (range, 1-60 mos). Prior to transplantation majority (85%) of the elderly patients received BEAM protocol as conditioning treatment. Bone marrow stem cell was used in only 1 patient. None of the patient had mobilization failure, the median peripheral CD34 level was $5.24x10^6$/kg. Forty-eight percent of the elderly patients experienced grade 3-4 mucositis and 77% of the patients had microbiology-documented infection. Sixty-two percent of the elderly patients had diarrhea with median duration of 8 days (range, 5-20 days). Renal toxicity was occurred in 7 (27%) patients while hepatic toxicity in 1 (10%) patient in the elderly cohort. There was no difference in the toxicity profile between patients ≥ 60 years and those aged <60 years. Median time to neutrophil recovery was 10 days (range, 8-18 days) and platelet recovery 11 days (range, 10-32 days) in elderly cohort. Interestingly, neutrophil and platelet engraftments had not occurred in six out of 102 patients in the younger group. Overall response was obtained from all elderly patients (23% CR). At the time of data collection, 4 patients (15%) of patients' ≥ 60 years have deceased. Relapse (n=3) was the main course of death. The probability of 4-year progression free survival (PFS) and estimated overall survival (OS) in elderly patients were 44.4% and 39.4%, respectively.

Conclusion: Based on this single center study, auto-HSCT is safe and efficacious in the treatment of elderly lymphoma patients. We emphasize the need for further research in order to determine the risk-benefit threshold for HSCT based on age coupled with comorbidity and fragility.

Keywords: autologous hematopoietic cell transplantation, non-hodgkin lymphoma, elderly

■ Acute Myeloid Leukemia

P-004 Abstract Referance: 137

SINGLE CENTER EXPERIENCE: COMPARISON OF REDUCED INTENSIVE CHEMOTHERAPY AND LOW-DOSE CYTARABINE TREATMENT AS REMISSION INDUCTION IN OLDER AGE AML CASES

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Aim: The aim of this study was comparison of treatment with reduced dose of cytosine arabinose (100 mg / m 2, continuous intravenous infusion) and daunorubicin (45 mg / m 2 2-3 days) treatment protocol versus low dose cytarabine treatment as the remission induction treatment of aged 65 years and older AML patients.

Methods: The data of the over the age of 65 years of cases diagnosed as AML between 2010 and 2018 at Hematology Clinic of Atatürk Training and Research Hospital were retrospectively analyzed. Statistical analyzes were performed using chi-square test using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A value of less than 0.05 was considered significant.

Results: The data of 67 cases with AML were evaluated. Eight cases were excluded because they were diagnosed with acute promyelocytic leukemia. In Table 1, clinical and laboratory findings at the time of diagnosis were compared according to the treatment choice. Mean survival of 59 patients was 19 (± 3,9) months. The mean survival of the patients who received Ara-C + daunorubicin treatment and low-dose cytarabine treatment was 26.4 (± 6.2) and 14.8 (± 4.1) months, respectively **(p = 0.044)** (Figure 1). After the first induction treatment, 16 (27.1%) cases were obtained in all series recovery in peripheral blood, and 12 (75 %) of these patients were treated with Ara-C + daunorubicin **(p = 0.001)**. Total survival of 21 (35.6%)cases with neutrophil recovery at the first month and 38 (64.4%) cases without neutrophil recovery at the first month were 36.1 (± 7.7) and 5.8 (± 0.9) months, respectively **(p = 0.001)** The OS was 27.7 ± (5.4) months in patients with platelet recovery at the first months of induction treatment, while the OS 2.1 ± (0.2) months in the patients who had no platelet recovery at the first months of induction treatment **(p = 0.001)** (Figure 2). The OS of the patients with erythrocyte recovery at the first months of induction treatment was 29.6 ± (5.7) months, while the OS of the patients without erythrocyte recovery was 2.4 ± (0.3) months **(p = 0.001)** (Figure 2). Table 2 was showed that the comparison of treatment response and treatment-related complications at the first months of induction treatment. There was 25 cases with neutrophil recovery during follow-up. 14 patients with neutrophil recovery at the first months of induction treatment, total survival rates of 11 cases without neutrophil recovery were 54.05 (± 11.7) and 20.8 (± 6.6) months, respectively (**p = 0. 042**) (figure 2). There were 9 (64.3%) patients treated by low dose Ara-C + daunorubicin induction chemotherapy among the 14 patients with neutrophil recovery at the first months of induction treatment (p=0.648). Among 41(69.5%) patients treated with low-dose ARA-C, the number of patients with ANC ≥ 0.5×10^3 cells/µL at the end of the first month was 7 (17.1%). The mean duration of neutrophil recovery was 21 days. The survival rates of cases with neutrophil recovery events and those without neutrophil recovery were 25.9 ± 14.6 months and 5.8 ± 0.9 months, respectively (p = 0.001).

Discussion: The choice of treatment for advanced age AML patients is decided by considering the performance status and comorbid diseases of the patient. We found that the absolute neutrophil count at ≥$0.5\ x10^3$ cells/µL (recovery of neutrophil) at the first months of induction treatment as low-dose ARA-C in patients with advanced age AML was associated with an increase in overall survival.

Keywords: acute myeloid leukemia

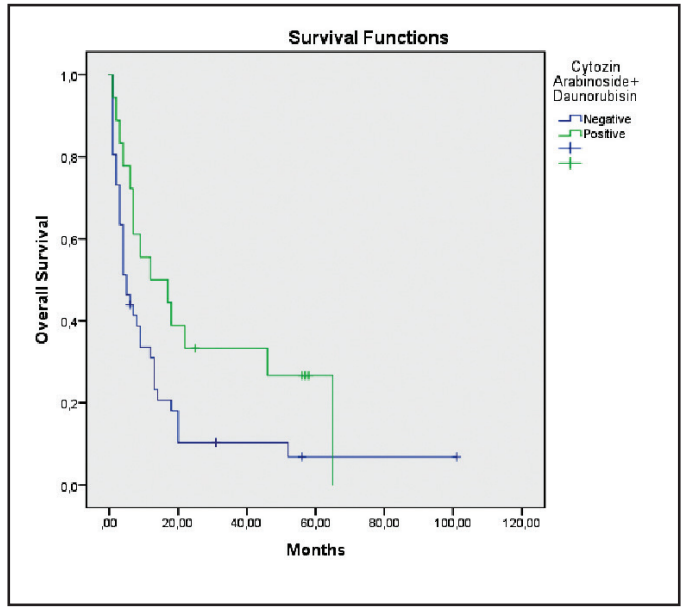

Figure 1. Comparison of the total survival of patients receiving low-dose cytarabine versus patients receiving Ara-C + daunorubicin

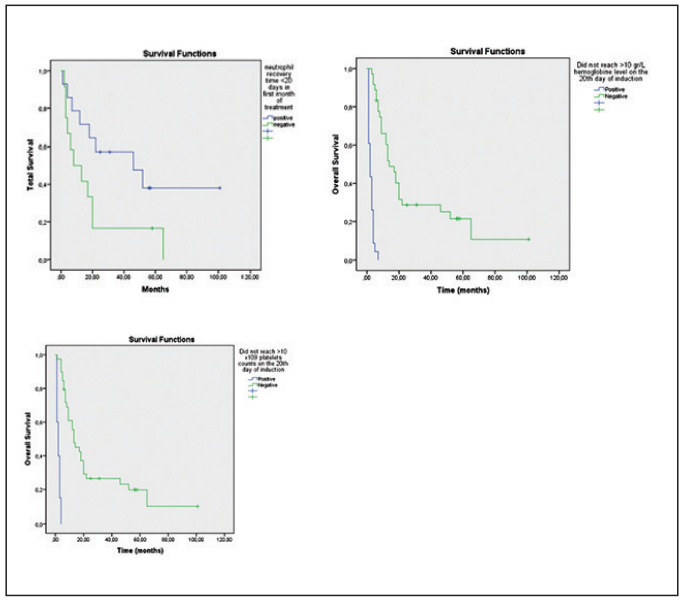

Figure 2. Overall survival curves according to neutrophil, platelet and erytrocyte recovery at the first months of induction treatment

Table 1. Comparisions of clinical and laboratory findings at the time of diagnosis according to the treatment choice.

	Total n:59 patients	*Low dose cytarabine n:41 (69.5%)*	*Reduced intensive chemotherapy (5+2) n:18 (30.5%)*	*P Value*
Gender (f/m)	21(35.6%)/38 (64.4%)	12 (29.3%)/29 (70.7%)	9 (15.3%)/ 9 (15. 3%)	0.109
Age (median)	73 (min 65 max 88)	75 (min 65 max 88)	70 (min 65 max 86)	
Age 65-75 years 75-88 years	34 (57.6%) 25 (42.4%)	20 (48.8%) 21 (51.2%)	14 (77.8%) 4 (22.2%)	0.048
Hemoglobine level(g/dL)	9.4 ±2.04	8.9 (±2.08)	10.3 (±1,6)	
Leucocyte count (x10cells/µL)	5600 (min 730 max 291000)	5750 (min 730 max 291000)	4900 (min 730 max 113000)	
Neutrophil count (x10 cells/µL)	2895 (±12691)	200 (min 0 max 92800)	280 (min 0 max 8700)	
Platelet count (x1000 cells/µL)	78.508 (±84.771)	40000 (min 7000 max 202000)	102500 (min 5000 max 451000)	
Sedimentation(mm/h)	57.4(±38.07)	57,3(±40.5)	57.6 (±32.8)	0.852
CRP (mg/L)	59.1(±60.6)	59.8 (±56.4)	65.3 (±63.7)	0.210
<="" td="">	41 (69.5%)	30(73.2%)	11 (26.8%)	0.374
Fit (ECOG 0) Unfit (Ecog 1-2-3)	13 (22%) 46 (78%)	5 (12.2%) 36 (87.8%)	8 (44.4%) 10 (55.6%)	0.014

Table 2. Comparison of treatment response and treatment-related complications at the first months of induction treatment

	Total 59 patients	*Low dose cytarabine 41 (69.5%)*	*Reduced intensive chemotherapy (5+2) 18(30.5%)*	*P Value*
Did not reach ANC of 0.5 × 1000 cells/µL after the first months of induction treatment	33(54.2%)	30 (90.6%)	3 (9.4%)	0.001
Did not reach >10 g/dL hemoglobine level after the first months of induction treatment	36 (61 %)	28 (77.8 %)	8 (22.2 %)	0.076
Did not reach >100x1000 cells/ µL platelets counts after the first months of induction treatment	32 (54.2 %)	28 (87.5%)	4 (12.5%)	0.001
Cases of recovery in all series of blood cells after the first months of induction treatment	16 (27.1%)	4 (25 %)	12 (75 %)	0.001
Grade 3-4 infection in first month of chemotherapy	11 (18.6%)	5 (45.5%)	6 (54.5%)	0.074
Presence of FEN	24 (40.7%)	13 (31.7%)	11 (61.1%)	0.046
Time of hospitalization at the first chemotherapy	15 day (min 1 max 51 day)	8 day (min 1 max 45 day	27 day (min 1 max 51 day	0.003
Hospitalization time for more than 1 month at the first chemotherapy period	11 (18.6%)	4 (36.4%)	7 (63.6%)	0.025

■ Non-Hodgkin's Lymphoma

P-005 Abstract Referance: 131

THE EFFECT OF SARCOPENIA ON PROGNOSIS IN PATIENTS WITH DIFFUSEL LARGE B-CELL LYMPHOMA

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Backgrounds: Sarcopenia is known to be associated with poor clinical outcome in patients with diffuse large B-cell lymphoma (DLBCL).

Methods: We retrospectively reviewed 139 DLBCL patients who treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab plus cyclophosphamide, vincristine, and prednisone R-CVP therapy. Sarcopenia was classified by the region where the pretreatment skeletal muscle index (SMI) was measured.

Results: Both the sarcopenia-L3 and sarcopenia-pectoralis muscle (PM) groups had increased incidences of severe treatment-related toxicities and treatment discontinuation compared with the non-sarcopenia-L3 and non-sarcopenia-PM groups, respectively. We compared the patients' sarcopenia status before and after treatment according to CT measurements. The sarcopenia and non-sarcopenia- groups had 5-year overall survival (OS) rates of 50 % and 63 % (p =0.028) in after treatment, respectively. We found that the sarcopenia and non-sarcopenia- groups had 5-year overall survival (OS) rates of 63 % and 59 % (p =0.9) in pre- treatment, respectively.When the sarcopenia and non-sarcopenia groups were compared, there were no differences in baseline characteristics, treatment toxicity.

Conclusions: L3- and PM-SMIs are equally useful to define sarcopenia. In this study, sarcopenia was associated with poor survival in patients' sarcopenia status after treatment of patients with DLBCL. More prognostic information can be obtained when examined the status of sarcopenia.

Keywords: Sarcopenia, diffuse large B-cell lymphoma (DLBCL).

■ Acute Lymphoblastic Leukemia

P-006 Abstract Referance: 106

A NEW MARKER IN CHILDHOOD CANCER: ZONULIN

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Introduction: Zonulin is an important protein synthesized by intestine and liver cells associated with intestinal permeability. It was identified to play an important role in maintaining tight junctions in the intestinal walls. Additionally, zonulin is reported to be associated with a variety of pathologic situations like autoimmunity and malignancies.

Material and Method: A prospective case-control study was performed with pediatric cancer patients monitored by the Pediatric Hematology and Oncology ward in Hatay State Hospital. The study included a total of 20 patients and 35 healthy controls. Demographic data, clinical findings and laboratory parameters were recorded. A total of 32 blood samples were taken from patients. Samples were centrifuged at 4000 rpm and then separated serum was stored at -40 degrees. Serum zonulin level was measured with the enzyme-linked immunosorbent assay (ELISA) method.

Results: In the study 12 female and 8 male pediatric patients were analyzed. Mean age was 7.3±4.4 years. Seven patients had acute lymphoblastic leukemia, 5 patients had Hodgkin's lymphoma, 3 patients had rhabdomyosarcoma, 3 patients had neuroblastoma, 1 patient had Wilm's tumor and 1 patient had hepatoblastoma. Serum zonulin levels were identified to be statistically significantly high in the patient group compared to the healthy control group (p=0.013).

Conclusion: The high level of serum zonulin identified in cancer cases may be associated with both the cause of malignancy, side effects of chemotherapy and disrupted gastrointestinal structure linked to causes like mucositis. This study is important as the first study in the literature to assess serum zonulin levels in pediatric cancer cases.

Keywords: Zonulin,Childhood Cancer

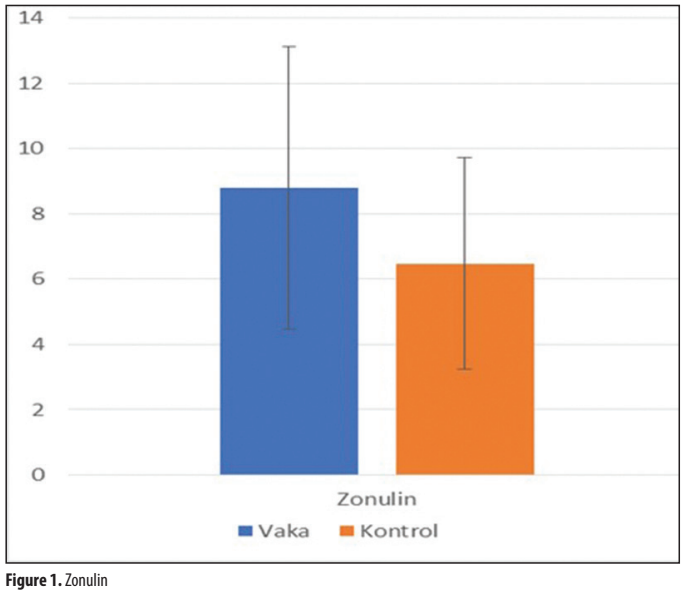

Figure 1. Zonulin

Table 1. Serum zonulin levels

	Case group	*Control group*	*P*
Zonulin (ng/ml)	8.80±4.33	6.48±2.52	0.013

■ Acute Myeloid Leukemia

P-007 Abstract Referance: 55

ALTERED EXPRESSION OF TGF-BETA SIGNALING PATHWAY COMPONENTS CONTRIBUTES TO ACUTE MYELOID LEUKEMIA

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Background: TGFβ signaling pathway is a crucial element with tumor suppressive effects, which its malfunction may lead to tumor formation. AML is a heterogeneous disorder caused by defective differentiation and enhanced proliferation in white blood cells and their precursors in the blood and bone marrow. In this study we measured gene expression levels of TGFβ, TGFβRII, smad3 and smad7 in peripheral blood and bone marrow samples of acute myeloid leukemia patients.

Methods & materials: Peripheral blood & bone marrow samples of 93 newly diagnosed AML patients & 13 healthy subjects as control group were examined. The gene expression of TGFβ, TGFβRII, smad3 and smad7 were examined by Real time PCR (polymerase chain reaction). We used SPSS statistical software release 16.0 for analysis between different groups.

Results: Expression levels of TGFβRII & smad3 were significantly increased in AML group versus control group. Also a significant decrease was observed in smad7 expression in AML patients compared with control group. There was no significant change in TGFβ expression between the two groups.

Conclusion: According to upregulation of TGFβRII and smad3 and downregulation of smad7, it seems TGFβ signaling pathway is over-activated in AML patients, which suggests in despite of conventional role of TGF-b in normal cell cycle, it could be controversial role in the leukomogenesis of these patients.

Keywords: Acute myeloid leukemia, TGFβ, signaling pathway

■ Multiple Myeloma

P-008 Abstract Referance: 107

SLEEP QUALITY OF GERIATRIC PATIENTS WITH MULTIPLE MYELOMA: AN UNDERESTIMATED QUALITY OF LIFE PROBLEM

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Introduction and aim: Multiple myeloma accounts for 1 to 2 percent of all cancers and 19% of all newly diagnosed haematological malignancies, and it is estimated that its incidence will rise considerably due to an increasingly aging population in the Western world[1]. Adults with cancer may have disturbed sleep regardless of age. In a study of 2646 patients with cancer, 39% reported insomnia[2]. A couple of previous studies have shown that myeloma patients reported day-time fatigue and sleep problems[3,4]. However, There is no study evaluating the sleep quality of geriatric patients with myeloma in the literature.

Methods: A total of 35 geriatric aged patients with multiple myeloma who were admitted to the hematology outpatient clinic between December 2018 and February 2019 were included in the study. while sleep quality of the patients were evaluated by Pittsburgh Sleep Quality Index (PSQI), geriatric

assessments were made by using G8 scale. In addition to these scores, serum hemoglobin (Hb), creatinine (Cr), β2 microglobulin (β2 MG), calcium, albumin levels were recorded.

Results: Median age of the patients was 73,3±5,7 years (range 65-91). Global PSQI score of 26 of patients (74.3%) were ≥5 indicating that they had poor sleep quality. An impaired G8 score was found in 18 (51.4%) of all patients (Table-1). There were no statistically significant relationship between serum Hb, Cr, β2 MG, calcium, albumin levels and PSQI or G8 score (Table-2). On the other hand, there was a statistically significant association between PSQI and G8 groups (p<0.05). There was a lineer, opposite, moderately strong (42.1%) and statistically significant correlation between total PSQI and G8 scores (Pearson correlation coefficient: -0.421, p<0.05).

Discussion: Poor sleep quality and impaired G8 scores are a frequent problem in geriatric multiple myeloma patients. Neither sleep quality nor G8 scores were related with serum Hb, Cr, β2 MG, calcium, albumin levels or disease activity. A routine evaluation of sleep quality and geriatric assesments in clinical practise might be helpful to identify this underestimated quality of life problem.

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Keywords: Multiple myeloma, sleep quality

Table 1. Descriptive statistics of the patients

		N	*%*
Gender	male	21	60
	female	14	40
	total	35	100
PSQI score	<5 (good sleep quality)	9	25.7
	≥5 (poor sleep quality)	26	74.3
	total	35	100
G8 score	≥14 (normal)	17	48.6
	<14 (impaired)	18	51.4
	total	35	100

Table 2. Comparisons regarding PSQI scores

	PSQI	*N*	*mean*	*std dev*	*median*	*min*	*max*	*25p*	*75p*	*p value*
hemoglobin	<5 (good sleep quality)	9	11.22	1.45	11.40	9.00	13.40	10.05	12.35	0.83
	≥5 (poor sleep quality)	26	11.18	2.08	10.85	6.80	15.70	9.58	12.85	
creatinine	<5 (good sleep quality)	9	0.96	0.37	0.86	0.60	1.80	0.70	1.13	0.97
	≥5 (poor sleep quality)	26	1.38	1.95	0.88	0.30	10.60	0.60	1.57	
beta2 microglobulin	<5 (good sleep quality)	7	4142.86	2863.48	3000.00	1600.00	8600.00	2000.00	7800.00	0.47
	≥5 (poor sleep quality)	22	4836.36	4165.22	4100.00	1800.00	22200.00	2675.00	5350.00	
albumin	<5 (good sleep quality)	9	3.65	0.60	3.80	2.40	4.30	3.35	4.19	0.77
	≥5 (poor sleep quality)	26	3.71	0.53	3.75	2.60	4.60	3.48	4.13	
calcium	<5 (good sleep quality)	9	8.93	0.48	9.00	7.90	9.60	8.70	9.20	0.38
	≥5 (poor sleep quality)	26	9.22	1.36	9.30	7.70	14.90	8.38	9.50	

Table 3. Association between PSQI and G8 scores

			PSQI			
			<5	*≥5*	*total*	*p value*
	≥14 (normal)	N	7	10	17	
		%within G8	41.2	58.8	100	
		%within PSQI	77.8	38.5	48.6	
		% of total	20.0	28.6	48.6	
G8	<14 (impaired)	N	2	16	18	
		%within G8	11.1	88.9	100	
		%within PSQI	22.2	61.5	51.4	0.038
		% of total	5.7	45.7	51.4	
	Total	N	9	26	35	
		%within G8	25.7	74.3	100	
		%within PSQI	100	100	100	
		% of total	25.7	74.3	100	

■ Myeloprofilerative Disorders

P-009 Abstract Referance: 58

DIAGNOSIS ISSUES IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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The aim of the study was to analyze the issues of clinical, hematologic and molecular-genetic diagnosis in chronic myeloproliferative neoplasms (CMPN).

Materials and methods: The study enrolled 247 patients (pts) with different phases of idiopathic myelofibrosis (IM), chronic myeloid leukemia (CML) and polycythemia vera (PV), who had been treated and followed up at the Institute of Oncology during 1995 – 2018 years. FISH interphase method was applied for diagnosis of CML. The abnormal mixt signal in nucleuses indicated the presence of t(9;22)(q34;q11) translocation. The quantitative RT PCR was used with the aim to detemine the expression of the BCR-ABL gene p210 and p190 transcripts at CML diagnosis and during the chemotherapy monitoring. Five transcription products (b2a2, b3a2, b2a3, b3a3 si e1a2) were analyzed by the usage of the quantitative PCR test. The quantitative detection of JAK2 V617F mutation served as a major criterion for diagnosis of IM and PV.

Results: CML was diagnosed in 125 (50.6%) pts, PV – in 92 (37.3%) and IM – in 30 (12.1%) pts. Prefibrotic stage of IM was determined in 12 (40.0%) cases, fibrotic stage – in 18 (60.0%). The diagnosis of CML was established in chronic phase in 113 (90,4 ± 2,32%) pts, in the accelerated and acute phases – in 12 (9,6 ± 2,02%). Erythremic phase IIA of PV was revealed in 87 (94.6 %) pts, phase IIB – in 5 (5.4 %). The age category of 50 – 59 years (46,6%) prevailed in the IM pts structure. The age subgroups of 40–49 (27.4%) and 50–59 (19.0%) years were common in CML, that indicated the predominant involvement of the workable population. The predominance of the age categories of 50–59 years (38.0%) and 60–69 years (22.7%) was registered in PV. Plethoric syndrom occurred in all 92 pts with PV and in 9 (33%) pts with Vaughan type of IM, being more significant in PV. Splenomegaly was detected in all pts with IM and CML and in 67 (72.8%) pts with PV. Hepatomegaly was found in 25 (83.3%) cases of IM, 42 (33.3%) of CML and in 46 (50.0%) of PV. The following blood count limits occurred in pts with IM: hemoglobin (Hgb) – 59–178 g/l, erythrocyte count (EC) – 2.3–5.7 x 10^{12}/l, leukocyte count (LC) – 3.6–54.0 x10 ^{9}/l, platelet count (PC) – 18.0–1302.0 x10^{9}/l. The bone marrow (BM) biopsy revealed panmyelosis or myelo-megakaryocytic myelosis, massive

proliferation of megakaryocytes and collagen fibrosis. In CML cases the LC range was 12.2–315.0 x 10^9/l and PC range – 115.0–640.0 x 10^9/l. In the BM aspirates, granulocytic series accounted 47.0–86.4%, blast cells – 1–69%, being increased in the accelerated and acute phases. The PV patients experienced the followig blood count limits: Hgb – 174–230 g/l, EC – 5.3–6.5 x 10^{12}/l, PC – 180–1620.0 x10^9/l. The iliac crest biopsy with the BM histological examination in PV demonstrated hyperplasia due to the proliferation of erythrokaryocites, megakaryocytes and granulocytopoiesis elements at all steps of maturation. In CML the rate of Ph-positive cells ranged between 20 – 100%, exceeding 80% in the majority of pts (70.6%). The quantitative RT PCR of the peripheral blood cells revealed the large variations of the BCR-ABL p210 and p190 transcripts: 21.84–100% IS.

Conclusions: The association of splenomegaly and hepatomegaly was registered more frequently in IM. The elevation of platelet count was higher in IM and PV. The accuracy of diagnosis of CMPN may be provided by the combination of the histologic, cytologic, cytogenetic or molecular examinations.

Keywords: chronic myeloproliferative neoplasms, myeloid splenomegaly, cytodiagnosis, real-time PCR, JAK2 kinase

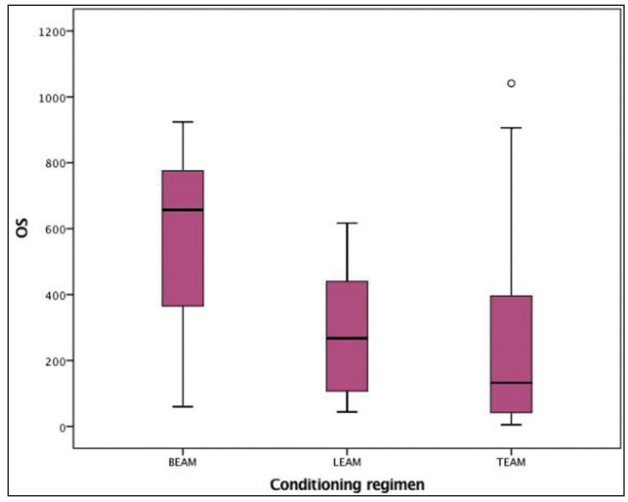

Figure 1. OS

■ Stem Cell Transplantation

P-010 Abstract Referance: 101

COMPARISION OF AUTOLOGOUS CONDITIONING REGIMENS AMONG LYMPHOMA PATIENTS

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Introduction: Salvage chemotherapy followed by an autologous stem cell transplant (ASCT) is still the standard of care for relapsed or refractory lymphoma. ASCT should be offered to patients whom have chemosensitive disease. Myeloablative conditioning regimens are used in this setting. Most commonly we use ; Carmustine (BCNU) or lomustine (CCNU) combination with etoposide, cytosine arabinoside and melphalan.

Methods: 41 relapsed or refractory lymphoma patients who were treated in Yuksek Ihtisas University Koru Hospital Hematology and Bone Marrow Transplant Unit between 2014-2019 are included in this study.12 patients were Hodgkin Lymphoma and 29 were Non Hodgkin Lymphoma Median age was 47 (range 18-72). Male ratio was 56,1% (n=23) and female patients was 44% (n= 18)of the patients .TEAM conditioning regimen is used for 14 patients LEAM is used for 12 patients and 12 patients for BEAM . The median CD34 amount is 5*10^6 for BEAM group ,4,9 *10^6 for LEAM group and 3,7*10^6 for TEAM group.

Results: Median neutrophil engrafments were 11,5, 14 and 12,5 days in BEAM , LEAM and TEAM groups respectively. Median platelet engrafments were 13, 12.5 and 12 days in BEAM , LEAM and TEAM groups respectively. PFS were 460, 267 and 83 days for BEAM,LEAM and TEAM. Four patients died because of transplant related mortality al were in TEAM group.

Conclusion:

1. BEAM ,LEAM and TEAM regimens have similiar engrafment days.

2. PFS and OS were longer in BEAM group. (BEAM patients have longer follow up)

3. Hospitilization days were equal in three groups.

As a conclusion LEAM and TEAM regimens can be preferred as autologous conditioning regimens beside BEAM.

Keywords: Beam Team Leam Lymphoma Autologous

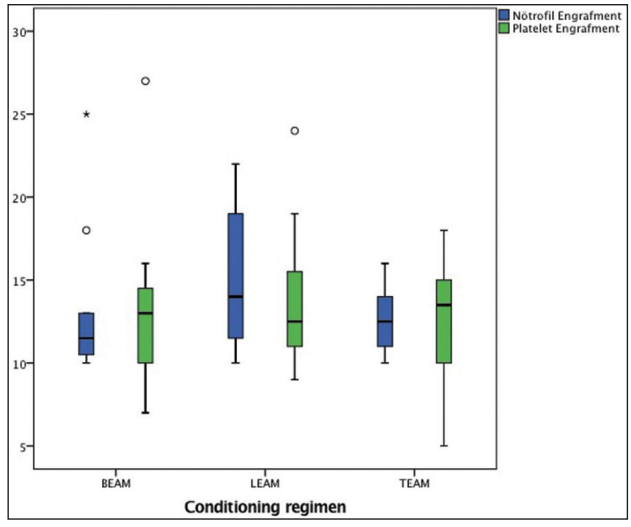

Figure 2. Plt Neu Engrafment

	Total	BEAM	LEAM	TEAM	BEAM/LEAM	BEAM/TEAM	LEAM/TEAM
	median (min-max)				p		
CD34+	4,8 (2,3-11,2)	5 (2,34-8,44)	4,93 (2,3-11,2)	3,76 (2,46-8,01)	0,665	0,190	0,520
Nötrofil Engrafment	12 (7-25)	11,5 (10-25)	14 (10-22)	12,5 (10-16)	0,153	0,502	0,258
Platelet Engrafment	13 (5-27)	13 (7-27)	12,5 (9-24)	12 (5-18)	0,663	0,642	0,339
Hospitalization time	27 (16-53)	26,5 (23-46)	29 (21-47)	27 (16-53)	0,954	0,796	0,897
PFS	244 (5-1041)	460 (60-924)	267,5 (44-614)	83 (5-1041)	0,133	0,027	0,100
OS	298 (5-1041)	657 (60-924)	267,5 (44-617)	132,5 (5-1041)	0,011	0,018	0,411

■ Non-Hodgkin's Lymphoma

P-011 Abstract Referance: 78

PROGNOSTIC SIGNIFICANCE OF FERRITIN LEVELS IN LOW GRADE NON HODGKIN LYMPHOMA PATIENTS

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Introduction: Low-grade Nonhodgkin lymphoma (LG-NHL) represent more than 50% of malignant lymphomas and charactarized by indolent clinical course, which consist of marginal zone lymphoma (MZL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma,

lymphoplasmacytic lymphoma/waldenstrom macroglobulinemia (WM) as the most common subtypes. These lymphomas usually have a slow clinical course and are limited to the reticuloendothelial system. Some patients may be followed up with the wait-and-see principle until they become symptomatic, while some patients require treatment. Factors which may have prognostic significance after being diagnosed in these patients have long been the subject of research.

Materials and methods: This study was conducted on patients diagnosed with LG-NHL in the Hematology Departments of two centres (Diskapi Yildirim Beyazit Training and Research Hospital and Gulhane Training and Research Hospital) between 2010 and 2018. MZL, FL, hairy cell leukemia (HCL)/ lymphoplasmacytic lymphoma and SLL patients were included. A total of 93 patients were retrospectively analyzed. Demographic information, specific diagnosis, date of diagnosis, treatment regimen, treatment response and follow-up periods were recorded for all patients. At the time of diagnosis, complete blood count (CBC) parameters, albumin, LDH levels, ferritin and B12 vitamin levels were examined. Using these data, response rates, overall survival (OS) and time to treatment duration were calculated. The effect of the parameters on OS and the need for treatment was analyzed.

Results: A total of 93 LG-NHL patients were included in this study, of which 40 were MZL, 28 were FL and 25 were others. The mean age of the patients was 62.96 years and 48 were female. Treatment was required by 69 patients during the follow-up period and was not required by 24. The median time to treatment was 29.8 [17.9-41.8] months in patiens who needed treatment. In the comparison of patients with and without treatment, there were significant differences in respect of the number of comorbidities, platelet count, neutrophil count, disease subgroups and ferritin level. Logistic regression analysis was performed and ferritin levels were found to be independent risk factors for the need for treatment (p=0.002). When the survival rates of the patients were examined, it was determined that the median OS of all the patients was 92.9 [34.2-151.6] months. The OS was not significantly different between the subgroups (p=0.990). Only ferritin level was found to be an independent parameter affecting OS in all patients.

Discussion: Several studies have focused on identifying prognostic factors to help clinicians to define the course of the disease and to determine treatment decisions. Some studies have shown that an elevated serum ferritin level is a poor prognostic marker for hematological malignancies. Ferritin levels show iron storage and are elevated in some clinical situations such as inflammation, infection, organ dysfunction, and malignancy without iron overload. In the current study, prognostic markers in LG-NHL patients were investigated and it was demonstrated that higher level of ferritin at the time of diagnosis is a determining factor for treatment requirement and poor prognosis. Given that it is easily available and low-cost at the time of diagnosis, ferritin can be used as a prognostic marker for patients with indolent lymphoma.

Keywords: ferritin, indolen lymphoma, prognosis

Table 1. The clinical and dermographic characteristics of patients

	MZL (n=40)	*FL (n=28)*	*Other (n=25)*	*All (N=93)*
Age (median, year)	64.13 (35-81)	63.39 (41-82)	60.60 (41-86)	62.96 (41-86)
Gender (female/male)	25 (62.5%) / 15 (37.5%)	16 (57.1%) / 12 (42.9%)	7 (28.0%) / 18 (72.0%)	48 (51.6%) / 45 (48.4%)
Comorbidty [Median (Min-Max)]	0.5 [0.0-4.0]	0.0 [0.0-4.0]	1.0 [0.0-3.0]	0.0 [0.0-4.0]
IPI/FLIPI score [Median (Min-Max)]	2.0 [1.0-5.0]	3.0 [0.0-4.0]		2.0 [0.0-5.0]
Hb (gr/dL) [mean±SD]	11.73±2.81	12.65±2.59	11.73±3.25	12.01±2.87
Plt (x105/L) [mean±SD]	194000±13200	238000±91000	141000±77000	193000±112000
Wbc (x106/L) [mean±SD]	10280±9360	8050±5890	9860±14160	9500±10300
LDH (U/L) [mean±SD]	294.4±149.6	305.2±320.7	211.4±107.8	276.5±212.4

Table 2. The comparison of patients with and without treatment

(N=93)	*Patients with treatment (n=69)*	*Patients without treatment (n=24)*	*p*
Age (year, mean±SD)	62.26±11.90	64.96±10.48	0.327
Comorbidty [n, Median (Min-Max)]	1.0 [0.0-4.0]	0.0 [0.0-3.0]	0.043
Hb (gr/dL) [mean±SD]	11.79±3.03	12.65±2.31	0.209
Plt (x103/L) [mean±SD]	179217.39±99414.89	234083.33±139107.69	0.039
Wbc (x103/L) [mean±SD]	6000.0 [1900.0-37800.0]	8100.0 [1670.0-65500.0]	0.077
Neutrophil (x103/L) [mean±SD]	2700.0 [500.0-21600.0]	3950.0 [770.0-29600.0]	0.045
Lymphocyte (x103/L) [mean±SD]	1700.0 [200.0-28900.0]	2400.0 [200.0-53700.0]	0.179
LDH (U/L) [mean±SD]	225.5 [111.0-1869.0]	217.50 [158.0-574.0]	0.715
Albumin (mg/dl) [mean±SD]	4.1 [2.4-4.9]	4.3 [2.4-4.8]	0.061
Ferritin (ng/mL) [mean±SD]	91.5 [4.0-1500.0]	44.0 [10.0-290.0]	0.002
Vitamin B12 (ng/mL) [mean±SD]	250.0 [78.0-2000.0]	245.0 [104.0-756.0]	0.575
Disease subtypes (MZL / FL / Other)	25 (%36.2) / 21 (%30.4) / 23 (%32.2)	15 (%62.5) /7 (%29.2) / 2 (%8.3)	0.030

Table 1. Logistic regression model according to treatment status in all patients

Variable	*p*	*OR*
Number of comorbidity	0.337	1.348
Platelets	0.101	1.000
Neutrophil	0.412	1.001
Ferritin	0.032	1.011
Disease subtypes (MZL / FL / Other)	0.084 / 0.391 / 0.028	/ 1.787 / 13.190

■ Non-Hodgkin's Lymphoma

P-012 Abstract Referance: 135

AST/ALT (DE RITIS) RATIO AS A PROGNOSTIC FACTOR IN DIFFUSE LARGE B-CELL LYMPHOMA

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Objective: This study aims to evaluate the prognostic significance of the aspartate aminotransferase (AST) / alanine aminotransferase (ALT) (De Ritis) ratio in diifuse large b-cell lymphoma (DLBCL).

Method: We evaluated the clinical and histopathological data of 225 patients who had diagnosed DLBCL, between December 2003-November 2016 at our hospital. The potential prognostic value of the De Ritis ratio with regard to BC was evaluated using ROC curve analysis. The effect of the De Ritis ratio on the overall survival (OS) was analyzed using the Kaplan-Meier method and multivariate Cox regression models.

Results: The mean age of the patients was 60,3 ± 16,4 (18–95) years, and 57,7 % of them were males. The cut-off value of the De Ritis ratio for OS was calculated as 1.300 in the ROC analysis. In KaplanMeier analyses, the group with a higher De Ritis ratio presented a more unfavorable prognosis for OS (p=0,0001)(Figure 1). Based on the Cox regression models adjusted for

clinical and pathological parameters, for OS, the De Ritis ratio (p=0.018), age (p=0.049) were determined as independent prognostic factors.

Conclusions: A higher De Ritis ratio can be considered as an independent prognostic factor in DLBCL patients who treated with lymphoma therapy (R-CHOP, R-CVP). Our results need to be confirmed and corroborated by comprehensive prospective randomized studies with an appropriate design.

Keywords: De Ritis, overall survival, Diffuse Large B-Cell Lymphoma

■ Myeloprofilerative Disorders

P-013 Abstract Referance: 139

RUXOLITINIB TREATMENT OUTCOMES-SINGLE CENTER EXPERIENCE

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Primary myelofibrosis (PMF) is the least frequent chronic myeloproliferative disorders that characterized by clonal proliferation of myeloid cells. It is more often seen in middle aged and older adults. Most common symptoms are fatigue and other symptoms that are correlated with splenomegaly. Anemia is the most frequent laboratory finding. Patients with polycytemia vera and essential thrombocytosis - two of other myeloproliferative disorders- can develop myelofibrosis (MF) as if it is a PMF. DIPSS-plus score is the best known prognostic tool in this issue.

Allogenic hematopoietic cell transplantation (HCT) is the standart treatment in transplant eligible patient in high risk group. In addition to symptom-related treatments (-like splenectomy, splenic radiation, interferons) , hydroxyurea and ruksolitinib are frequently used in transplant ineligible patients. These two agents are good in reducing symptoms but none of them has been proven to improve survival and reduce leukemic transformation.

Although ruxolitinib is a JAK-2 inhibitor, it is not necessary for a patient with MF to have JAK-2 mutation for using this agent. Its mainly goals are to suppress the symptoms and to reduce spleen size. According to COMFORT-1 (Ruxolitinib vs Plasebo) and COMFORT-2 (Ruxolitinib vs Best available treatment) study, ruxolitinib was more effective in reducing spleen volume by ≥35 percent.

Here we report our single center experience about ruksolitinib treatment and outcomes in both primary and postessential thrombocytosis (ET) /postpolicytemia vera (PV)/postKMML- MF.

Methods: Regardless of prior treatments, 21 patients with MF who are treated with ruxolitinib in hematology department of Mersin University Research Hospital between 2012-2019, are included in study. Primary endpoint of this study is to determine the decrement in spleen size and secondary endpoint is to determine adverse effects on hemogram.

Results: All patients well tolerated and none of them had to interrupt the treatment because of side effects. Median age was 62,5. 11 of 21 patients were PMF, 3 were postET-MF,5 were postPV-MF.1 was postKMML-MF. JAK-2 mutation status was explored in 12 patients, and 8 of them were positive. DIPPS plus score was calculated in 14 patients and 11 of them were intermediate II in score. Mean hb value was 10.0 gr/dl before the treatment, after 12.7 months-median follow up period, mean hb value decreased to 9.8 gr/dl. Mean spleen was 21.1 cm and 16 cm in size before and after treatment in 10 patients, respectively. Mean leucocyte value was 9053/mm^3 and 8790/mm^3, before and after the treatment respectively. Mean thrombocyte value was 220300/ mm^3 and 185250/ mm^3 before and after the treatment, respectively.

Conclusion: Ruksolitinib is the rising star in MF treatment area. Espescially spleen size is one of the main items for determinig outcomes of this agent. Our results were similar with literature in median age, advers affects on hemogram and decrease in spleen size. Our patient population is very small in number and median follow up time is a little short. And some of the patients have irregular follow-up condition who have inadequate imaging and laboratory tests. It would be more informative with large patient populatian and more disciplined follow up style

Keywords: Myelofibrosis, Ruxolitinib

■ Other

P-014 Abstract Referance: 61

EVALUATION OF CLINICAL MANIFESTATION IN FEBRILE NEUTROPENIC PATIENTS

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Introduction: Neutropenia is one of the most life-threatening and significant complication of intensive chemotherapy treatments. Febrile neutropenia is the major cause of mortality and morbidity in these patients (1).

The aim of this study, was to evaluate the epidemiology and the surveillance factors in febrile neutropenic patients retrospectively.

Methods: This study was undertaken in the Medipol Mega University Hospital Department of Clinical Hematology from December 2014 to December 2017 (3 years).This was a longitudinal retrospective study, which was conducted among 195 patients 400 febrile episodes.

Blood culture was studied by Bact-Alert automated blood culture system.. Antibiotic susceptibility tests were performed according to CLSI (Clinical and LaboratoryStandards Institute) criteria by Kirby Bauer Discus Fusion Method. Resistant pathogens were identified by VITEK-2 ® (Biomerieux, France) automated systems.

Results: A total of 195 patients, 400 febrile neutropenic attacks were assessed. The demographic characteristics of the patients are demonstrated in Table1.

In our study, all the patients categorized as high risk. During FNEs of these patients, 178 of the them(45%) had piperacillin-tazobactam, 145 (36%) had meropenem, 195 (49%) had teicoplanin and 17 (4%) had cefepime.Table 2 shows the distribution of antibiotics applied in the first episodes and 72th hour following the fever-free follow-up in new episodes(secondaryinfections).

In the study, 127 (32%) blood cultures positivity was detected in 400 FNEs. In some cultures more than one growth of microorganisms were detected. 33(8%) urine cultures positivity was detected in 372 FNEs. Table 4 shows the positivity of blood and urinary culture and its distribution.

Sensitivity was studied in 83 of 127 blood culture positivity in FNEs. ESBL was the most common detected resistance mechanisms.Table 5 shows the distribution of the antibiogram results of blood and urinary culture.

Conclusion: For the management and determining empirical antibiotic policies of each centers, it is important to identify their pathogenic microorganisms, to determine their antimicrobial susceptibility and to know resistance profiles for improving survival rates in FEN process.

A shift was detected from gram-positive bacteria to gram-negative in the etiology over the years. The most frequently isolated agents in our hospital were Gram-negative microorganisms.

Infections foci, culture positivity rates, isolated microorganisms consistent with the rates reported in the literature.

Keywords: Febrile neutropenia, Bloodstream infection

Table 1. Demographic characteristics of the febrile neutropenic episodes

	n=400(%)
Age/median (range)	50(18-83)
Female/male	7 3 / 122 (37%/63%)
Chemotherapy/stem cell tranplantation(HSCT)	220/180 (55%/45%)
Autologous/Allogenic HSCT	65/115 (16%/29%)
Hypotension(sys.BP<100mmHg)	38 (9%)
Absolute neutrophil count (<100/>100 mm3)	270/130 (68%/32%)
Mucositis (grade3-4)	59 (15%)
Catheter CVC/HD/PORT	285/85/13 (41%/18%/2%)
GCSF treatment	276 (69%)
Duration of fever (median)	3
Duration of antibiotics therapy (median)	10
Mortality	26 (7%)

Table 2. Categories of infections

	n=400 (%)
Microbiological documented infection	93 (23%)
Clinical documented infection	99 (25%)
Microbiological + clinical documented infection	33 (8%)
Responding to empirical antibiotic treatments without documantation	171 (43%)
Non-infectious fever	2 (0.5%)

Table 3. Positivity of blood and urinary culture and sensitivity of the cultıre

	Blood culture n=400 (%)	*Urinary culture n= 372(%)*
Culture Positivity	127 (32%)	33 (8%)
E.coli	50(39%)	17 (51%))
Klebsiella	35 (27%)	10 (30%)
Pseudomonas aeruginosa	8 (6%)	2(6%)
Acinetobacter baumannii	1	1
MSSA	14 (11%)	
MRKNS	21 (17%)	
Sensitivity :		
Sensitive gram -	24 (29%)	8 (27%)
Sensitive/resistant pseudo	6 (7%)/1	
CRE	19 (23)	7(25%)
ESBL	33 (40%)	12 (41%)
VRE		2 (7%)

■ Acute Myeloid Leukemia

P-015 Abstract Referance: 22

IMPACT OF TIME FROM INDUCTION CHEMOTHERAPY TO COMPLETE REMISSION ON OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA PATIENTS

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Background and Aim: The majority of patients with acute myeloid leukemia (AML) receive intensive induction chemotherapy for obtaining a complete remission (CR). Despite consolidation chemotherapy and advances in allogeneic hematopoietic stem cell transplantation (alloHSCT), most of these patients finally relapse and die from AML. The aim of this study is to determine the impact of duration of remission achievement on survival of patients with newly diagnosed AML who achieve CR after one course of chemotherapy.

Materials and Methods: We retrospectively analyzed patients with AML who received first induction chemotherapy between 2001 and 2018 years. Definition of CR was the presence of less than 5% blasts in the bone marrow, the absence of extramedullary leukemia, and normal values for absolute neutrophil count (>1000/mm^3) and platelet count (>100,000/mm^3), independence from red cell transfusion. The median time to remission was 29 day (16-48) for all patients. Therefore, in the first 29 days remission was defined as early remission (ER) and entering remission ≥30 days was defined as delayed remission (DR).

Results: Of the 113 patients, 58 (51.3%) patients had ER (<30 days) after induction chemotherapy, 55 (48.7%) patients had DR (≥30) after induction chemotherapy. Median follow-up time was 27 months (range 4-186) for all patients. The 5-year OS for patients who had early remission after induction chemotherapy and patients who had delayed remission after induction chemotherapy were 83% (95% CI: 0.79-0.87) and 35% (95% CI: 0.31-0.39), respectively (p<0.001). The 5-year DFS for patients who had early remission after induction chemotherapy and patients who had delayed remission after induction chemotherapy were 83% (95% CI: 0.78-0.88) and 40% (95% CI: 0.32-0.40), respectively (p<0.001). The OS and DFS were statistically significant higher in patients who had early remission after induction chemotherapy than patients who had delayed remission after induction chemotherapy.

Conclusion: In conclusion, time to entering CR is a predictor factor of overall survival and disease-free survival times for patients with newly diagnosed AML who achieve CR after 1 course of chemotherapy. Patients achieving CR only after a lengthy time, eg. more than 29 days, should be considered to have high relapse rate and should undergo alloHSCT.

Keywords: Acute myeloid leukemia, complete remission, early remission, delayed remission.

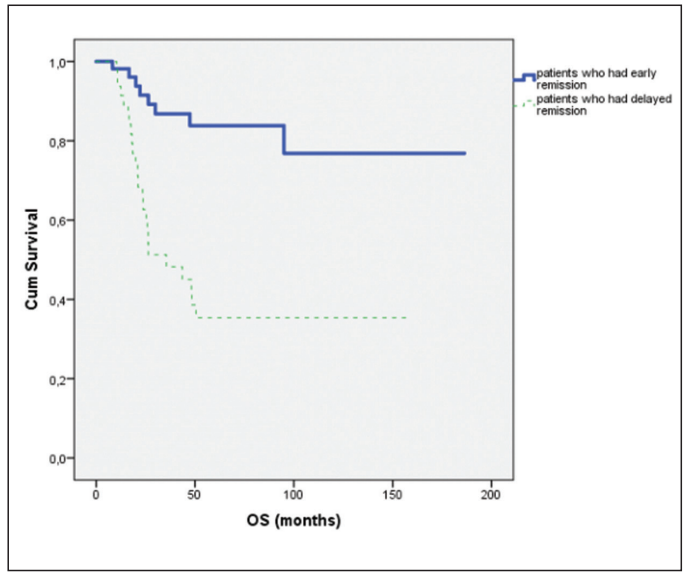

Figure 1. Overall survival for patients who had early CR and patients who had delayed CR after induction chemotherapy (p<0.001).

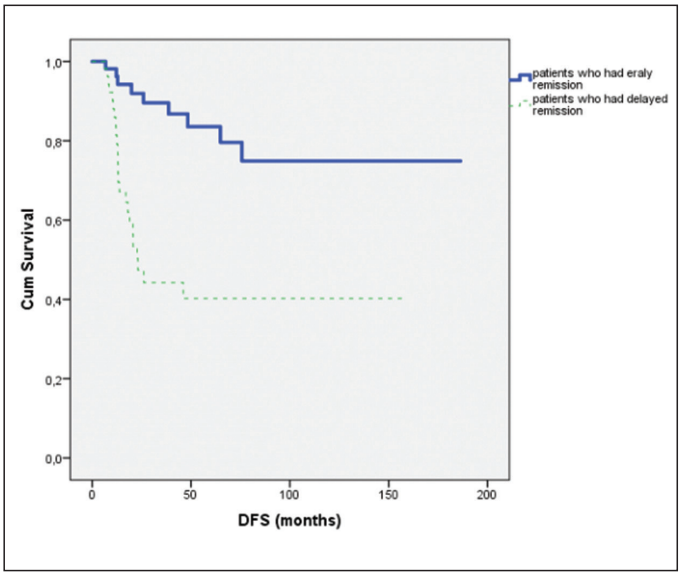

Figure 2. Diseases free survival for patients who had early CR and patients who had delayed CR after induction chemotherapy (p<0.001).

Table 1.

Parameters	*Patients who had early remission*	*Patients who had delayed remission*	*p*
N	58 (51.3%)	55 (48.7%)	
The median age (range), years	46 (20-65)	34/21 (61.8%/38.2%)	0.26
Conditioning regimen			0.78
RIC	30 (51.7 %)	27 (49.1%)	
MAC	28 (48.3 %)	28 (50.9%)	
ECOG Performance Status			0.08
0	15 (25.9%)	10 (18.2%)	
1	29 (50%)	21 (38.2%)	
2	14 (24.1%)	24 (43.6%)	
Cytogenetic risk group			0.86
Intermediate	40 (69%)	40 (72.7%)	
Adverse	7 (12%)	5 (9.1%)	
Missing	11 (19%)	10 (18.2%)	
GVHD			0.39
Acute GVHD	8 (13.8%)	9 (14.5%)	
Chronic GVHD	18 (31%)	11 (20%)	
Relapse rate (%)	9 (15.5%)	24 (43.6%)	0.001
Mortality (%)	8 (13.8%)	24 (43.6%)	<0.001
Non-relapse mortality (%)	4 (6.9%)	5 (9.1%)	0.66

■ Acute Lymphoblastic Leukemia

P-016 Abstract Referance: 41

RISK OF ACUTE LYMPHOBLASTIC LEUKEMIA: RESULTS OF A CASE-CONTROL STUDY IN HAMADAN DURING 2015-2017

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Objective: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Different environmental factors might be effective in the occurrence of this malignancy during childhood. The aim of this study was to find environmental risk factors in childhood ALL in Hamadan-Iran.

Methods: This case-control study was done on 57 children younger than 15 years suffering by ALL during 2015-2017. Patients were matched with 63 controls in respect to age, sex and residential area. Diagnosis of risk factors for ALL was sought based on the comparison of studied variable between cases and controls individuals.

Results: We found a statistically significant increased risk for ALL association with type of delivery (OR: 0.43, 95% CI: 0.20 - 0.92, *P*<0/02), child care (OR: 4.58, 95% CI: 0.95 - 22.20, *P*<0/04), father education level (OR: 2.67, 95% CI: 1.10 - 6.45, *P*<0/02), and father job (OR: 0.2 95% CI: 0.08 - 0.51, *P*<0/001). We also observed increased odds for ALL regarding boy gender, high mother education level and freelance job, and medium or high family income. No association with ALL incidences was observed for the age, sex, malignancy in first and second-degree relatives, and Use of hair dye during pregnancy by mothers (*P*> 0.05).

Conclusion: This study showed that father education level and job, delivery type and child care can play a role in incidence of childhood ALL.

Keywords: Acute Lymphoblastic Leukemia, Children, Parents, Risk Factors

Table 1. Comparison of case and controls characteristics and relative risk (odds ratio) of ALL incidence

Characteristics	*Cases n = 57*	*Controls n = 63*	*Odds ratio (95% CI)*	*P-value*
Sex; n (%) Boys Girls	33 (57.8%) 24 (42.2%)	38 (60.3) 25 (39.7)	1.25 (0.61 - 2.57)	0.54
Type of birth; n (%) Caesarian Normal	41 (71.9) 16 (28.1)	33 (52.4) 30 (47.6)	0.43 (0.20 - 0.92)	0.02
Father's smoking; n (%) Yes No	12 (21) 45 (79)	22 (35) 41(65)	0.50 (0.22 - 1.13)	0.09
Family income; n (%) Low Medium or high	20 (35.1) 37 (64.9)	9 (14.2) 54 (58.8)	3.24 (1.33 - 7.91)	0.08
Malignancy in first-degree relatives; n (%) Yes No	1 (1.7) 56 (98.3)	6 (9.5) 57 (90.5)	0.17 (0.02-1.46)	0.07
Malignancy in second-degree relatives; n (%) Yes No	20 (35.1) 37 (64.9)	23 (36.5) 40 (63.5)	0.94 (0.44 - 1.98)	0.87
Child care; n (%) Home Kindergarten	55 (96.4) 2 (3.6)	54 (85.8) 9 (14.2)	4.58(0.95 - 22.20)	0.04
Father's education level; n (%) ≤ High school ≥ High school	48 (84.2) 9 (15.8)	42 (66.6) 21 (33.4)	2.67 (1.10 - 6.45)	0.02
Mother's education level; n (%) ≤ High school ≥ High school	46 (80.7) 11 (19.3)	46 (73.1) 17 (26.9)	1.55 (0.65 - 3.66)	0.32
Father's job; n (%) Employee Freelance	7 (12.2) 50 (87.8)	26 (41.2) 37 (58.8)	0.20 (0.08 - 0.51)	0.001
Mother's job; n (%) Employee Freelance	4 (7.1) 53 (92.9)	7 (11.1) 56 (88.9)	0.60 (0.17 - 2.18)	0.43
Use of hair dye during pregnancy by mother; n (%) Yes No	8 (14.1) 49 (58.9)	10 (15.8) 53 (84.2)	0.87(0.32 - 2.37)	0.77

■ Non-Hodgkin's Lymphoma

P-017 Abstract Referance: 156

HAPLOIDENTICAL STEM CELL TRANSPLANTATION MAY BE A GOOD ALTERNATIVE AS SALVAGE TREATMENT FOR HEAVILY PRETREATED PATIENTS WITH LEUKEMIA

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Introduction: In the absence of HLA-matched related donor, allogeneic stem cell transplantation from haploidentical donors are potential alternatives for patients with hematological malignencies with an indication to allogeneic stem cell transplantation.Herein, we retrospectively assessed the outcome of haplo-SCT for patients with refractory hematological malignancies.

Patients and Methods: This analysis included 27 consecutive patients who underwent haplo-SCT for various hematological malignancies at our center between October 2010 and May 2018. We used our institutional database to evaluate details and characteristics of patients and transplant outcomes.

Results: Demographic features of the patients and donors have been summarized in Table 1. All of the patients had advanced disease with a high risk of relapse. The majority of patients underwent haplo-SCT from their parents. Out of 24 patients, early transplant-related mortality was seen in this cohort of 5 patients. Four patients treated with second haplo-SCT and recovered hematopoiesis after second transplant. The remaining 19 patients were followed in a median of 4 months. Donor type ABO group switch was observed in a median of 45 days (30-60 days) after transplant. The median time for engraftment was 19 days (range, 15-60) for all patients. After the first transplant, 9 patients developed acute GVHD (37.5%) with 7 patients having grade II-III acute GVHD. Five (18.5%) had chronic GVHD, none of them with extensive manifestation. The prepative regimen was relatively well tolerated with limited regimen-related toxicity. CMV reactivation occurred in 11 patients (40.7%) during the follow-up of the study. Eight patients (29.6%) relapsed after a median of 132 days post transplant (range, 45-588 days). CR was achieved in 17 (63%) patients after haplo-SCT. Mean estimated 5-year OS and PFS are 66.7%±0.9% and 92.3%±0.7% , respectively. **Conclusion:** Given the growing data on the similarity of outcomes after HLA-matched and haploidentical SCT, further studies are required to determine whether factors may be more important for donor selection than HLA-matching.

Keywords: acute leukemia, haploidentical stem cell transplantation

Table-1: Patient, donor and transplantation characteristics

Variable	n (%)
Median Age, yr (range)	34 (19-66)
Gender (M/F)	11 (40.7%)/16 (59.3%)
Graft stem cell source	
Bone marrow	7 (25.9%)
Mobilized peripheral blood	17 (63%)
Both	3 (11.1%)
Conditioning regimen	
Myeloablative	19 (70.4%)
Reduced-intensity	8 (29.6%)
GvHD propylaxis	
PostCy	17 (63%)
CSA+Mtx	10 (37%)
MMF+Tacro	17 (63%)
Median cell dose infused	
TNC, $x10^8$/kg	10.26 (1.5-21.1)
CD34+ cells, $x10^6$/kg	5.62 (0.97-11.5)
CD3+ cells, $x10^7$/kg	15.1 (1.1-11.6)
Engraftment kinetics, day (mean±SD)	
Neutrophil ($0.5x10^9$/L)	14.2±9.9
Platelet ($20x10^9$/L)	17.8±2.4
Reticulocyte ($30x10^9$/L)	18.2±1.7

■ Other

P-018 Abstract Referance: 38

LIFE STYLES, MOTHER AND CHILD HEALTH STATUS AND RISK FACTORS FOR CHILDHOOD LEUKEMIA IN THE GAZA STRIP: CASE-CONTROL STUDY

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Background: Childhood leukemia is one of the most common types of cancer developed in children until 12 years old in Palestine without unknown causes and form 30% of pediatrics cancer, leukemia is one of the top ten-cancer type's killers and has good prognosis if early discovered. The aim of this study is to identify the main life styles and health status risk factors for childhood leukemia among children in Gaza Governorates

Methods: A case control study conducted from five Gaza strip governorates and consisted of 132 child divided in two groups (44 cases who had confirm of childhood leukemia and 88 controls had not). Controls and cases were matching by age, sex and residency. The cases distributed on Gaza Governorates. The cases were matching as 1 case: 2 control

Finding: The results of the study showed 54.5% were males and 45.5% were females, and the risk factors associated with childhood leukemia were as follows: Family history (P value= 0.001), child admitted to hospital with infection (P value= 0.027) and drug giving during pregnancy stages (P value= 0.005), also, there was association between child hood leukemia and pregnant exposed to passive smoking as (P value = 0.009), child beverage intake (P value= 0.013), and additive in artificial juices (P value= 0.001), while the study found child age, birth weight and child exposed to (passive smoking and X ray) were not association for childhood leukemia. Also, mother age, mother exposed to X ray, white phosphorus and explosive material were not relevant for childhood leukemia. Likewise, live status and additives in food were not associated with childhood leukemia.

Interpretation: The main of the life styles and health status risk factors appeared are avoidable and can prevented.

Keywords: childhood leukemia, risk factors, Gaza Strip, life styles, health status factors.

■ Acute Lymphoblastic Leukemia

P-019 Abstract Referance: 67

THE COMPARISON OF OUTCOMES OF TBI AND NO-TBI CONDITIONING REGIMEN FOR ACUTE LYMPHOBLASTIC LEUKEMIA UNDERGOING ALLOGENEIC HEMATOPOETIC STEM CELL TRANSPLANTATION: A COHORT STUDY

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Allogeneic hematopoietic stem cell transplantation (Allo-HCT) is a potentially curative method for acute lymphoblastic leukemia (ALL) patients. Total body irradiation (TBI) is a standard backbone for myeloablative conditioning regimen in allo-HCT. In this study, we aimed to compare outcomes of TBI and no-TBI conditioning regimen for allo-HCT. The primary endpoint of study was overall survival (OS) and disease free survival (DFS). The number of patients of TBI group and no-TBI group was 23 and 58, respectively. According to conditioning regimen, CY/TBI is the most preferred regimen in TBI group (17/23, 73.9%). 36.3%, 32.8%, 22.4% of patients were received Bu/Flu/ATG, Mel/Flu and Bu/CY regimen in no-TBI group, respectively. According to the FISH and PCR results, 16/56 (28.5%) patients were pH positive ALL. The 1-year and 3-year OS rates were 87% and 67.6% in TBI group. The 1-year and 3-year OS rates were 76.1% and 56.3% in no-TBI group, respectively. There was no statistically significant difference among the groups (p=0.34). The 1-year and 3-year DFS rates were 76.2% and 66.7% in TBI group. The 1-year and 3-year DFS rates were 63.1% and 48.9% in no-TBI group, respectively (p=0.16). 8 patients were died in TBI group. 23 patients were died in no-TBI group. In conclusion, although there was an improvement in allo-HCT results with TBI, there was no significant difference in OS and DFS among TBI and no-TBI groups.

Keywords: Acute lymphoblastic leukemia, conditioning regimen, hematopoietic stem cell transplantation.

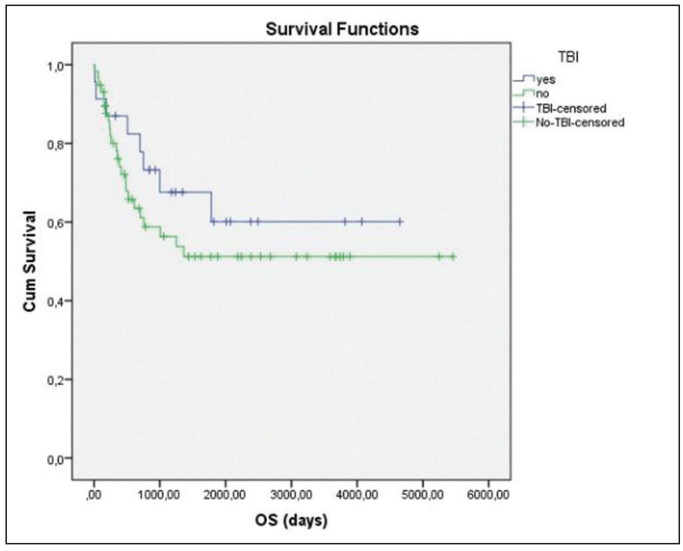

Figure 1. Overall Survival in TBI and no-TBI groups

Table 1. Baseline clinical characteristics of the groups.

	TBI-group (n=23)	**no-TBI group** (n=58)	**p**
Age (mean±SD)	***29±9.5***	***33.7±10.2***	***0.05***
Sex (M/F)	15/8	32/26	0.40
B cell ALL	18	42	
T cell ALL	3	11	0.47
Mix phenotype ALL	1	1	
Burkitt ALL	1	4	
Pre Allo-HCT CR disease	19	55	0.08
Pre Allo-HCT Refractory disease	4	3	

■ Acute Lymphoblastic Leukemia

P-020 Abstract Referance: 152

CAN NELARABINE RESCUE THE GRAFT AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN T-ALL?

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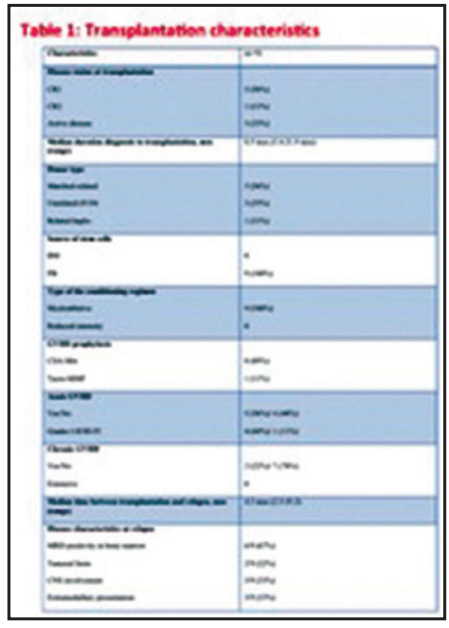
Introduction: Adult ALL is a rare disease, T-ALL accounts for nearly %20 of all ALL and T-ALL is more common in adults than children. The success of treatment is less than B ALL treatment for both children and adults. Survival for adult ALL is poor. The use of pediatric intensive chemotherapy regimens in AYAs improved outcomes and nelarabine for relapsed and refractory diseases has resulted in significant response and allogeneic SCT still remains an important component of treatment. Nevertheless relapse is inevitable. Aim of the study is to evaluate the effect of nelarabine as salvage therapy after ASCT, in terms of disease control, GVHD, PFS and OS.

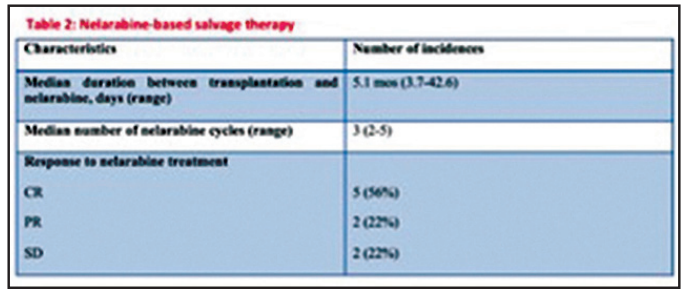
Patients and Methods: Nine (F/M= 1/8; median age= 28 years (21-45)) patients are evaluated retrospectively. None of them received nelarabine, before ASCT. Transplantation characteristics are given in table 1. Between 2014-2018 nine patients from one center received nelarabine as salvage therapy. Patients were treated at the time of relapse with nelarabine alone 1.5g/M2/day on days 1, 3, 5 every 28 days.

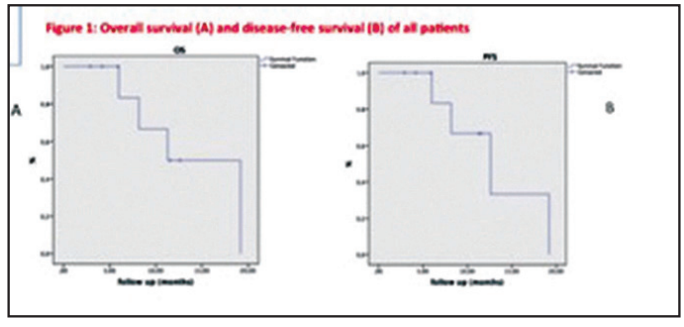
Results: Among the 9 patients 67% achieved hematologic remission during 8.2 months (range; 2.9-19.2 mos) follow-up. The features of nelarabine based salvage therapy are shown in table 2. The main toxicity was neurological and involved 22% of patients. At 1 year, disease- free and overall survival rates were 66.7% and 50% respectively (Figure1). Only one patient (11%) received DLI and MRD was lost. On the other hand patients who had MRD and received nelarabine had a stable MRD disease those did not transform to hematologic disease.

Conclusion: The OS at 1 year for salvage treatment with nelarabine at first and secondary relapse is 28%. There is no data about interaction between immune reconstitution, relapse prevention and nelarabine after HSCT. Nelarabine is a well tolerated drug with minimal toxicity and can be considered for maintenance therapy post HSCT in both MRD positive, bulky and CNS disease. Even though it does not show graft versus tumor effect, it can just prevent T-ALL transform to an aggressive leukemia.

Keywords: T-ALL, nelarabine, allogeneic hematopoietic stem cell transplantation







■ Multiple Myeloma

P-021 Abstract Referance: 151

CAN THE DRUGS USED BEFORE AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (ASCT) HAVE IMPACT ON CMV REACTIVATION THAT RESULTS IN DECREASED OS IN MYELOMA PATIENTS AFTER ASCT?

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Introduction: The prevalence of active cytomegalovirus (CMV) infection is lower after conventional single autologous stem cell transplantation (ASCT) than after allogeneic stem cell transplantation; however, little is known about the overall incidence of active CMV infection in patients with multiple myeloma (MM) receiving more intensive treatment regimens, such as proteasome inhibitors (PI) and/or immunomodulatory (IMID) agents.

Patients and Methods: This study involved a retrospective review of all patients with who underwent ASCT between January 2015 and November 2018 at our stem cell transplantation center. A total of 144 consecutive adult patients with a diagnosis of MM (median age at diagnosis: 58, range: 35-77) underwent ASCT following induction treatment with novel agents (PIs and/or IMIDs). All patients received antiviral prophylaxis with acyclovir 600 mg/day (n=104) or valaganciclovir 1000 mg/day (n=36). CMV serostatus was determined for all patients before transplantation (Immulite CMV IgG; Siemens, Tarry-town, NY).

Results: Baseline patient characteristics, according to induction treatment, are summarized in Table-1. The study population was predominantly male (60.4 %), and had a median age of 58 (range: 35-77). The majority of patients received PI-based induction treatment (97.2%) and IMID+PI were administered 35.4% (n=51) of the patients before the ASCT. The entire group received a median number of one line (range;1-4) myeloma treatment before the ASCT. One hundred-five of the 144 patients (97.2%) were CMV IgG-positive before ASCT. Overall, 14.6% (n=21) of CMV-seropositive patients developed at least one episode of CMV viremia (CMV DNA >100 copies/ml) after a median 24 months (range; 3-48 mos) follow-up. Persistent CMV viremia (detectable CMV DNA load in more than 2 sequential plasma specimens) occurred in 4.9% (7 of 144) of the seropositive ASCT recipients and all of them were preventive treated with ganciclovir (n=5) or valganciclovir (n=2). The time from stem cell infusion to the development of CMV viremia ranged from 3 days to 48 days. None of the patients with untreated viremia developed identifiable CMV sequelae. No case of primary infection in seronegative patients at transplant was observed. Adding to that none of the patients developed CMV disease post ASCT. If we analyzed the subgroups of patients according to induction therapy (PI-based, IMIDs, PI+IMID), the incidence of post-ASCT CMV reactivation was higher but not statistically significant, in patients who received only PI vs PI+IMID (13 (61.9%) vs 8 (38.1%); p=1.00). In univariate analysis, we could not demonstrate the importance of induction therapy with novel agents the occurrence of a post-ASCT CMV reactivation requiring antiviral treatment. However, statistically significant association found between the disease <VGPR status at ASCT and CMV reactivation (61.1% vs. 38.9%; p=0.035). After a median follow-up 14.3 months (range; 1-45.9 months), there was no significant impact on PFS, however there was significant decrease in estimated mean OS who had CMV reactivation when compared to those without CMV reactivation (34.1±4.5 vs. 41.9±1.3; p=0.002) (Figure-1). **Conclusion:** Our data suggests that MM patients treated with PI-based induction regimens and immunological response <VGPR at time of ASCT seem to have higher risk of developing symptomatic CMV reactivation. However, further studies on a large number of patients are warranted to clarify these findings.

Keywords: Multiple myeloma, cytomegalovirus infection, autologous stem cell transplantation

■ Acute Myeloid Leukemia

P-022 Abstract Referance: 39

EVALUATION OF SURVIVAL IN MONOSOMAL KARYOTYPE IN ACUTE MYELOID LEUKEMIA

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Objective: Cytogenetic karyotype analysis is used to determine the risk stratification and prognosis of hematologic diseases such as Acute myeloid leukemia (AML), myelodisplasia or primary myelofibrosis. AML is a disease caused by uncontrolled proliferation and dismaturation of hematological precursors due to idiopatic or chromosomal anomalies. For this reason, cytogenetic assessment is particularly important in AML disease. Monosomal karyotype (MK) is defined as 2 or more monosomies, or a single monosomy in the presence of structural abnormalities and known as a poor prognostic indicator in AML. The aim of the present study is to analyze the survival of AML patients with monozygous karyotypes in a single center.

Methods and Results: A total of 181 AML patients who diagnosed and followed in the Hacettepe University department of hematology between 2000-2017, were enrolled . A cytogenetic anomaly was obtained in 58 of 181 patients. The overall survival of patients with cytogenetic disorders was 85 months (range 0-141), whereas those without cytogenetic disorders were 124.5 months. (1-136)(p:0.01). 6 of 58 patients with cytogenetic abnormalities had monozygous karyotype (10,3%). 4 of 6 patients with monosomal karyotypes were died within 15 months. 3 patients with monosomal karyotypes did not response the chemotherapy (idarubicin-ara-c) and 1 patient,despite showing response to chemotherapy,developed relapse after 5 months. Of 85 patients with cytogenetic disorder, 11 (18.9%) had complex karyotypes. Overall survival of these patients were 37 months (2-45), but no statistically significant difference was observed between complex and monozygous karyotype. (p: 0.7)

Conclusıon: Monosomal karyotpe and complex karyotype are poor prognostic indicator for AML. In this study, overall survival were decreased in both of two groups but there was no significant difference between the two groups.

Keywords: monosomal, myeloid, leukemia

■ Chronic Lymphocytic Leukemia

P-023 Abstract Referance: 17

ASSOCIATION OF INITIAL PROGNOSTIC PARAMETERS AND REQUIREMENT FOR TREATMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Aim: B-cell chronic lymphocytic leukemia (CLL) is the most common haematological malignancy in advanced age. The clinical course of the disease is highly variable, therefore there is a need to investigate the various prognostic factors. The CLL cell typically expresses CD5, CD19, CD23 and a monoclonal surface Ig (K or λ) while CD20 is moderately/weakly expressed. We aimed to analyze the clinical, genetic and immunophenotypic features which might have prognostic value in CLL.

Materials and methods: Between February 2010 and June 2018, 87 cases diagnosed with CLL were retrospectively analyzed. Patients who were followed without treatment (T0 group) and who required at least one line treatment (T) were compared. Patients who required 1 line treatment (T1) were also further compared with patients who required >1 line treatment (T2). Statistical analyzes were performed using chi-square test using SPSS

version 16.0 (SPSS Inc., Chicago, IL, USA). A value of less than 0.05 was considered significant.

Results: The mean age of our patient population was 65 (±SD12,8) with Male/Female 56/31. At diagnosis, 68(78.2%) patients were at early stage (0, I, II) and 19 (21.8%) were at advanced stage (III,IV). Del17p, del13q and trisomy 12 were evaluated in 49, 41 and 31 patients and 5, 13 and 4 patients were found out to be positive, respectively. Anemia and thrombocytopenia were present in 25 (28.7%) and 16 (18.4%) patients, respectively. Twenty one (24.1%) patients had B symptoms. Splenomegaly, lymphadenopathy and hepatomegaly were present in 34(39%), 67(77%) and 21(24.1%) patients, respectively. Four of the 15 patients who had direct coombs positivity also had clinical evidence of hemolytic anemia. Four patients had immune thrombocytopenia, 2 of them had concurrent direct coombs positivity and one also had hemolytic anemia. The median Hb, leukocyte and platelet counts were 13.2 gr/dl (4.4-17.5 gr/dl), 23.6 x 10^9/L (1,7-527 x 10^9/L) and 200 x10^9/L (10-345 10^9/L), respectively. Follow up period was median 38 months (3-180 months). Twenty five (28.7%) patients were treated at the time of diagnosis. Thirty three (37.9%) patients had T1 and 6 (6.9%) patients required T2. The ratio of male patients in group T were significantly higher than female patients (p=0.038). All patients in group T2 were male. More patients in group T had CD38 expression than group T0 (p=0.04). There was no significant difference between the groups in terms of FMC7 and CD11c expressions. Of the 5 patients with del17p, 2 patients required treatment at diagnosis, 2 patients required treatment after 13 and 48 months of follow up, respectively.

Conclusion: In our CLL patients, requirement for treatment was associated with CD38 expression, del17p positivity at diagnosis and male gender.

Keywords: chronic lymphocytic leukemia,

■ Chronic Myeloid Leukemia

P-024 Abstract Referance: 47

SIGNIFICANCE OF LYMPHOCYTE COUNT, MONOCYTE COUNT, AND LYMPHOCYTE-TO-MONOCYTE RATIO FOR PREDICTING MOLECULAR RESPONSE IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: SINGLE CENTER EXPERIENCE

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Background: Chronic myeloid leukemia (CML) is a neoplastic disease characterized by the translocation of chromosome 9 and 22 to form BCR-ABL fusion gene. Currently, it is possible to quantify the efficacy of CML treatment by molecular monitoring of BCR-ABL via advanced techniques. However, there is need for more simple and rapid biomarkers to assist follow-up of patients with CML. Lymphocyte-to-monocyte ratio (LMR) is a popular and simple marker which is shown to be associated with prognosis in various neoplasms. In this study, we aimed to evaluate the significance of absolute lymphocyte count (ALC), absolute monocyte count (AMC), and LMR in relation with molecular response status in patients with chronic phase CML.

Methods: Samples from chronic phase CML patients admitted to our hematology laboratory for BCR-ABL quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) between April 2012 and October 2018 were retrospectively reviewed and concurrent hemogram testing were noted. Data were grouped according to the molecular response status: absence of major molecular response (MMR), presence of MMR and presence of deep molecular response (DMR). Then, the groups were compared for ALC, AMC and LMR.

Results: A total of 224 samples from 95 patients were included. For each sample, the molecular response status of the corresponding patient together with the values of ALC, AMC and LMR are summarized in table 1. Analysis revealed significant difference between groups when results from newly diagnosed patients are compared with the patients on treatment regardless of response status (p< 0.05). However, when the samples from patients on treatment are grouped according to molecular response status (without MMR, with MMR and with DMR) analysis failed to reveal difference between groups considering ALC, AMC or LMR (p > 0.05).

Conclusion: ALC, AMC or LMR are not potential biomarkers projecting the molecular response status in patients with chronic phase CML. Different studies with larger scales are needed to find simple markers which will aid follow-up of these patients in the future.

Keywords: chronic myeloid leukemia, lymphocyte, monocyte, lymphocyte-to-monocyte ratio

Table 1. Data of ALC, AMC and LMR relative to molecular response status

Response	*n (%)*	*ALC (k/mm³) Median (Min-Max)*	*AMC (k/mm³) Median (Min-Max)*	*LMR Median (Min-Max)*
Newly diagnosed	29 (13)	5.18 (1.13-67.96)	3.29 (0.03-15.91)	2.07 (0.74-135)
Without MMR	94 (42)	2.02 (0.75-28.76)	0.42 (0.01-19.42)	5.33 (0.56-358)
With MMR	36 (16)	2.05 (1.12-10.43)	0.36 (0.16-1.10)	5.65 (2.11-20.58)
With DMR	65 (29)	1.85 (0.85-7.34)	0.38 (0.20-1.38)	4.82 (1.32-10.83)

■ Chronic Lymphocytic Leukemia

P-025 Abstract Referance: 86

17P AND 13Q DELETION FREQUENCY IN OUR CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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Introduction: Deletions 17 p and 13q14 are associated with prognosis in CLL.The data in our country is limited. In a national thesis study at 2010 (Dr Canan Belin Cirit, et al), among 45 CLL patients, there was a percentage of 71% in 13q14 deletion (32 patients) and 31.1% of 17 p deletion (14 patients). Based on the literatüre, 13q14 deletion percentage is about 55% and 17p deletion is about %7. In our study we aimed to evaluate the frequency of 17 p and 13q14 deletions and their demographic data among 72 patients.

Material and Method: Sevety two patients who have been diagnosed of CLL based on the International Working Group (IWG) criteria were included in the study. Thirty of them were female. Fourty two patients were Binet B and 2 patients were Binet C stage.The positivity level of deletions was determined as 15% and above. Four patients who had inadaquete interphase were excluded from the study.

Results: The mean age of our study was 66 ±10. Deletions of 17p and 13q14 were evaluated with FISH method.Mean lyphocyte count was 46365 ± 8910 , hemoglobin value was 12.1 ± 1.5 gr/dl and platelet count was 203647 ± 94508 /mm^3 Deletion 17 p ratio was 5.6 %(4 patients) and 13q ratio was 27% (20 patiens). Two deletions were both positive in 1 patient. Only 5 patients (3 of them were blood type A and 2 of them were type B) didn't have Rhesus(Rh) antigen(Rh negative). There was no relation between 17p and 13q14 deletions and the stage. All of the patients who have the associated deletions were Binet B stage.

Discussion: There was no relationship between 17 p and 13q14 deletions and the lymphocyte count. CLL was dominantly present in the Rh(+)group. The treatment hasn't been initiated any of the patients with deletion 17 p positivity, known as the poor prognosis, at the time of their diagnosis. The patient who had both 13q14 and 17p deletions is being followed as Binet A stage. The life curve analysis of the patients is planned and deletion 11q results are awaited.

Keywords: lymphocyte, del 17p, del 13q14,

■ Stem Cell Transplantation

P-026 Abstract Referance: 43

MESENCHYMAL STEM CELL INFUSION IN GRAFT VERSUS HOST DISEASE: A SINGLE CENTER EXPERIENCE

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Background: Human mesenchymal stem cells (MSC) are non-hematopoietic multipotent cells which may differentiate in osteogenic, adipogenic and chondrogenic series. Steroid refractory graft versus host disease (GvHD) remains to be an important therapeutic challenge in allogeneic hematopoietic stem cell transplantation (HSCT) recipients. Although corticosteroids have been considered as first-line therapy for acute and chronic GvHD, salvage treatment options are limited in refractory cases. Several studies demonstrated that MSC infusion may be a feasible alternative for steroid refractory GvHD. The aim of this study is to determine the therapeutic efficacy of MSCs in acute and chronic GvHD cases who did not respond to several treatment lines including corticosteroids and combined immunosuppressive approaches.

Methods: A total of 16 allogeneic HSCT recipients [median age: 51(19-68) years; male/female: 9/7], who had received MSC infusions for steroid refractory GvHD, were included in this study. Medical records of the participants were retrospectively evaluated.

Results: Of 16 patients, 5 patients (31.3%) were diagnosed as acute myeloid leukemia, 4 patients (25%) as acute lymphoblastic leukemia, 2 patients (12.5%) as Hodgkin lymphoma, 2 patients (12.5%) as myelodysplastic syndrome, 1 patient (6.3%) as primary myelofibrosis and 1 patient (6.3%) as aplastic anemia. Fourteen patients (87.5%) were in complete remission, while 2 patients (12.5%) had progressive disease at the time of MSC infusion. A total of 11 patients (68.8%) had acute and 3 patients (18.8%) had chronic GvHD whereas 2 patients (18.8%) had overlapping features. Eleven patients (68.8%) had gastrointestinal GvHD, 1 patient (6.3%) cutaneous GvHD, 2 patients (12.5%) hepatic GvHD and 2 patients (12.5%) had concomittant cutaneous and pulmonary GvHD. Median day of GvHD onset was +105 (30-2155) and median GvHD grade was found to be 3(1-4). Corticosteroids were the first-line treatment in all patients. All patients were refractory to multiple immunosuppressive and monoclonal antibody combinations including steroids, calcineurin inhibitors, mycophenolate mofetil, ruxolitinib, ibrutinib and rituximab. Standard MSC dose was 1 x 10^6/kg for the first and recurrent infusions. Median 4(1-13) infusions were performed based on treatment response. Infusion related side effects were vasovagal syncope and headache which were observed in 2 patients (12.5%). Cytopenia was seen in 4 patients (25%) and infections in 8 patients (50%). Optimum clinical response was achieved on day 15(7-60) of the first MSC infusion. Six patients (37.5%) were evaluated as complete response, 5 patients (31.3%) as partial response and 5 patients (31.3%) as refractory (Table 1). At the end of median 366(100-3325) days of follow-up, overall survival was found to be 35% in the study population (Figure 1). GvHD related mortality was observed in 9 patients (56.3%) and relapse related mortality in 1 patient (6.3%).

Conclusions: Our retrospective results in a limited number of cases demonstrated that MSC therapy may be considered as a feasible option for the treatment of steroid-refractory GvHD with its acceptable toxicity profile in short term follow-up.

Keywords: Mesenchymal Stem Cells, Graft versus Host Disease, Allogeneic Hematopoietic Stem Cell Transplantation

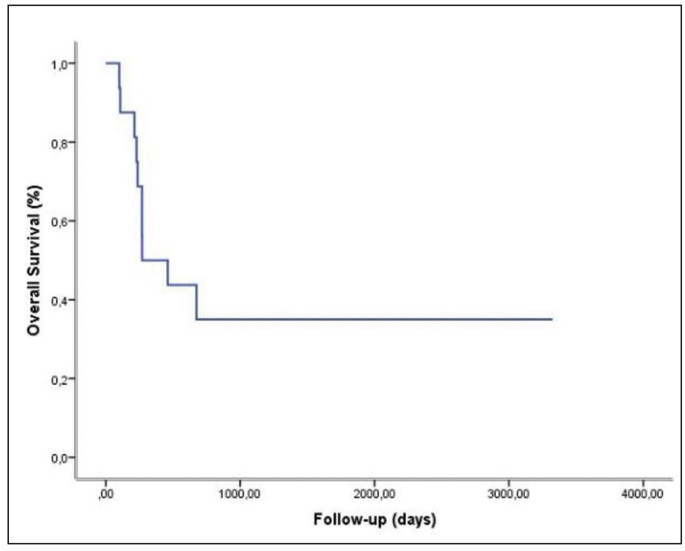

Figure 1. Overall survival was 35% at the end of median 366(100-3325) days of follow-up

Table 1. Mesenchymal Stem Cell Therapy Responses Based on Graft versus Host Disease Type and Localization

		Response			*Total*
		Complete Response	*Partial Response*	*Refractory*	
Type	Acute	4	3	4	11
	Chronic	0	2	1	3
	Overlap	2	0	0	2
Total		6	5	5	16
Localization	Cutaneous	0	0	1	1
	Hepatic	1	0	1	2
	Gastrointestinal	5	3	3	11
	Cuteneous+ Pulmonary	0	2	0	2
Total		6	5	5	16

■ Stem Cell Transplantation

P-027 Abstract Referance: 112

THREE-YEAR EBV PCR RESULTS IN ALLOGENEIC STEM CELL TRANSPLANTATION

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Epstein-Barr virus (EBV) associated posttransplant lymphoproliferative disorders (PTLD) is a major morbidity in patients undergoing hematopoietic stem cell transplantation, and is a cause of mortality. The incidence of EBV DNA-emia and EBV-PTLD varies according to transplant centers. EBV DNA positivity was reported between 0.1-63% according to the type of transplant. According to the donor family donor types of data EBMT 1.2%, or incompatible family donors haplo 2.8%, 4% matched unrelated donor, mismatched unrelated donor was reported to be 11.2%.

Materials and Methods: The EBV PCR results, which were sent once a week between 2016-2018, were retrospectively screened. The files of patients with EBV PCR positive were examined and clinical features were evaluated during positivity.

Results: When evaluated according to years, 216 cases were requested from 38 patients in 2016 and 6 patients (16%) had positive results at 14

tests (6.4%). In 2017, 238 patients were requested from 48 patients, and 11 patients (22%) were positive in 24 (10%) patients. In 2018, 217 investigations were requested from 47 patients and positivity was found in 8 cases (3,68%) in 1 patient (2%)(Table1). Of 18 cases with EBV PCR positive, 5 (27%) were haploidentic and 3 (16%) were transplant. In patients with thalassemia who had positive EBV PCR, Pesaroclass 3 had hemorrhagic cystitis due to BK viremia. Some of our patients had CMV PCR positivity at the same time. EBV Ig G values of all our patients and donors were positive before transplantation. None of our patients had lymphoproliferative disease. We did not receive rituximab treatment except CD27 deficiency and our patient who was positive for EBV PCR before transplantation.

Result: In high-risk (haploidentic, second-line) transplantations, it is useful to perform EBV PCR with CMV PCR.

Keywords: EBV PCR, Children, Allogeneic Stem Cell Transplantation

Table 1. EBV-PCR results by year

	Number of EBV PCR test	*Number of positive tests*	*Number of Patient*	*Number of Patients with EBV PCR+*
2016	216	14 (6,4%)	38	6 (16%)
2017	238	24 (10%)	48	11 (22%)
2018	217	8 (3,68%)	47	1 (2%)

■ Stem Cell Transplantation

P-028 Abstract Referance: 109

CAN ELTROMBOPAG TREAT THE THROMBOCYTOPENIA AFTER STEM CELL TRANSPLANTATION?

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Statement: None

Introduction and Aim: Eltrombopag is an oral nonpeptide thrombopoetin receptor agonist, approved by the Food and Drug Administration for immune thrombocytopenia and aplastic anemia. It is common for the stem cell transplant patient to experience delayed thrombocyte recovery and thrombocytopenia due to poor graft function, and many of them require thrombocyte suspensions throughout this process due to severe and deep thrombocytopenia Here, we present our center's experience with this molecule in post-hematopoetic stem cell transplantation settings.

Methods: We have retrospectively analyzed our list of HSCT patients shown in the table 1. The patients who failed to achieve adequate graft functioning were given eltrombopag between 25- 75 mg/ day (except 150 and 175 mg/ day in two consecutive patients).

Results: Female to male ratio was 4: 11 and the median age at transplant was 50. The median platelet count was 9000/ mL (3000 to 15000/ mL) at the beginning of treatment and 43000/ mL (6000/ mL in one patient who is reported to be eltrombopag refractory, to 80000/ mL) at the end. The median duration of treatment was 82 days and the median platelet count increase was 38000/ mL and found statistically significant (p= 0.026). The median eltrombopag dose was 50 mg per day. No serious adverse effects such as hepatotoxicity or myelofibrosis related to eltrombopag were seen and the treatment cost was acceptable.

Conclusion: As thrombocytopenia is closely associated with transplant related mortality and overall survival, eltrombopag is an eligible option in posttransplant thrombocytopenia management

Keywords: Hematopoetic cell transplant, eltrombopag, primary isolated thrombocytopenia, secondary failure of platelet recovery, post transplant thrombocytopenia

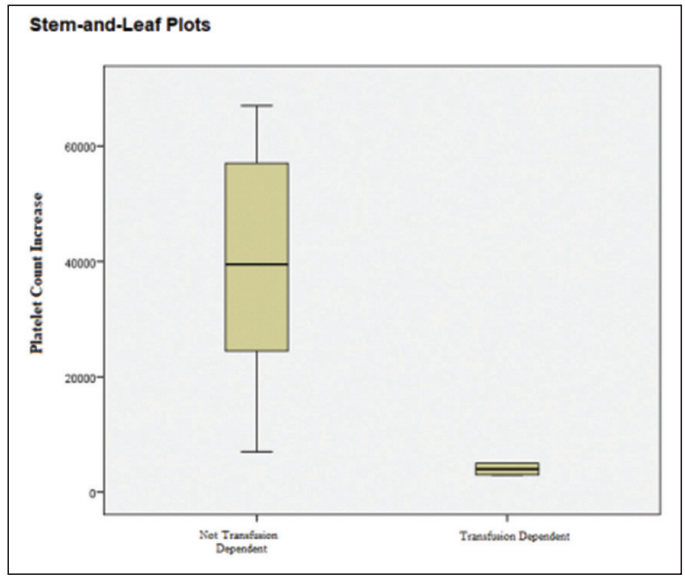

Figure 1. Platelet increase count and transfusion dependency

Table 1. Patient Characteristics

Age (median)	21- 62 (50)
Sex F: M	 4: 11
Disease AA AML MF CLL ALL Blastic plasmacytoid dendritic cell neoplasia MM	 6 (40 %) 2 (13.3 %) 1 (6.6 %) 1 (6.6 %) 1 (6.6%) 1 (6.6%) 3 (20.3 %)
Donor (Allogeneic) Related Unrelated	 6 6
Conditioning Myeloablative Reduced intensity	 12 3
Stem cell source Peripheral blood Bone marrow	 10 5
Platelet count before starting eltrombopag, median (range), per mL	9000 (3000- 15000)
Platelet count increase, median per mL	38500
Median time from transplant to eltrombopag	145
Median eltrombopag use duration (days)	82

■ Non-Hodgkin's Lymphoma

P-029 Abstract Referance: 129

BORTEZOMIB FOR TREATMENT OF NON-HODGKIN'S LYMPHOMAS; A SINGLE CENTER EXPERIENCE

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Introduction: Bortezomib, an ubiquitin proteasome system inhibitor, is used for multiple myeloma treatment, usually in a combination with other agents. Several aggresive lymphomas such as activated B-cell subtype of diffuse large B-cell lymphoma (DLBCL) and mantle cell lymhoma (MCL) are characterized substantially also NF-kB pathway activation. Considering that, this activation is sensitive to proteasome inhibitors, so bortezomib may be effective for treatment of aggresive lymphomas. In this poster, we present eight relapsed NHL patients treated with bortezomib.

Materials and Methods: We reviewed patients with relapsed and refractory Non-Hodgkin's Lymphoma (NHL) treated during 2000-2019, retrospectively, using patient files and computerized documents. Descriptive and demographic data, type of NHL, treatment sequence of bortezomib, number of totally cure and of complete response, survival after bortezomib treatment and overall survival were analized by IBM SPSS version 22.

Results: The median age of the patients was 61.4 ± 9.4 (49-81), number of patients with MCL, DLBCL and marginal zone lymphoma (MZL) were 6 (%75), 1 (%12,5) and 1 (%12,5) respectively. Mean survival after bortezomib treatment was 22.8 ± 16.2 (7-46) months, and overall survival was 79.3 ± 37.2 (35-152) months. Half of the patients were responsive to bortezomib, and 50 percent of these were still alive. Comparison of response to bortezomib between the sub-type of lymphomas was not analized due to inadequate number in each of groups.

Discussion: Aggresive lymphomas such as DLBCL and MCL often relapsed after first and subsequently remissions throughout treatment. Several study of combination/single agent bortezomib for sub-type of NHL shows that response rates including CR and PR are up to %50 of patients as our study. Because of limited number of patients and therefore comperative analysis cannot be done, our study may be evaluated as case experience.

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Keywords: Non-Hodgkin, Lymphoma

■ Acute Myeloid Leukemia

P-030 Abstract Referance: 144

DEMOGRAPHIC FEATURES AND CLINICAL CHARACTERISTICS OF MYELOID SARCOMAS : SINGLE-CENTER EXPERIENCE

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Aim and objective: Myeloid sarcoma (MS), also known as granulocytic sarcoma, is an extramedullary tumor mass composing malignant blastic myeloid cells. MS generally presents as the first finding of AML at the time of diagnosis or at the time of relapse. Myelodysplastic syndrome and myeloproliferative neolplasms can also transform into MS less commonly. MS prognosis generally entails poor outcomes. In case of isolated MS, there is myeloblastic infiltration of single or multiple extramedullary organs without any evidence of leukemia in bone marrow and peripheral blood. The diagnosis of isolated MS is very difficult. Here in we report the clinical features and survival outcomes of our MS patients.

Materials and methods: Patient records of the hematology department from September 2011 to October 2011 were screened for myeloid sarcoma. Overall, 10 cases MS were identified and included into this study. Clinical and pathological presentations, demographic features, survival outcomes were reviewed retrospectively.

Results: There were 5 females (50 %) and 5 males (50 %) with a median age of 60 ± 13.8 years (34–75 years). The primary involved sites of MS could be classified into 5 groups as follows: head and neck (N=2, 20%), skin (N=3, 30%), gastrointestinal (GI) tract (N=2, 20%), lymph node (N=2, 20 %), and muscle-skeletal (N=1 10%). 6 patients (60%) had solitary lesion and 4 patients (40%) had multıple MS lesions at the time of diagnosis. 3/10 patients had also bone marrow infiltrations. 9/10 patients had normal caryotype, one patient had complex caryotype. Nine patients were treated with systemic AML therapy (3+7 induction and ara-C consolidation). One patient were treated with hypomethylating agent due to older age. Complete remission was obtained in seven patients (70%). Partial remission was obtained in two AML with MS patient. One of them was referred to allogeneic bone marrow transplantation. Progression free survival was 11.8 (1-59 months), overall survival was 22 months (1-60). Local radiotherapy was not used in any patients.

Conclusion: MS is rare and unique entity of myeloid neoplasm which diagnosis is difficult. There are not large prospective studies to determine optimal therapy. In our study, systemic chemoterapy seems to be acceptable for fit patients. But to identify novel and selected therapies, larger prospective studies are needed.

Keywords: Myeloid sarcoma, granulocytic sarcoma, acute myeloid leukemia

■ Acute Lymphoblastic Leukemia

P-031 Abstract Referance: 34

LEVEL OF SENSITIZATION BY LEUCOCYTE ANTIBODIES OF PATIENTS WITH ACUTE LEUKOSIS

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Introduction: Ensuring immunological safety of blood transfusion remains one of the most important problems of transfusion medicine. In its decision, the main importance belongs to measures aimed at preventing allosensitisation of recipients and the prevention of posttransfusion complications, including refractoriness to therapy with blood components.

The aim: To study the dynamics of the increase in the level of sensitization of patients receiving blood platelet hemotransfusions in Kazakhstan.

Materials and methods: In scientific-production center of transfusiology of Astana city, 23 patients with hematological diseases receiving platelet transfusions were examined for the level of sensitization level. Samples of sera were examined for the presence of antibodies directed to leukocyte antigens of the first class of the HLA system. A flow cytofluorometry method was used on the LABScan 3D analyzer (One Lambda, USA).

Research results: Research of blood serum of patients performed prior to the initiation of transfusion therapy with platelets showed the presence of leukocyte antibodies to class I of HLA in 14 patients (61%), 9 patients (39%) of leukocyte antibodies were not detected.

Further detection of antibodies in 9 patients with initially negative status showed that in 7 of them antibodies appeared within 2 weeks from the beginning of blood transfusion therapy. Antibodies were detected in the remaining 2 patients in study conducted 4 weeks after the onset of platelet transfusions. Two- and four-week monitoring of antileukocyte antibodies among 14 patients with an initially positive status revealed an increase in the level of sensitization available at the beginning of treatment.

Keywords: Acute leukosis, transfusion, patients, antibodies, donors

■ Acute Lymphoblastic Leukemia

P-032 Abstract Referance: 45

METHOTREXATE, VINCRISTINE, L-ASPARAGINASE AND DEXAMETHASONE FOR ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN BRIDGING BEFORE AND SALVAGING AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Despite recent developments in the treatment options,relapsed/refractory acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are still worse diseases in adults with low salvage and cure rates compared to childhood. L-asparaginase is one of the mainstay differences in the back-bone of multidrug regimens used in children. In our center, we have been using an L-asparaginase integrated combination of methotrexate, vincristine and dexamethasone (MOAD protocol) as a salvage regimen since 2017. In this study, we aimed to summarize our experience with this combination and to the best of our knowledge, there are only limited studies reporting MOAD protocol in the relapsed/refractory disease setting.

Materials and Methods: The adult patients followed at our institution over the course of 2 years (2017-2018) with a diagnosis of relapsed/refractory ALL or LBL were retrospectively reviewed and cases treated with MOAD protocol were enrolled for the study. One treatment cycle of our protocolwas 28 days and it combined methotrexate 200 mg/m^{2}intravenously (IV) on days 1 and 15; vincristine 1.4 mg/m^{2}IV on days 1,8 and 15; L-asparaginase 10 000 IU/m^{2}IV twice in a week; and dexamethasone 40 mg given IV or orally (PO) on days 1 to 4 and 15 to 18 of each cycle. Demographic and clinical characteristics of the patients, response to treatment and adverse events related to therapy were analyzed.

Results:A total of 8 patients included in the study are summarized in table. The median age was 37 years (range: 21-58 years). Half of them have had a history of HSCT and MOAD was used for salvaging after transplantation. The lineage of ALL was B-cell in 4 patients, but all were negative for Philadelphia chromosome. Complete remission (CR) was obtained in 38% after the first cycle and for two of them MOADprotocol worked as a bridging regimen for allogeneic HSCT. Another 2 patients with lymphomatous disease had PR after the first cycle and one of them has also had a successful allogeneic HSCT. All of the 3 patients proceeded to allogeneic HSCT had T-cell disease. No clinically evident hypersensitivity reactions were seen with L-asparaginase and the most common adverse events associated with MOAD protocol were hypofibrinogenemia, anemia and febrile neutropenia.

Conclusions: The MOAD protocol is found to be an effective and tolerable regimen which enables bridging before and salvaging after HSCT, particularly in the setting of relapsed/refractory T-cell ALL and LBL. Yet, the issue warrants more studies with large-scale patient populations.

Keywords: Acute lymphoblastic leukemia, Lymphoblastic lymphoma, L-asparaginase

Table 1. Summary of the patients' clinical course

Patient	*Sex/ Age (years)*	*Lineage*	*HSCT before MOAD*	*Response to MOAD*	*Cycles of MOAD*	*HSCT after MOAD*	*Follow-up after MOAD*	*Outcome*
1	M/26	T	Allogeneic	PR after first cycle	3	No	Progression following the 3rd cycle	Exitus
2	M/50	B	Allogeneic	CR after first cycle	3	No	Progression following the 3rd cycle	Continuing treatment with inotuzumab
3	F/21	T	Autologous	CR	1	Yes	Progression at the 123rd day of HSCT	CR after liposomal vincristine
4*	F/58	T	No	CR	1	Yes	Progression at the 90th day of HSCT	Exitus
4*			Allogeneic	NA	1**	No	NA	Exitus
5	F/58	T	No	PR	1	Yes	Keeping PR at the 4th month of HSCT	Keeping PR
6	M/21	B	No	RD	1	No	NA	Exitus
7	M/43	B	No	NA	1**	No	NA	Exitus
8	M/22	B	No	NA	1**	No	NA	Exitus

NA: not applicable; **CR:** complete response; **PR:** partial response; **RD:** refractory disease;
* The patient has taken MOAD protocol twice at different time points of her follow up: before and after HSCT; ** Exitus before completing the cycle

■ Multiple Myeloma

P-033 Abstract Referance: 7

IMPACT OF BONE MARROW PLASMA CELLS PERCENTAGE ON SURVIVAL AT DIAGNOSIS AND PRE-TRANSPLANT PERIOD IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background and Aim: The current definition of complete remission (CR) in multiple myeloma (MM) includes negative serum and urine immunofixation (IFE) tests and <5% bone marrow plasma cells (BMPCs). The aim of this study was to examine the impact of BMPCs percentage on survival at diagnosis and pre-transplant period in newly diagnosed multiple myeloma.

Materials and Methods: One hundred and fourty eight patients with newly diagnosed MM who received an autologous stem cell transplantation (ASCT) in our HSCT (hematopoietic stem cell transplant) center at Hacettepe University Hospital between the years of 2008 and 2018 were evaluated retrospectively.

Results: The median follow-up period was 27.4 months (range, 4.5-122) for the entire group. The 3-year OS was 87% in pre-transplant BMPCs <5% group when compared to pre-transplant BMPCs ≥ 5% group as 92% with no statistically significant difference. The 5-year OS for pre-transplant BMPCs <5% group and pre-transplant BMPCs ≥ 5% group were 73% and 70%, respectively (p=0.50). The 3-year the PFS in pre-transplant BMPCs <5% group and pre-transplant BMPCs ≥ 5% group were 77% and 57%. The 5-year PFS in pre-transplant BMPCs <5% group and pre-transplant BMPCs ≥ 5% group were 43% and 13%, respectively. There was statistically significant difference between two groups on PFS (p=0.04).

Conclusion: In conclusion, this study focuses on determination of survival outcome based on the best response obtained before ASCT and particularly highlights the significance of reaching <5% plasma cell pre-transplant period. OS and PFS were better in patients who had pre-transplant BMPCs <5% than pre-transplant BMPCs ≥ 5%.

Keywords: Autologous stem cell transplantation; bone marrow plasma cell; multiple myeloma

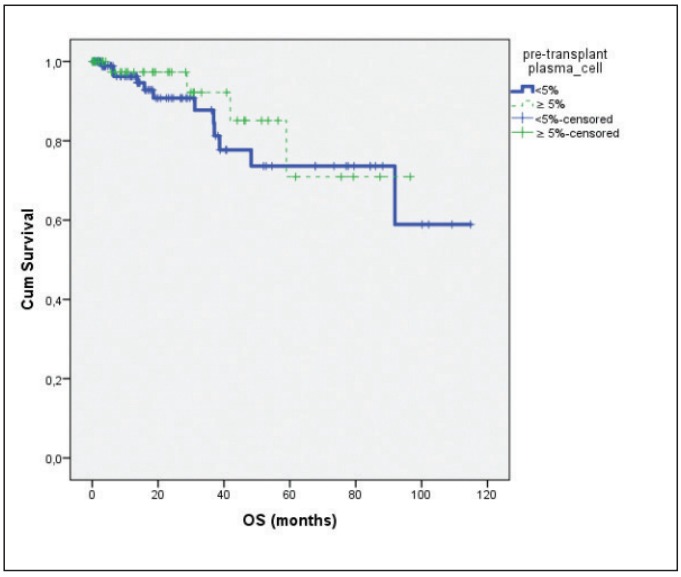

Figure 1. Overall survival according to the pre-transplant bone marrow plasma cells (p=0.50)

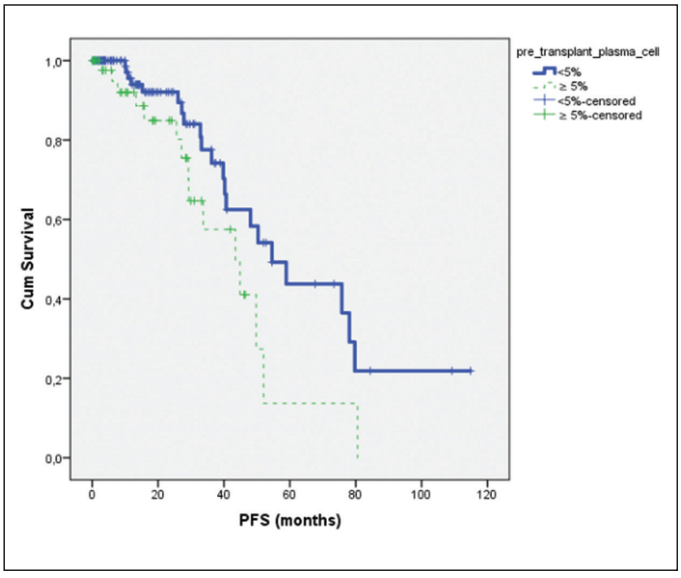

Figure 2. Progression free survival according to the pre-transplant bone marrow plasma cells (p=0.04)

■ Multiple Myeloma

P-034 Abstract Referance: 6

COMPARISION OF BORTEZOMIB-CYCLOPHOSPHAMIDE-DEXAMETHASONE (VCD) VERSUS BORTEZOMIB-DEXAMETHASONE (VD) BASED REGIMENS AS INDUCTION THERAPIES IN MULTIPLE MYELOMA

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Background and Aim: The treatment landscape and clinical outcome of multiple myeloma (MM) patients have changed in the last decades, with an improved median survival of 8-10 years. This study aimed to evaluate the VCD regimen versus bortezomib and dexamethasone (VD) in patients with newly diagnosed MM.

Materials and Methods: This study has been performed in a retrospective manner. One hundred and three patients with newly diagnosed MM who received IT at Hacettepe University Hospital between the years of 2009 and 2018 were evaluated.

Results: A total of 103 patients were included. The 5-year overall survival for patients who received VD regimen and patients who received VCD regimen were 75 % and 83 %, respectively. The OS for VD patients was 113.1±12.5 versus 122.2±9.5 months for VCD patients with no statistically significant difference (p=0.47). The 5-year PFS for patients who received VD regimen and patients who received VCD regimen were 66 % and 75 %, respectively. The PFS for VCD patients was higher than the PFS for VD patients (99.3±13.6 versus 72.4±8 months), but no statistically significant difference was observed (p=0.59). Relapse rate (p=0.002) and mortality rate (p=0.01) were higher in VD group than VCD group and they were statistically significant.

Conclusion: The OS and PFS were clinically longer in patients receiving VCD regimen than in patients receiving VD regimen, although not statistically significant. Cyclophosphamide should given to patients at physician discretion and depending on patient's frailty function.

Keywords: Multiple myeloma, VD regimen, VCD regimen

Figure :

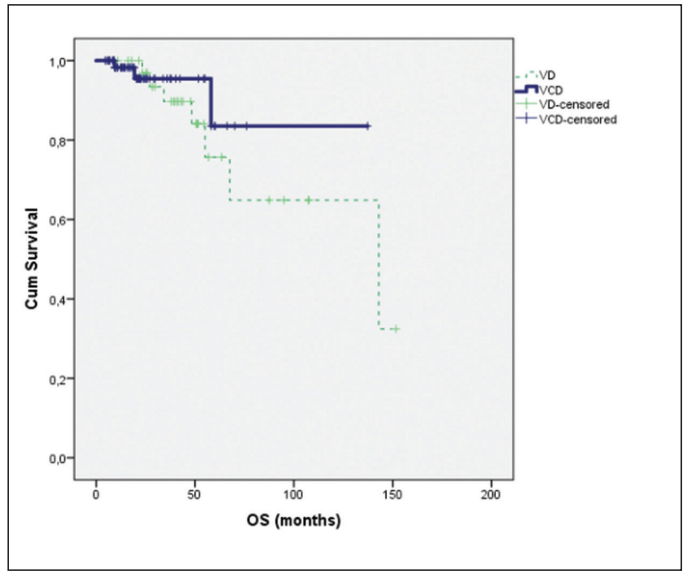

Figure 1. The overall survival for VD and VCD patients (p=0.47)

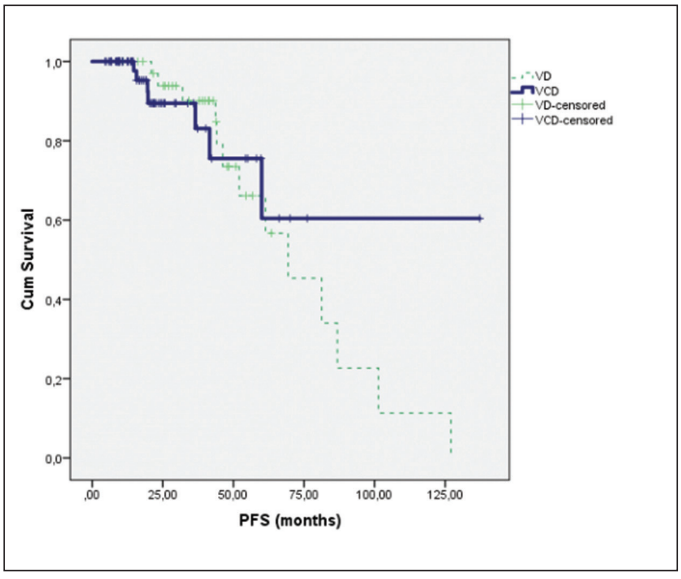

Figure 2. The progression free survival for VD and VCD patients (p=0.59)

■ Non-Hodgkin's Lymphoma

P-035 Abstract Referance: 95

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE (PTLPD)-CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT IN A CASE WITH LIVER TRANSPLANTATION: CASE REPORT AND REVIEW OF THE LITERATURE

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Post transplant lenfoproliferative diseases (PTLPDs) are generally seen in cases with solid organ transplantation (SOT) and related with EBV infection in 70-90% of the cases. PTLPDs are classified as polymorphic, monomorphic, early lesion and classical Hodgkin lymphoma like type. Here a case with PTLPD with CNS involvement has been reported and literature has been reviewed.

Case: 55 year-old-man admitted to the hospital with one week of fever, cough, sputum, headache and difficulty in writing. He had the history of liver transplantation from related living donor and had been treated by mycophenolate mophetile for 18 months, everolimus a few months and then tacrolimus for 2 years. Physical exam showed fever (37.8^{o}C) and he had been treated by tazobactam piperacillin and moxifloxacin combination. Cranial MRI showed bilateral parietal and left cerebellar lesions compatible with metastatic lesions. Systematic evaluation including CT scanning and PET/CT scanning did not show extracranial lesion. Hydrocephalus developed in a short time and ventriculo-peritoneal shunt was performed and cerebellar mass was excised. Histopathologically mass was reported as PTLPD-polymorphic type. Immune-histochemically LMP-EBV, CD20, LCA, Pax5 and CD30 were found to be positive and CD15 was negative. Rituximab and methotrexate containing regimen was planned but he died due to oppurtunistic infection.

Discussion: The majority of PCNS-PTLDs are B-cell non-Hodgkin lymphomas, 20- to 120-fold higher incidence of lymphomas/PTLD have been reported in cases with SOT. Age, type of transplantation and intensity of immunosuppression are the most significant risk factors. Although PTLDs typically occur in the first year post-transplant period, late recurrences of EBV+ PTLPD are common and 40% of cases are diagnosed later than 6 years after SOT. PTLPD in our case was detected at 4th year of transplantation. Isolated CNS involvement of PTLD is uncommon, about100 patients have been reported so far. Presenting signs and symptoms of PCNS-PTLD are similar to intracranial mass lesions as in our case. MRI is the preferred imaging as in our case. Multifocal supratentorial involvement is more frequent but periventricular region may be involved and may cause to hydrocephalus as in our case. Diagnosis is based on biopsy to confirm the diagnosis and also to exclude opputunistic infections. Surgical resection is the treatment of choice but this may be possible in the minority of the cases. Surgery can not be performed in cases with multicentric disease as in our case and poor prognostic indicator. Other treatment options are reduction of immunosuppression, whole-brain radiotherapy, and systemic chemotherapy and/or monoclonal antibody therapy. Although reduction of immunosuppression alone is useful in cases with early systemic polyclonal PTLPD this is not sufficient in cases requiring rapid disease control as in our case. Rituximab-containing regimens and/or cranial radiotherapy are frequently used. Autologous or allogeneic EBV-specific cytotoxic T-lymphocytes (CTL) may be useful but it requires time and is not appropriate in cases requiring urgent treatment.

Keywords: Post transplant lenfoproliferative diseases, EBV, solid organ transplantation

■ Acute Lymphoblastic Leukemia

P-036 Abstract Referance: 21

SUCCESSFUL TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA DURING PREGNANCY RESULTING IN A SAFE DELIVERY: CASE REPORT

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Introduction: Acute leukemia is a rare event during the course of pregnancy. There is almost always a dilemna between optimal maternal treatment and fetal well-being. The maternal interest favors the immediate initiation of leukemia. However, possible teratogenic effects may result in the delay of leukemia treatment.

Case: A 22-year-old female primigravida at 20 weeks gestation presented to the emergency department with a 2 week history of progressive fatigue and dyspnea. Complete blood count showed a white blood cell count of 12000/mm^3, hemoglobin 3.9 g/dl and platelets 95000/µl. Bone marrow biopsy revealed precursor B-cell Acute Lymphoblastic Leukemia (ALL). Bone marrow cytogenetic analysis showed 46 XX karyotype and RT-PCR analysis revealed the expression of MLL-AF4 fusion. Ultrasound revealed a single living fetus at 20 weeks with weight corresponding to the 39th percentile and normal amniotic fluid. The decision was made to wait until at least 30 weeks to deliver the baby via caesarean section. As remission induction treatment, HyperCVAD regimen was initiated. Intrathecal treatment was not planned due to possible risk of induction of labor due to lumbar puncture. For initial prophylaxis, acyclovir and flucanazole were given. Bone marrow biopsy on day +25 of HyperCVAD1A showed hematological remission. HyperCVAD1B and HyperCVAD2A were initiated at 24th and 27th week of gestation, was initiated. The fetal follow-ups showed no abnormality. HLA matched sibling donor was identified. It was planned that the patient undergoes caesarean section after completion of HyperCVAD2B and subsequently undergoes allotransplantation due to high risk ALL. At 31st week of gestation, HyperCVAD2B was started. On day +6 of HyperCVAD2B, her birth contractions began and the patient gave birth to a 1250 mg female following caesarean section. The baby required transient respiratory assistance for 36 hours post delivery due to cyanosis and poor respiratory effort. One month after delivery, the patient has now been hospitalised for allogeneic stem cell transplantation form her matched related donor. The baby continues to do well as well.

Discussion: Each pregnant patient with malignancy represents a peculiar challenge requiring the treating physician to take into consideration the gestational age at presentation, the type of malignancy and the chemotherapy regimen and its doses while focusing on optimal outcome for both the mother and the infant. Treatment of acute leukemia during pregnancy remains an even greater challenge than treating solid tumors or lymphoma due to the requirement of using much higher doses of induction chemotherapy. Our

case represents the feasibility of treating ALL with HyperCVAD during the second trimester of pregnancy with optimal outcomes.

Keywords: acute lymphoblastic leukemia, pregnancy

■ Non-Hodgkin's Lymphoma

P-037 Abstract Referance: 87

EXCEEDINGLY RARE PATHOLOGIC EVOLUTION AFTER ALLOGENIC STEM CELL TRANSPLANTATION: FOLLICULAR HELPER T CELL TYPE NODAL PERIPHERAL T CELL LYMPHOMA

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T cell lymphomas are rare and heterogenous types of lymphomas and development of follicular T helper phenotype T cell lymphoma after the treatment of B cell lymphomas are exceedingly rare. Here we present a case,which autologously transplanted years ago because of diffuse large b cell lymphoma(DLBCL) and relapsed, then treated wih chemotherapy and allogenic stem cell transplantation(ASCT), and relapsed early and showed characteristically T cell lymphoma phenotype.

Fourty one year old male patient was diagnosed DLBCL(stage 4 A, International prognostic Index:2) from axillary lymph node biopsy at year 2014 and received 8 cycles of R-CHOP-21 chemotherapy. While he was being followed up at remission, at 2015 ,he developed back pain and cervical lymphadenopaty(LAP) and PET-CT was performed, new developping retroperitoneal(SUV max:4) and cervical LAP(SUV max:4.9) were detected. (Deauville-3) Cervical lymph node biopsy was performed and relapsed DLBCL diagnosis was confirmed.R-ESHAP-28 protocol was begun .After 2 cycles, autologous stem cell transplantation was performed at May 2016.The patient was followed up in remission without treatment until semptember 2017,but relapsed again as new developping axillary, mediastinal,mesenteric and peripancreatic LAP(SUV max:6). Donor screening for allogenic transplantation and lenalidomide treatment was initiated. After 6 cycles, repeat PET-CT at June 2018 showed progression of abdominal and retroperitoneal LAP(SUVmax:5.7, size:2.1) Lenalidomide treatment was changed with GDP-21 (gemcitabine,dexamethasone,cisplatin) regimen .After 2 cycles, although new PET showed progression of present LAP, the patient received allogenic stem cell transplantation with myeloablative conditioning regimen from his full match (10/10) healthy sister at November 2018. He was discharged from hospital with no obvious sign of graft versus host disease to be followed at outpatinet clinic.After 2 months from the transplantation , a persistent axillary LAP was detected by physical examination ,and excisional biopsy showed nodal peripheric t cell lymphoma, phenotyped as follicular helper T cell type. The biopsy showed CD19 ,CD 20 and cycline D1 positivity and EBER(Ebstein Barr Virus encoded RNA) negativity. Ki-67 index was 70 %. He admitted to hospital again and received donor lymphocyte infusion(DLI) as one single CD3 dose of $1x10^7$ /kg from his sister, 2 additional DLI infusions are planned in the future.İbrutinib monotherapy was started for the relapsed lymphoma. Control PET-CT showed regression of previous involved abdominal and complete remission of supraclavicular,axillary and cervical LAP(Deauville 4).

De novo CD20 (+) T cell lymphomas are rare malignities, but patological evolution from B cell lymphoma after ASCT is extremely rare. We want to emphasize careful examination of treatment resistant B cell lymphomas and the importance of DLI's at early phase of post-ASCT.

Keywords: lymphoma, DLI

■ Stem Cell Transplantation

P-038 Abstract Referance: 117

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH CD27 DEFICIENCY

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CD27 deficiency, also known as lymphoproliferative syndrome 2, is an autosomal recessive immunodeficiency disorder. Persistent symptomatic EBV viremia, hypogammaglobulinemia and T cell dependent B cell response are associated with impairment of specific antibody formation and T cell dysfunction. The clinical presentation ranges from symptomatic, borderline hypogammaglobulinemia, to EBV-associated life-threatening systemic inflammatory response, to hemophagocytic lymphohistiocytosis and malignant lymphomas.

In this article, we present allogeneic hematopoietic stem cell transplantation after CD27 deficiency was detected in the advanced investigation of two siblings diagnosed as Hodgkin lymphoma and Burkit lymphoma.

Case-1: A 9-year-old female patient was diagnosed with CD27 deficiency in advanced investigations due to stage 3 Burkit lymphoma 6 years ago and nodular sclerosing Hodgkin lymphoma 5 years ago. She received rituximab treatment 2 times before transplantation; because of EBV PCR was high titer positive. Conditioning regimen was consisted of rituximab, fludarabine, busulfan, thiotepa and ATG. A bone marrow-derived stem cell transplantation containing $2.75x10^6$/kg CD34+ cells, $3.98x10^8$/kg nucleated cells was performed from the HLA 10/10-compatible cousin. Gaft versus host prophylaxis was consisted of Cyclosporine + short MTX. Neutrophil engraftment was on day +17, thrombocyte engraftment was on day +35. During follow-up, EBV PCR was negative. The patient who completed the 12th month after transplantation had no acute or chronic GVHD. The first year of chimerism was 99% donor.

Case-2: A 13-year-old female patient was treated 6 years ago with the diagnosis of mixed cellularity classic Hodgkin lymphoma. In further investigation, she was diagnosed with CD27 deficiency and allogeneic stem cell transplantation was performed by a HLA 10/10 cousin. The preparation regimen included fludarabine, busulfan, thiotepa and ATG. A bone marrow-derived $2.3x10^6$/kg CD34 + cells were given. Neutrophil engraftment was on day +14, thrombocyte engraftment was on day +52. She received defibrotide for sinusoidal obstruction syndrome on day +32. The patient who completed the 4th month after transplantation had no acute or chronic GVHD. The third month resulted in chimerism as 99 % donor.

Discussion: Treatment with CD27 deficiency varies according to clinical presentation. Allogeneic cord stem cell transplantation has been reported in 3 patients who developed lymphoma in the literature with a reduced intensity preparation regimen (Bu-Flu-ATG / Bu-Cy-ATG / Cy-Flu-TBI). In these cases, HHV6, CMV and EBV reactivation were post-transplanted. In our first case, EBV PCR was decreased with rituximab, and EBV PCR was decreased. The EBV PCR results were negative during and after transplantation and post-transplant lymphoproliferative disease free. No viral infection or reactivation was observed in the second case.

Keywords: CD27 deficiency, Allogeneic Hematopoietic Stem Cell Transplantation, Hodgkin lymphoma, Burkit lymphoma.

■ Chronic Lymphocytic Leukemia

P-039 Abstract Referance: 49

LATE ONSET LEFT VENTRICULAR DYSFUNCTION AND CARDIOMYOPATHY INDUCED WITH IBRUTINIB

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Bruton tyrosine kinase is an important part of B cell receptor and is very essential for B cell survival, proliferation and differentiation. We report a case with left ventricular dysfunction and cardiomyopathy developed 1 year after treatment with ibrutinib for relapsed CLL.

In our case, a 66-year-old, presented with widespread itching in her body and lymphocytosis. Bone marrow biopsy was performed in July 2011, pathology was diagnosed as CLL. The del17p mutation was negative. She (Stage 1 CLL- according to RAI staging) was followed up for 2 years without treatment. R-FC treatment was started in January 2013, due to the fact that lymphocyte doubling time decreased below 6 months. She received 4 courses of R-FC and 4 courses R-bendamustine. She complained of palpitations in April 2015 and did not have any cardiac history other than hypertension (HT). Atrial fibrillation (AF) was detected on electrocardiography (ECG). Echocardiograpy (ECHO) was performed and the ejection fraction (EF) was 60%. The patient was evaluated as Grade 2a AF and sinus rhythm was achieved with medical treatment. In October 2017, because she was unresponsive to 2 treatment, ibrutinib 420mg po was initiated to the patient by obtaining non-indication, due to the fact that the lymphocyte doubling time was below 6 months. The patient received ibrutinib 420mg between October 2017 and October 2018 and applied to the cardiology department on October 2018 due to dyspnea, exertional dyspnea and pretibial edema. ECG revealed normal sinus rhythm, transthoracic ECHO revealed EF 15%, left ventricle and atrium dilated and systolic dysfunction. The patient's low EF status was noted after 1 year of ibrutinib use and ibrutinib treatment was discontinued. In the control transthoracic ECHO performed 1 month after cessation of treatment, the patient's EF was 41%.

Clinical study data show only two main cardiac side effects, HT and AF by this time. AF is frequently observed with the use of ibrutinib and 5% -6% with 18 months follow-up and up to 16% in longer follow-ups. In HELIOS study; 7% patients in the ibrutinib group, 2% patients in the placebo group, AF observed. Median time until beginning of AF, was 3-10 months in the ibrutinib group and 2-4 months in the placebo group. In our patient, there was a history of grade 2a AF and heart failure was detected in the 12th month of ibrutinib treatment. The development of cardiomyopathy with ibrutinib is reported with two cases. In these 2 cases left ventricular dysfunction and cardiomyopathy was presented with arythima which was not present in our case. One of the routes regulated by BTK is the phosphoinositide 3-kinase (PI3K)-Akt pathway. PI3K-Akt path is important for prevention of stress-induced cardiomyopathy. Ibrutinib irreversibly inhibits BTK and causes blocking of a pair of pathways. It has been hypothesized that blocking PI3K-Akt pathway is mainly involved in atrial fibrillation development. Similar to this, inhibition of tec protein tyrosine kinas pathway with ibrutinib may be the reason AF. Even though both mechanisms are involved, the exact cause of atrial fibrillation and heart failure development by ibrutinib have not yet been fully clarified. Particular attention should be paid to the emergence of AF and other unexplained cardiac complications in patients treated with ibrutinib and other agents acting on the PI3K-Akt pathway inhibiting PI3.

Keywords: ibrutinib atrial fibrilation cardiac failure

■ Non-Hodgkin's Lymphoma

P-040 Abstract Referance: 84

PRIMARY SKELETAL MUSCLE DIFFUSE LARGE B CELL LYMPHOMA WITH SEVERE NECROSIS SUCCESSFULLY TREATED WITH CHEMOTHERAPY: CASE REPORT

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Introduction: Diffuse large B cell lymphoma is the most common form of non-Hodgkin lymphomas. Twenty to 30% of them are presented as extranodal disease. Primary skeletal muscle presentation is a very rare form of the disease [1]. Patients typically present with a painful and swollen mass.

Case report: A 71-yo woman was presented to the dermatology clinic with pruritus in the right thigh area. No overt lesion was present and symptomatic medications were prescribed. In the follow-up, a diagnosis of abscess was made and, antibiotherapy was prescribed. However, the antibiotherapy did not improve the mass and it continued to become larger and deeper. Six months after the initial presentation, the MRI reported a mass of 10cmx12cm in the rectus femoris muscle and in the soft tissue anterior to the muscle.

Biopsy was performed and diffuse neoplastic infiltration on a desmoplastic area with extensive coagulation necrosis was described. The tumoral cells were CD20+, CD3-, Bcl6+, CD10-, MUM1-, Bcl2+ and, Cmyc+, with a Ki67 proliferation index of 90-95%. The findings were reported to be consistent with double expressor high grade B cell lymphoma.

Our patient was presented to our outpatient clinic with an open wound of 10cmx4cmx5cm (Figure 1a), with an extensive malodorous discharge. She was a frail elderly patient, with a severe walking disability due to muscle loss in the right thigh, using crutches. In her past medical history, she had a cerebrovascular accident probably related to the atrial fibrillation. In her CBC, she had neutrophilic leucocytosis, with a WBC of 18600/mcl. The serum LDH level was within normal limits. In the PET/CT scan, the only area involved was the anterior thigh, with a mass of 10.3x6.3x15.3 cm (Figure 2a). We could not perform bone marrow biopsy due to her physical condition.

Considering her fragility and her cardiac problems, we initiated the treatment with three cycles of rituximab 375mg/m2, cyclophosphamide 750 mg/m2 and oral methyl-prednisolone 80 mg/day D1-5 q21d. Her wound was improved (Figure 1b) and her physical performance was better, we switched to R-miniCHOP regimen (Rituximab 375mg/m2, cyclophosphamide 400mg/m2, doxorubicin 25mg/m2, vincristine 1mg and methylprednisolone po 80mg D1-5). Following 4 cycles q21d, the wound was almost totally closed (Figure 1c), with a concordant complete response on the PET/CT (Figure 2b). Curative radiotherapy for the primary involved area is planned for our patient.

Discussion: The common clinical symptoms of primary skeletal muscle lymphoma are related to extremity pain, muscle swelling and, edema. They may occur as isolated lesions. The thigh muscles, which were involved in our case, constitute an atypical area for this type of presentation. The initial lesion was confused firstly with dermatitis, then with abscess. Although it is a very rare type of DLBCL, it should be kept in mind especially in elderly patients presenting to the orthopedics clinics with related symptoms. The choice of treatment may be challenging as it is an aggressive disease which presents in the elderly patients and which develops its own disabilities due to muscle necrosis. Our patient responded well to R-mini CHOP treatment and we need long term follow-up to evaluate the durability of response after radiotherapy.

1. Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-2390.

Keywords: Primary skeletal muscle lymphoma diffuse large B cell lymphoma, elderly

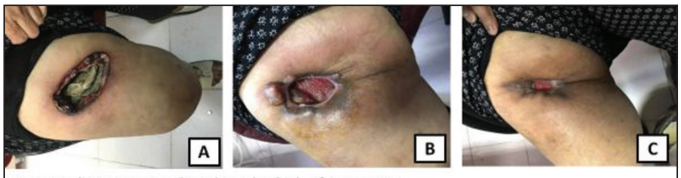

Figure 1: The open wound on the right thigh of our patient.
A: at the time of presentation to our clinic
B: After 3 cycles of R-CP
C: After 4 cycles of R-miniCHOP

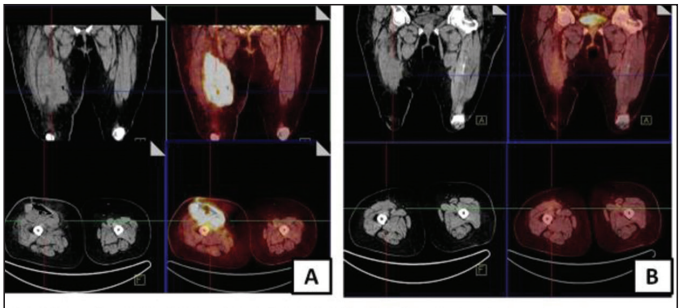

Figure 2: The open wound on the right thigh of our patient.
A: Initial PET/CT scan
B: End-of-treatment PET/CT scan

■ Acute Myeloid Leukemia

P-041 Abstract Referance: 124

ACUTE MYELOID LEUKEMIA ASSOCIATED WITH NON LANGERHANS CELL HISTIOCYTOSIS, CHALLENGING CASE

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Introduction: Necrobioticxanthogranuloma (NXG) is a rare, chronic, progressive granulomatous disorder, it is also a subgroup of non langerhans cell histiocytosis (NLH). It manifests as cutaneous papules and nodules that evolve to form infiltrated plaques. Extra-cutaneous involvement is also known. A systemic association in the form of serum monoclonal gammopathy and there is also an increased risk of hematological and lymphoproliferative malignancies. We represent NXG with multiple organ involvement and associated with acute myeloid leukemia.

Case: A 59-year-old woman presented with complaints of yellowish brown swellings around both the legs since 3 years. These lesions were mostly asymptomatic other than the occasional itching. During the follow -up, the punch biopsy result is compatible with 75% of necrobiotic xanthagranuloma which is a subgroup of non langerhans histiocytosis. Lesions were gradually progressive in nature and both upper eyelids and face were also involved with plaques and nodules. During the follow up she also complained of total restriction of her field of vision, which was worse on the left side. Uveitis like lesion detected and she was treated with methylprednisolon successfully. After 1 month treatment of methyl prednosolon the lesions were relapsed and massive stiff leg edema was detected. Her blood count was WBC:20,670 /mm^3, Neut:13,500/ mm^{3}Monocyte: 4,140/ mm^3 Hb: 8,8 g/dL, Plt: 260.000/ mm^3 creatinin: 1,2 mg /dl, LDH: 462 IU (N: 125-220IU), üric acid:10,2 mg/ dL (N: 2,6-6,0 mg/dL) Ca:9,54 P:3,5 AST: 17, ALT: 13 ALP: 262 GGT: 379 total bilirubin: 0,54 mg/dL direct bil: 0,31 mg/dL, and hepatosplenomegaly was revealed at physical examination. On the peripheral smear examination myeloid blast cells was seen. Liver biopsy showed the myeloid infiltration of liver tissue. She was diagnosed as acute myeloid leukemia with spontaneous tumor lysis syndrome and liver involvement. Acute myeloid leukemia was confirmed with the bone marrow biopsy and hyper cellular bone marrow with grade 3 reticular fibrosis and diffuse infiltration of CD61 (+) myeloblasts was detected. She was treated with the 3+7 chemotherapy protocol. After the chemotherapy treatment cholestasis and stiff leg edema was resolved. Complete remission was detected with bone marrow biopsy at the 27th day of the treatment. Eye, liver, muscle and skin lesions are also in remission. She was refereed to allogeneic stem cell transplantation with secondary acute myeloid leukemia.

Discussion: NXG is a very rare disease and can presented with variable systemic involvement. This patient also had liver and possibly musculoskeletal tissue involvement but we could not performed muscle biopsy. Liver and muscle tissue involvements are also extremely rare. Non Langerhans cell histiocytosis may be transform into acute myeloid leukemia and have a very poor prognosis. This transformed patients should be treated with stem cell transplantation.

Keywords: Histiocytosis, Leukemia, Langerhans

■ Chronic Lymphocytic Leukemia

P-042 Abstract Referance: 25

LONG-LASTING REMISSION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN A VERY REFRACTORY CLL PATIENT

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Allogeneic hematopoietic stem cell transplantation (AHSCT) in chronic lymphocytic leukemia (CLL) is particularly considered in younger patients with either a high risk of refractoriness or actual refractory disease to targeted therapy.

A 42-year-old female with heavily pretreated refractory CLL was referred to our transplantation unit for allogeneic stem cell transplantation evaluation. Her history dates back to 2009 after when she had several relapses of CLL requiring multiple lines of treament, including FCR, R-bendamustin and ibrutinib. Her physical examination in January 2015 revealed bulky cervical and axillary lymph nodes (Figure 1). CT scan revealed right cervical 48x27 mm, left cervical 43x20 mm, right axillary 49x12 mm, left axillary 58x38 mm, infracarinal 43x20 mm, paraaortocaval 38x32 mm, perihiler 39x25 mm, mesenteric 34x57 mm, right external iliac77x49 mm, left external iliac 65x45 mm lymph nodes. Deletion of 17p was detected by FISH analysis (25%). She underwent a matched related peripheral blood SCT (13.02.2015) from her 46-year-old male sibling donor with a myeloablative conditioning regimen (fludarabine, busulfan and cyclophosphamide). Graft-versus-host disease (GVHD) prophylaxis included cyclosporine (starting day -1) and methotrexate 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6 and 11. Neutrophil and platelet engraftment occured on day +10 and +12. Acute GVHD grade II (stage 3) with skin involvement was diagnosed on day +20. She was treated with methylprednisolone, cyclosporine, mesenchymal stem cells and extracorporeal photopheresis. Mixed donor chimerism (75% donor) was detected on day +28. She was diagnosed with progressive chronic GVHD (cGVHD) with lichenoid skin involvement on day +87. She was treated with methylprednisolone, mycophenolate mofetil and ECP. On day +100, her bone marrow showed patchy CLL infiltration and CT scan showed right cervical 29x11 mm, left axillary 23x15 mm, right axillary 30x13 mm and left paraaortocaval 14x12 mm lymph nodes. Deletion of 17p and mixed donor chimerism persisted. He was in partial remission. On day +125, ibrutinib 420 mg/day was started to obtain complete response (CR) and to treat cGVHD. On day +180, the patient's peripheral blood chimerism showed 100% donor engraftment. A repeat bone marrow biopsy showed no evidence of CLL. Subsequent CT scans showed no lymph nodes. On repeat FISH analysis, 17p deletion was negative. CR was obtained. She remained free of cGVHD for 1 year under ibrutinib. She subsequently had multiple flares of cGVHD involving the skin, mucosa and liver. Multiple agents including bortezomib, methotrexate and rituximab were used. During the treatment course, she was complicated with hypogammaglobulinemia, recurrent bacterial infections and recurrent CMV viremia. She continued to remain in CR for about 25 months when she

succembed to her disease 31 months after AHSCT due to cGVHD induced immunosupression and E.coli septisemia.

AHSCT may enable longer-lasting progression-free survival especially in patients who achieve MRD-negativity. The results of AHSCT is better in patients with responsive disease. Herein, we report a refractory CLL patient with bulky disease in whom CR was obtained 180 months after AHSCT in the concomitant presence of cGVHD and post-transplantation ibrutinib treatment. Her remission period waslong-lasting but immunosupression in the setting of recurrent cGVHD and E.coli septisemia were the causes of late mortality after AHSCT.

Keywords: Allogeneic hematopoietic stem cell transplantation, chronic lymphocytic leukemia

Figure :

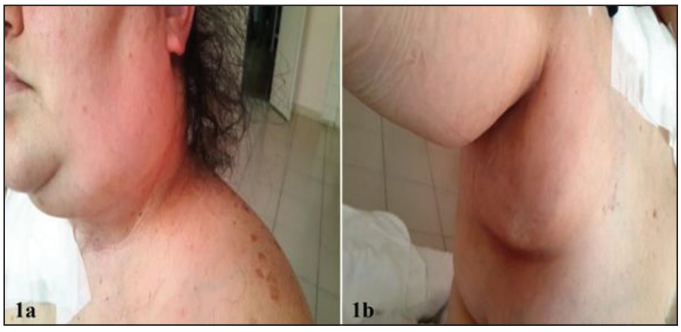

Figure 1. On physical examination bulky servikal and axillary lymph nodes were detected before transplantation

■ Myeloprofilerative Disorders

P-043 Abstract Referance: 42

THE VERY RARE MAST CELL LEUKEMIA PRESENTING WITH ANASARCA EDEMA

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Mast cell leukemia represents a rare and aggressive subtype of malignant mastocytosis characterized by the presence of atypical mast cells in the peripheral blood and/or ≥ 10% of total WBC count in blood, mast cells ≥ 20% of hematopoietic cells in bone marrow aspirate.

It is usually characterized by leukemic spread of mast cells with multiple organ involvement such as the liver, peritoneum, and spleen.

Here we present an unusual case with mast cell leukemia referred to our clinic via hypervolemia and edema.

Case: A 64-years-old malepresented with shortnessof breath,abdominal discomfort and weakness Physical examination revealed rhonchi and anazarca edema . The laboratory results revealed albumin: 2,93 g/dL LDH: 268 U/L ALT: 21 creatinine: 0,92 mg/dL Total bilirubin: 0,47 mg/dL Hb : 7,9 g/dL WBC 28,69 x 10e3/uL (differential count of 54.5% monocytes, 15.5% lymphocytes) and platelet count 27 x 10e3/uL. There was an infiltration of monotypic myeloid cellss with bold-violet large granules both in the cytoplasm and the nucleus. There were no myeloblasts but this picture was alarming for mast cell neoplasias. We performed bone marrow aspiration and biopsy.The bone marrow aspirate smear showed 60% of the hematopoietic myeloid cells similar to the ones we found in the peripheral smear.

Evaluation of bone marrow biopsy revealed diffuse leukemic infiltration. These cells were widespread-to-moderate cytoplasmic expression of CD45, CD117 and mast cell tryptase was positive.(Picture 1) No pathology was detected in caryotype.

The patient was diagnosed as mast cell leukemia and cladribine protocole was initiated. He is still on follow up in remission.

Discussion: Mast cell leukemia(MCL) which is one of the rarest myeloid malignancies, presents with severe clinical symptoms but our patient was investigated for isolated monocytosis and anazarca edema with no sign of organ metastasis.

MCL was relatively rare (1%) in the previous series; the prognosis in most cases was dismal with median survival of only 2 months.

In addition to WHO systemic mastocytosis subtype, a significant and independent association between inferior survival and advanced age (P<0.0001), history of weight loss (P < 0.01), anemia (P <0.007), thrombocytopenia (P< 0.0008), hypoalbuminemia (P< 0.0008), and excess BM blasts (>5%; P<0.004) has been shown in the literature.

We suggest, therefore, patients with monocytosis and edema should be considered for mast cell leukemia.

Current therapy in systemic mastocytosis is largely palliative and directed at degranulation symptoms (e.g., pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks), symptomatic skin disease (e.g., urticaria pigmentosa) and/ or organ dysfunction from mast cell tissue infiltration (e.g., hypersplenism or pathologic fracture).

Treatment options range from observation, to symptom management (e.g., managing pruritus or diarrhea), to supportive measures (e.g., red blood cell transfusion or osteoporosis treatment), to cytoreductive therapy for debulking in the setting of aggressive, advanced, or treatment-refractory disease. In our patient we planned to performe cytoreductive treatment for his aggressive disease.

Keywords: mast cell leukemia,edema,myeloproliferative neoplasms

■ Multiple Myeloma

P-044 Abstract Referance: 20

SIMULTANEOUS MANIFESTATION OF CHRONIC MYELOMONOCYTIC LEUKEMIA AND PLASMA CELL DYSCRASIA

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Introduction: Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin.

Chronic myelomonocytic leukemia (CMML) is a malignant hematopoietic stem cell disorder with clinical and pathological features of both a myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS) and it is characterized by a peripheral blood monocytosis accompanied by bone marrow dysplasia.

Patients with MM have a significantly high risk of developing MDS, CMML, or acute myeloid leukemia (AML) compared with healthy controls.

Here we present 59-year-old man with synchronous diagnosis of both CMML and MM.

Case: A 59-year-old male patient was admitted to our center with symptoms of B and abdominal pain. Physical examination revealed massive splenomegaly and moderate hepatomegaly with skin and mucous paleness. Biochemical evaluation revealed macrocytic anemia, thrombocytopenia, monocytosis and 1300 mg/day proteinuria. The monocyte value was 5620/mm³ on the hemogram. M spike in serum protein electrophoresis, IgG / Lambda monoclonal band in serum immunoelectrophoresis, and free monoclonal lambda band in urinary immunfixation were detected. Bone marrow biopsy showed 20% in lambda monoclonal plasma cells and increase of monocyte population with erythroid dysplasia. No bone lesion involvement was observed in PET / CT. In the cytogenetic analysis, 48, XY, + 8, + 8 (4) / 46, XY (6) were observed. Based on all these findings, the patient was diagnosed with MM and CMML.

Six cycles of azacitidine treatment for CMML was administered. After treatment with azacitidine, bone marrow biopsy revealed 30-40% lambda monoclonal plasma cells and 2% monocytic cells. Serum protein electrophoresis revealed M spike. We obtained IgG/Lambda monoclonal band in serum immunoelectrophoresis, and free monoclonal lambda band in urinary immunfixation. Velcade-cyclophosphamide-dexamethasone (VCD) chemotherapy protocol for MM was started and 4 cycles were applied. After 1 month of last VCD treatment AML developed in the patient. Standart remission induction therapy was administered but he died due to the development of septic shock in the later period.

Discussion: The risk of development of AML and MDS due to cytotoxic agents in the treatment of MM is increasing. The risk of development of AML and MDS increases by 2.4 -8.1 fold even if no cytotoxic treatment is applied in MM. Simultaneous manifestation of CMML and MM are very rare. When we made a literature review, we encountered only one case. Lenalidomide would be another treatment option for both CMML and MM. Clinical trials with combination therapy of lenalidomide and azacitidine for myeloid neoplasies and plasma cell dyscrasias have been reported which includes %44 with complete response.

Keywords: Multiple myeloma, Chronic myelomonocytic leukemia

■ Stem Cell Transplantation

P-045 Abstract Referance: 15

CNS TOXOPLASMOSIS IN HAPLOIDENTICAL BONE MARROW TRANSPLANT RECIPIENT: CASE REPORT OF SUCCESSFUL TREATMENT

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Central nervous system (CNS) toxoplasmosis is a rare and frequently fatal complication of stem cell transplantation (SCT). Definitive diagnosis of this infection requires detection of Toxoplasma gondii in histologic sections. Since biopsy of the brain is associated with serious risks, the diagnosis based on neuroradiologic imaging, positive serologic tests and typical lesions, which resolve after appropriate therapy. Polymerase chain reaction (PCR) of cerebrospinal fluid and blood is sensitive and specific non-invasive methods for detection.

Case report: In our 27-year-old patient with diagnosis of the Hodgkin's lymphoma after three lines of chemotherapy, autologous SCT and anti CD 30 antibody treatment, refractory disease is pointed. Haploidentical SCT had been performed. In pre transplant phase because of serological positivity for Toxoplasma gondii he had been treated with antibiotics therapy until negativity of finding. He also received post transplant prophylaxis. Three months after transplant procedure patient presented with tremor and pain of arms, thereafter clinical status rapidly got worse until quadriplegia. Magnetic resonance imaging (MRI) of brain and cervical spine pointed numerous cerebral hemispheres and cervical spinal cord lesions. Biopsy of the lesions was associated with high risks. MRI lesions match to toxoplasma infection, PCR showed positive signal for Toxoplasma gondii in CSF. Therapy approach was pyrimethamine and sulfadiazin. After 6 months of treatment patient, MRI of involved area showed complete resolution of lesions, with significant improvement of patient clinical state. After we stopped antibiotic therapy he had recidivism of Toxoplasmosis, but retreatment with the same antibiotics resolved disease again. We continued prophylactic treatment with sulfadiasin and clindamicin, his findings and status are stable two years after haploidentical SCT.

Conclusion: CNS toxoplasmosis is a rare complication of BMT. Beside adequate antibiotic treatment, absence of immunosuppressive treatment and graft-versus-host disease in our patient at the time toxoplasmosis developed were probably major contributors to the favorable outcome.

Keywords: CNS toxoplasmosis, Hodgkin lymphoma, haploidentical SCT

■ Other

P-046 Abstract Referance: 80

ROSAI-DORFMAN DISEASE DIAGNOSED WITH THE NASAL CAVITY INVOLVEMENT: CASE REPORT

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Introduction: Rosai-Dorfman Disease (RDD) is a rare disease with unknown histiocyte origin. The clinical course of the disease has a wide range from spontaneous remission to vital organ involvement leading to morbidity and mortality. RDD is frequently involves the head and neck region. It is frequently seen in childhood and young adulthood. Extranodal involvement is seen in 43% of all cases. Head and neck involvements are observed in 22% of the patients. In this article, the clinical follow-up of a young male patient with a diagnosis of RDD involving the nasal cavity is presented.

Case Report: A 43-year-old male patient was admitted to the otorhinolaryngology clinic with left sided nasal obstruction for about 7 months. Otorhinolaryngology examination revealed a 25 cc mass formation in the left nasal passage. The mass was excised. The patient was referred to our clinic after the pathology result reported as RDD. His physical examination revealed left submandibular semimobil, painless, non-fluctuating lymphadenopathy and 1 cm palpable splenomegaly. There were no significant findings in laboratory tests. At this stage, systemic screening was performed for visceral and nodal involvement. The neck, thorax, abdomen CT imaging was performed. In CT results; multiple lymph nodes with oval configuration in both submandibular and submental regions and splenomegaly (140 mm) were observed. Because of complete removal of the mass and lack of pathological lymphadenopathy and visceral involvement, it was decided that the patient did not require treatment and clinical follow-up was appropriate.

Discussion: RDD usually occurs in the first two decades with massive painless bilateral cervical lymphadenopathy. The etiology is not fully known. It is characterized by leukocytosis, elevated erythrocyte sedimentation rate, fever and polyclonal hypergammaglobulinemia. Diagnosis of the disease is made by histological examination of the biopsy materials taken from the lymph nodes or the involved organs. In the microscopy, the normal organization of the lymph gland is disrupted. Lymph sinuses have a large number of lymphocytes, plasma cells and histiocytes with large vesicular nuclei and clear cytoplasm with neutral lipid. Most of these histiocytes have a large number of intact lymphocytes, red blood cells and few plasma cells in their cytoplasm. This feature is called "emperipolesis" and it's pathognomonic for RDD. The clinical course of the disease varies according to the affected area. After diagnosis, the involvement areas of the disease should be evaluated. The majority of cases show a benign course and do not require treatment. Those with extranodal disease affecting vital organs and life-threatening nodal disease require treatment.

Conclusion: Patients described in the literature are usually patients with a large mass in the neck. In our patient, an involvement originating from the nasal cavity and affecting the nasal passage was observed. Therefore, RDD should be kept in mind in the differential diagnosis of head and neck masses. We would like to emphasize the role of RDD in the differential diagnosis of head and neck lesions since early diagnosis will affect the management of the disease in patients with visceral involvement.

Keywords: Rosai-Dorfman Disease

■ Non-Hodgkin's Lymphoma

P-047 Abstract Referance: 26

INDIVIDUALIZED MANAGEMENT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER: CASE REPORT

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Introduction: Post-transplant lymphoproliferative disorder (PTLD), is seen in allogeneic hematopoietic stem cell and more commonly in solid organ transplantation. Risk is increased with increased immune suppression. Early lesions like infectious mononucleosis, polymorphic PTLD and more monoclonal monomorphic PTLD are subtypes. All the subtypes need different management options. Herein we aimed to present our management approach in a case with monomorphic PTLD after renal transplantation.

Case: Forty-two year old male admitted to our clinic with inguinal lumps. He had no complaints of fever, night sweats or weight loss. He had mechanical aortic valve replacement at 22 year old age and renal transplantation at 35 year old age. He also had an operation for papillary thyroid carcinoma. He was using warfarin and clopidogrel and also was heavily immune suppressed (prednisolon, mycophenolate mofetil and sirolimus). Computed tomographies of neck-chest and abdomen revealed 3 cm diameter pathological inguinal lymphadenopathies and incidentally discovered superior vena cava thrombosis and hypersensitivity pneumonitis. Excisional lymph node biopsy was consistent with CD 10, CD20 and bcl-6 positive monomorphic PTLD with Grade 1-2 Follicular Lymphoma. Positron Emission Tomography scan was done and left inguinal and left iliac lymph nodes had increased metabolic activity. Lymphoma involvement was not seen in bone marrow aspiration and biopsy. Radiation oncologists were consulted for possible local radiotherapy option. They recommended not performing radiotherapy as involved nodes were very close to transplanted kidney. Ebstein-Barr viral load was negative. Nephrologists were consulted and de-escalation of immune suppression was planned. mycophenolate mofetil was stopped. It was decided to wait for response to reduced immune suppression and give immunotherapy or chemo-immunotherapy in case of progression.

Conclusion: Our case was monomorphic PTLD with Grade 1-2 Follicular Lymphoma histological subtype. Bone marrow aspiration and biopsy was recommended in Follicular Lymphoma in order to confirm early stage, so we performed it. Diffuse bcl-6 positivity is associated with poor response to reduction in immune suppression. Radiotherapy was not a good choice for our patient due to localization of the involved nodes. Our case had much comorbidity, so we decided to give a chance to wait a response to reduced immune suppression. Clinicians also should not forget that there were no studies showing overall survival differences between different treatment modalities in Follicular Lymphoma.

Keywords: Follicular Lymphoma, Post-transplant Lymphoproliferative Disorder

■ Acute Myeloid Leukemia

P-048 Abstract Referance: 110

EFFICACY OF GEMTUZUMAB OZOGAMICIN IN TREATING ISOLATED EXTRAMEDULLARY RELAPSED AML EVEN AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Gemtuzumab Ozogamicin (GO) is approved by FDA in the treatment of Relapsed/Refractory AML, but its efficacy in treating isolated extramedullary relapse is not well defined. Here we present a case, who relapsed with extramedullary skin lesions, even after allogeneic hematopoietic stem cell transplantation and responded to the treatment of GO.

Case Report: 40-years-old woman admitted to our outpatient clinic with pain in her joints and redness in her back and stomach. She was diagnosed with CD33-positive Acute Myeloid Leukemia according to the immunophenotyping of bone marrow blasts. Idarubicin and ARA-C (7+3) combination initiated as a frontline induction therapy and morphological remission was achieved after the first cycle of induction. After the first cycle of consolidation chemotherapy with high dose ARA-C she has relapsed with skin myeloid sarcomas and diffuse bone marrow infiltration. Soon after the relapsing disease she was put on to ida-flag salvage chemotherapy and she responded well with the disappearance of skin lesions and morphological complete remission of bone marrow. After achieving response, an allogeneic stem cell transplantation (HSCT) was applied from her sibling donor with a myeloablative conditioning. Unfortunately patient had a relapsing extramedullary disease with reappearance of skin lesions even with an ongoing acute skin gvhd (Figures 1 and 2) soon after allogeneic HSCT. Bone marrow biopsy revealed no increase in blast count.

We have decided to initiate a novel targetted therapy to control the extramedullary disease. As her blasts infiltrating the skin were universally CD 33 positive we considered to put her on GO therapy with the approval obtained from health authority. GO was applied according to the dosage approved by FDA for relapsing disease. After the first cycle of GO she had a rapid disappearance of all skin lesions just complicated with a febrile neutropenic episode and re-activation of CMV infection which was easily controlled with Gancyclovir.

She is still in remission regarding both skin lesions and bone marrow after the first cycle of GO.

Conclusion: Our case demonstrated that GO can also be considered as a therapeutic approach in AML patients who relapses with isolated extra-medullary sarcomas even after allogeneic HSCT.

Keywords: Gemtuzumab Ozogamicin (GO) , Acute Myeloid Leukemia, Extramedullary relapse

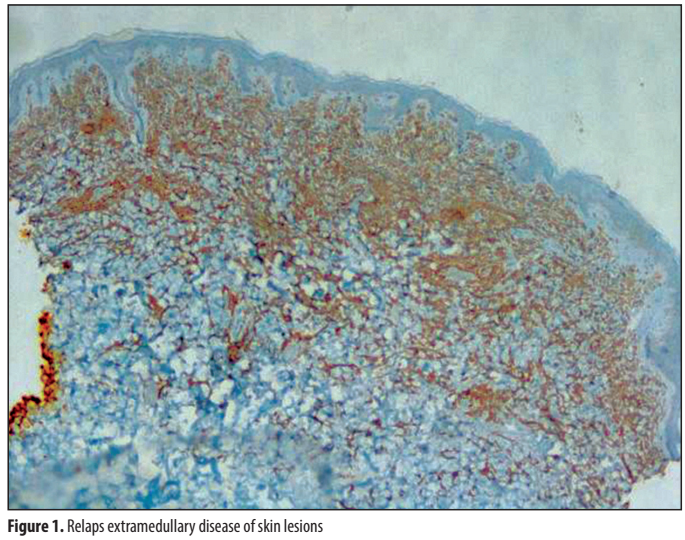

Figure 1. Relaps extramedullary disease of skin lesions

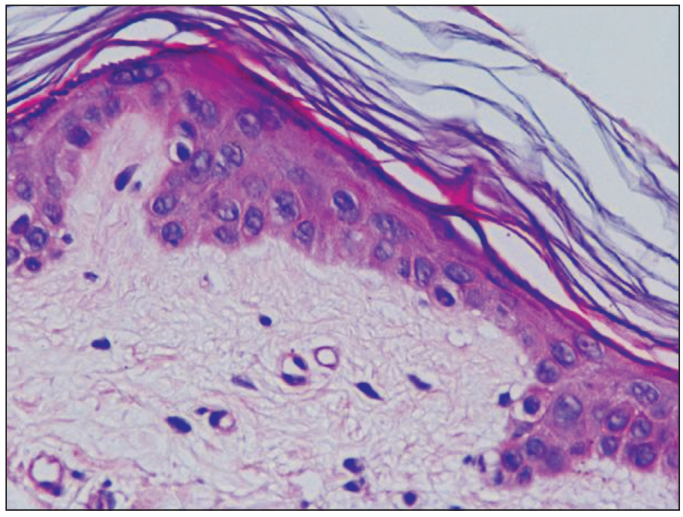

Figure 2. Skin GVHD

■ Other

P-049 Abstract Referance: 118

EVALUATION OF SYRIAN REFUGEE CHILDREN WITH HEMATOLOGIC CANCERS BETWEEN 2016-2018 : SINGLE CENTER EXPERIENCE

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Turkey is the leading country among the countries that accept Syrian refugees. We surveyed the demographic data,treatment and the outcome of the refugee children with leukemia and lymphoma that were treated in our clinic between 2016-2018. There were 28 patients; 25 boys and 3 girls. Median age was 94 months (min 24mos-max 194 mos). Of the twelve children who were diagnosed with leukemia one had AML , three had T cell leukemia, three had pre-B cell ALL, five had B cell leukemia. Sixteen children had lymphoma; eight of them were Hodgkin's lymphoma and the other eight were non-Hodgkin lymphoma. One patient with non-Hodgkin lymphoma progressed despite therapy. Eighteen patients were alive, five patents died and five were lost to follow up.

Keywords: refugee children,leukemia,lymphoma

■ Myeloprofilerative Disorders

P-050 Abstract Referance: 92

CO-OCCURRENCE OF MULTIPLE THROMBOPHILIC FACTORS WITH A POPLITEAL ARTERY EMBOLISM HISTORY: A CASE REPORT

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Factor V Leiden mutation is the most common cause of hereditary thrombophilia. Co-occurence of prothrombin gene mutation, MTHFR C677T and Factor V Leiden mutation is a rare condition. Prefibrotic myelofibrosis (pre-PMF) is a distinct entity among chronic myeloproliferative neoplasm defined by the revised 2016 WHO classification. Although clinical features of pre-PMF patients is heterogeneous, the incidence of thrombotic events is similar to essential thrombosis.

A 37-year-old male patient was admitted to the hematology outpatient clinic with leukocytosis, polycythemia and thrombocytosis without any complaints. He had a history of right popliteal artery embolectomy in 2009 and ischemic, cyanotic changes and amputation in his right toes. He also had a 20 pack-year smoking history. There was no specific trait in his family history. The patient was examined for thrombophilia during the period of popliteal arterial thrombosis, and Factor V Leiden heterozygous, prothrombin G20210A heterozygous and MTHFR C677T heterozygous mutations were determined. On examination, only w 4 cm palpable splenomegaly (SM)was found. In his blood test: WBC: 20.200 uL, hemoglobin:18.7 g/dL, platelet : 688.000 uL were showed, his biochemical parameters were normal. Antiphospholipid syndrome and systemic lupus erythematosus antibodies were not revealed. The patient's liver structure were normal; the diameter of the portal vein was considered to be within normal limits(10 mm) and the spleen size was increased (164 mm) in his portal doppler USG. The patients was considered as myeloproliferative disease due to SM and JAK2V617F mutation positivity .He was diagnosed with pre-PMF as a result of bone marrow biopsy and described as a low risk (0 points) patient by DIPSS plus score. Besides he had leukocytosis, thrombocytosis, SM and a history of thrombosis, Hydroxyurea 500 mg/day was added to the current acetylsalicylic acid treatment. Phlebotomy was performed at regular intervals. He was advised to quit smoking. The patient does not have a newly developed history of thrombosis and is in a clinically stable condition.

We have found it worthy of presenting our case because there is no case previously reported in literature with 4 thrombophilic markers (Factor V Leiden heterozygous, prothrombin G20210A heterozygous, MTHFR C677T heterozygous and JAK2V617 mutation) involved together. We believe that thrombophilia should be approached with a wider perspective , especially in patients with atypical thrombosis, and that the JAK2V617F mutation should be screened as a thrombotic marker in addition to hereditary thrombophilic factors. The presence of multiple thrombophilic risk factors not only determines the increased risk of thrombosis but also change the treatment approach.

Keywords: Factor V Leiden Mutation, Prefibrotic Myelofibrosis, Hereditary Thrombophilia

■ Other

P-051 Abstract Referance: 63

A CASE OF APLASTIC ANEMIA AFTER SHORT-TERM ISOTRETINOIN USE

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Isotretinoin is an effective treatment that is widely used in acne treatment. There are various side effects affecting many systems.We would like to present a case of aplastic anemia after short-term isotretinoin use.

A 20 year old female patient had been using isotretinoin tablets for acneiform lesions on her face for a month. She was referred to our hematology outpatient clinic because his blood values were low during routine controls. The patient did not have a known chronic disease and was not taking any medication other than isotretinoin tablet. There was no addiction to alcohol or cigaret or any other substance. Hemogram values were found to be normal before the initiation of the drug. About 1 month after taking the drug in the laboratory; white blood cell 0,87x 10^3 /µL neutrophil 0,39x10^3 hemoglobin 7,2 g/dl and platelets:31x10^3 /µL. Peripheral smear was compatible to the hemogram and there was no atypical cell. Tests on the patient's etiology of pancytopenia; serum level of LDH, BUN, creatinine, cyanocobalamin, folic acid were normal. The patient's procalcitonin and CRP levels were normal. There was no feature in the detailed viral serology (in the hepatitis panel, toxoplasma, rubella, CMV, herpes virus type1 and type 2,EBV and parvovirus infections). Brucella IgM and IgG were negative. Antinuclear antibody and ds dna were negative. Peripheral lymphadenopathy and splenomegaly were not detected in physical examination. Abdominal, neck and superficial ultrasonography confirmed the physical examination and no lymphadenopathy

or splenomegaly was detected.For the etiology bone marrow aspiration and biopsy were performed. Bone marrow aspiration was hypocellular by age. No blast or other atypical cells found in bone marrow smear. The patient's bone marrow biopsy was consistent with aplastic anemia.The patient was hospitalized in our hematology clinic and followed-up.The medication he had used was discontinued.

Oral isotretinoin has been used in the treatment of severe acne for more than 25 years. The use of isotretinoin is becoming increasingly widespread, however, several case reports are presented which are not previously reported on the side effects and new studies are being carried out. Depending on the use of isotretinoin in the literature; Side effects such as anemia, lymphadenopathy, neutropenia, thrombocytopenia have been reported but hematological parameters generally do not show any deterioration in the studies. There was no data about the development of aplastic anemia due to isotretinoin use when the literature was reviewed.

Severe aplastic anemia is a life-threatening hematological disease characterized by suppression of bone marrow. The diagnosis is made in the context of pancytopenia associated with a permanent hypocellular cellular marrow without major dysplastic symptoms or marrow fibrosis. The treatment includes patients having anti-thymocyte globulins and cyclosporin or immunosuppressive therapy with allogeneic stem cell transplantation, in particular a donor.

In our case, it was seen that aplastic anemia may be possible due to the use of isotretinoin when Naranjo adverse drug reaction scale is applied. Chloramphenicol is one of the best known drugs to cause hematologic dyscarrosia. Although the cause of chloramphenicol-related aplastic anemia has been described in the literature, we believe that more studies are needed to explain the development of isotretinoin-induced aplastic anemia.

Keywords: Pancytopenia, aplastic anemia, isotretinoin

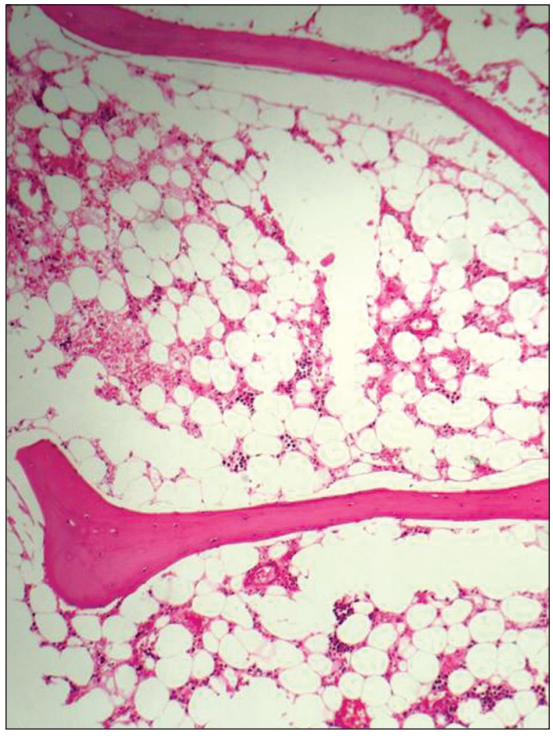

Figure 1. Bone marrow biopsy section

■ Non-Hodgkin's Lymphoma

P-052 Abstract Referance: 76

PRIMARY INVOLVEMENT OF THE BREAST IN DIFFUSE LARGE B-CELL LYMPHOMA: TWO CASE PRESENTATIONS AND REVIEW OF THE LITERATURE

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Introduction: Diffuse large B-cell lymphoma (DLBCL); is an aggressive lymphoma of B cell origin, which constitutes 50% of all non-hodgkin lymphomas (NHL). Lymph node excisional biopsy is the gold standard in the diagnosis. DLBCL, which is characterized by rapidly developing lymphadenopathy (LAP), is frequently associated with the involvement of extranodal organs such as central nervous system (CNS), gastrointestinal tract (GIS), kidneys and lung. However, primary involvement of the breast in DLBCL, are quite rare. In this presentation, we report 2 cases that were diagnosed with primary involvement of breast in DLBCL with the opinion that they would contribute to the literature

Case 1: A 66-year-old female patient with a known history of diabetes mellitus, hypertension and heart failure, was referred to our hospital with a mass in the upper quadrant of the left breast when magnetic resonance imaging was performed. In the computed tomography (CT) images, a mass lesion (87x42 mm) with irregular borders was found in the left breast retromammarian area. The tru-cut biopsy of this mass was reported as DLBCL which myc and bcl-2 negative, bcl-6 positive, and a Ki-67 score of 90%. PET-CT images showed elevated metabolic involvement of soft tissue mass defined in the proximity of the pectoral muscles and in left axillary, interpectoral, retropektoral, internal mammarian lymph nodes. Due to the lack of involvement in bone marrow biopsy, the patient was accepted as stage II E and IPI score was considered as 1. Because of the patient's comorbidities and poor performance, it was decided to give him R-CHOP treatment instead of R-EPOCH. The patient received 8 cycles of R-CHOP treatment and radiotherapy. Prophylactic intrathecal chemotherapy was given. At the end of the treatments, the patient received the complete response (CR) in the PET-CT scan and the patient is still under follow-up in the second year after CR.

Case 2: A 63-year-old male patient with known HT and hypothyroidism was diagnosed with DLBCL as a result of tru-cut biopsy from the mass detected in the left chest. Ki-67 score of tumor is 80%, myc negative; bcl-2 and bcl-6 were positive. In the CT images of the patient, periferic LAP was not detected. Bone marrow biopsy revealed disease involvement and the patient was accepted as Stage 4 E.The patient's IPI score was evaluated as 2. 6 cycles of R-EPOCH chemotheraphy regimen were received with prophylactic intrathecal chemotherapy. Complete response was obtained after PET-CT imaging at the end of treatment. In order to perform autologous stem cell transplantation if patients will have relapse, stem cells were successfully collected by mobilization with Endoxan + GCSF protocol.Follow-up of the patient at the 8th month following the treatment is continued under complete response.

Discussion: DLBCL is an aggressive NHL and in some cases, extranodal involvement can also be seen. Although especially CNS, GIS, pulmonary and renal involvement are detected, it is rarely seen primary breast tissue involvement and can be diagnosed with breast biopsy.

Result: Although primary breast DLBCL cases are rare, it should be kept in mind in the differential diagnosis to avoid unnecessary mastectomy and axillary lymph node dissections.These two case presentations show that; breast DBBHL is should be included in the differential diagnosis of breast malignancies and it can be seen in both sexes and can be treated successfully with early diagnosis.

Keywords: breast, lymphoma, rare

■ Stem Cell Transplantation

P-053 Abstract Referance: 153

SUCCESSFUL TREATMENT OF GRAFT FAILURE WITH SECOND ALLOGENEIC STEM CELL TRANSPLANTATION WITHOUT CONDITIONING REGIMEN

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Here we report a case of secondary graft failure that was effectively treated with second allogeneic hematopoetic stem cell transplantation (Allo-HSCT). A 49-year-old female patient with Philadephia-positive acute lymphoblastic leukemia obtained first complete remission with BFM protocol and subsequently underwent unrelated allogeneic bone marrow transplantation (BMT). After confirming successful engraftment and achieving complete remission with incomplete blood count recovery, she was subsequently followed up at an outpatient clinic. A routine test performed by day 80 after BMT revealed the presence of pancytopenia. A bone marrow aspirate did not reveal any evidence of disease relapse or hemophagocytic syndrome but demonstrated hematopoietic insufficiency. Donor chimerism also declined over time; thus, the patient was diagnosed with secondary graft failure. Supportive treatment, including granulocyte-colony stimulating factor, eltrombopag and blood transfusion, failed to improve the blood parameters. The patient developed Gram-negative sepsis and invasive fungal infection. After CRP has started to decline and the patient's general condition has improved, we performed a second Allo-HSCT without conditioning regimen on day 120 after BMT (CD34+ cells: 3.45×106/kg). Consequently, the blood cell count improved promptly and dramatically without adverse events.

Keywords: allogeneic hematopoetic stem cell transplantation, Philadephia-positive acute lymphoblastic leukemia, graft failure

■ Non-Hodgkin's Lymphoma

P-054 Abstract Referance: 75

PRIMARY THYROID MARGINAL ZONE LYMPHOMA CASE REPORT

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Introduction: Marginal zone lymphomas (MZL) are low-grade (indolen) lymphomas that classified among non-hodgkin lymphomas (NHL). It is seen in the 3rd frequency among the NHLs, and it is more common in women than in men. The average age is 60 years. MZL has 3 subtypes. Extranodal MZL, splenic MZL and nodal MZL. Extranodal MZL constitutes 65% of MZL and is most commonly seen in the stomach, but it can also be seen in the eye, brain, breast, intestine, skin, bladder, kidney, salivary glands. Primary thyroid MZL is an extremely rare extranodal MZL. We concluded that MZL cases with primary thyroid involvement are rare and may contribute to the literature

Case Report: A 49-year-old female patient who was under follow-up for known MNG; has an USG scan and revealed a 13x13x17 mm isohypoechoic, predominantly cystic nodule with no apparent blood flow to the right lateral lobe in may 2018. Primarily parathyroid adenoma was considered and parathyroid scintigraphy confirmed that no evidence of parathyroid adenoma. Posterior localized focal activity involvement in the left inferior lobe of the thyroid gland was detected in the SPECT screening. Fine needle aspiration biopsy (FNAB) was performed but resulted in nondiagnostic. In June 2018, right thyroid lobectomy + bilateral inferior parathyroidectomy + left central region exploration was performed. The pathology results were reported as low Ki-67, negative Bcl-2, low grade B cell lymphoma, compatible with MZL. PET-CT was performed on the patient who with no B symptoms such as fever and night sweats. PET-CT revealed pathological involvement in the left lobe of the thyroid gland and left lobectomy was performed too. Postoperative pathology results were reported as chronic lymphocytic thyroiditis consistent with hashimato thyroiditis. Bone marrow biopsy revealed no lymphoma. Patient was accepted as stage 1E. The evaluation was made according to the GELF / BNLI criteria and the patient was planned to be followed up without any treatment. The patient is being followed up without treatment for 5 months from the diagnosis.

Conclusion and discussion: In primary thyroid lymphomas, which usually constitute only 2% of all thyroid malignancies, usually as NHL, women are 4 times more risky than men and the average age is between 65-75. In primary thyroid lymphomas, extranodal MZL is at the 2nd place with a rate of 30% and it is frequently associated with hashimoto thyroiditis which is considered to be one of the most important risk factors for the development of all thyroid lymphomas. In more than 90% of patients who were diagnosed with thyroid lymphoma, have the fast growing goiter which is the main symptom however as seen in this case, slow-growing thyroid nodules in the follow-up of hashimoto thyroiditis are among the rare symptoms. As a result, primary thyroid lymphomas are rare; it can also occur in the background of hashimoto thyroiditis. Therefore, it should be kept in mind that in the presence of slow-growing thyroid nodules as well as accompanying indolen lymphoma. On the other hand, Hashimoto association in primary thyroid lymphomas also suggests that autoimmunity may have an effect on lymphoma development.

Keywords: thyroid, lymphoma

■ Other

P-055 Abstract Referance: 126

A CASE OF HL WITH A RARE EXTRANODAL INVOLVEMENT OF HODGKIN LYMPHOMA (HL) WITH LIVER INVOLVEMENT AND RESPONSE AFTER TREATMENT

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Introduction: Classical Hodgkin lymphoma is a malignant disease of lymphoid tissue, often derived from germinal centered B cells. Its specific cellular structure and immunotypic properties are characterized by the presence of Reed-Sternberg cells. The annual incidence of hodgkin lymphoma is 2-3 / 100.000 and it is observed more frequently in men than in women (1.4 / 1). 11% of all lymphomas constitute. The disease has a bimodal distribution, 15-34 and above 60 years of age.

Case: A 61-year-old female patient was admitted to our hospital with complaints of weakness, loss of appetite, weight loss and fever for 3 months. LDH: 1311U / L, AST;: 316U / L, ALT: 138U / L, ALP: 1150U / L; GGT: 293U / L; T.BIL: 3.4mg / dl,D.bil:2,4 mg/dl.

In the abdominal section of the abdomen bt 2 cm hypodense lesion in the liver segment 4, 17 mm LAP in the portal hilus, a few LAPs in the spleen hilus 19 * 29 mm in size,multiple paraaortic in the parakaval LAPs, in the thorax bt mediastinal Multiple LAPs were detected ,and 14 mm LAP in the right axilla. In the abdomen usg of the patient with multiple LAPs, hypoechoic metastatic mass in multiple number and size lesions in the parenchyma of the liver were detected.During the follow-up period, liver enzyme elevation continued increasing bilirubin levels (t.bilirubin 17.94 mg / dl, d .bilirubin14.42 mg / dl) In order to reduce increasing bilirubin levels of the patient made excessive day to day plasmapheresis.Minimal regression of the knowledge after plasmapheresis.Classic HL from the right axillar 1.5 cm LAP obtained from trucut bx.

Reduced Bleomycin-Vinblastine-Dakarbazine (BVD) to the patient with elevated liver enzyme and bilirubin levels.In the follow-up, adriamycin was added to the treatment of ABVD and 6 cycles were completed.After 6 cycles of ABVD, liver enzymes and biliubin levels were completely normal.

Discussion: This case is uncommon in the literature, however, because of the improvement in liver enzymes and bilirubins after 6 cycles of ABVD, and as a result of complete recovery, Classical HL considers liver involvement.

Conclusion: It should be kept in mind that HL liver involvement may be present in patients with weakness, lack of appetite, weight loss and fever, lymphadenopathy and plasmapheresis response with elevated liver enzyme and bilirubin**.**

Keywords: Hodgkin lymphoma

■ Non-Hodgkin's Lymphoma

P-056 Abstract Referance: 111

PERIPHERAL T-CELL LYMPHOMA IN A CHILD WITH PULMONARY INVOLVEMENT

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Introduction: Peripheral T-cell lymphoma (PTCL) is rare in pediatric patients and is associated with worse outcome compared with other pediatric non-Hodgkin lymphomas. pulmonary non-Hodgkin's lymphoma is a rare diagnosis. Most of the cases originate from B cell lineage and arise from mucosa associated lymphoid tissue of the bronchus.Few cases of pulmonary T-cell lymphoma have been reportedWe report here on an rare case of pulmonary peripheral T-cell lymphoma not otherwise specified (PTCLN), and we present the CT and Radiation therapy for oncological emergencies (airway obstructıons).

Case Presentation: A 8-year-old man was hospitalized on Octomber, 2018, for an lower respiratory tract infection and weakness, shortness of breath. Physical examination was; no hepatosplenomegaly or lymphadenopathy was noted. Hematologic studies, including complete blood counts and marrow biopsy, were normal. Blood chemistries were unremarkable except for slightly elevated serum lactic dehydrogenase. Abdominal and cervical tomography normal.The contrast enhanced chest CT scan revealed variable sized masses in the right upper lobe and and both lower lobes, big mediastenal mases and the masses displayed central necrosis . A small fluid collection was seen in the left hemithorax. .(Figure 1, 2) A CT-guided percutaneous transthoracic needle biopsy (PTNB) was done for the mass in the left lower lobe. Pathological diagnosis was primary pulmonary T-cell precursor lymphoblastic lymphoma.Patıent received external beam radiotherapy 400 Gy / day in 2 fractions total 800 Gy with 3D planning tools. Patient continuing chemotheraphy

Discussion: PTCLs have been the"poor step-child"of the diseases we refer to aslymphomas. The aggressive PTCLs were lumped in clinical trials withthe aggressive B-cell lymphomas. PTCLs are uncommon and heterogeneous malignant lymphoproliferative disorders that originate from post-thymic (peripheral) T cells or mature natural killer (NK) cells. PTCL seem to be somewhat less radiosensitive than the aggressive B-cell lymphomas , and higher radiation doses may be needed, although still lower than for most solid tumours.Our patient has got superior vena cava syndrome and airway obstructıons. We recieved high doses radiation therapy. Results ; Peripheral T-cell lymphoma (PTCL) is rare in pediatric patients. Because histopathological findings and staging of the disease are necessary for diagnosis and treatment plans, we should carefully perform strategic examinations with the knowledge of this rare malignant disease.

Keywords: Peripheral T-cell lymphoma , pulmonary ,Child

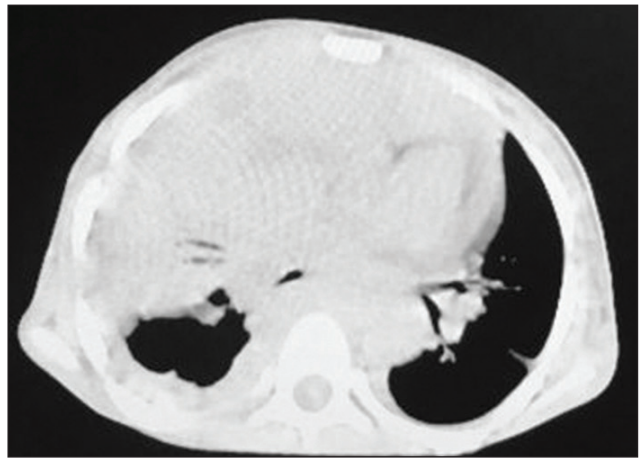

Figure 1. CT scan revealed variable sized masses in the right upper lobe and and both lower lobes, big mediastenal mases and the masses displayed central necrosis

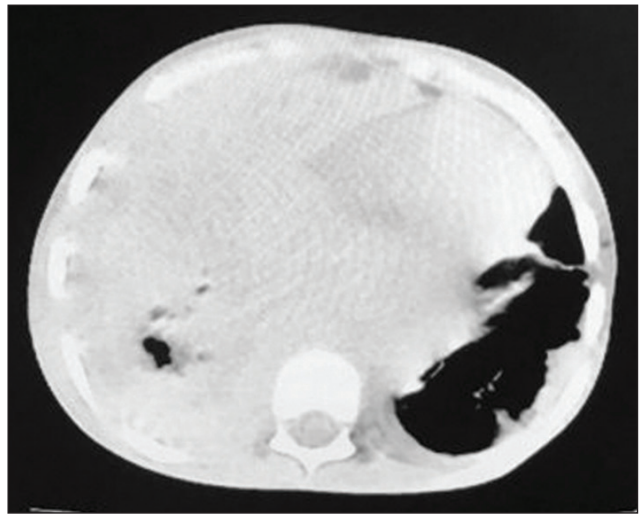

Figure 2. CT scan revealed variable sized masses in the right upper lobe and and both lower lobes, big mediastenal mases and the masses displayed central necrosis

■ Multiple Myeloma

P-057 Abstract Referance: 96

HEMATURIA AND HEMATOCHEZIA; COULD IT BE THE FIRST ADMISSION TO A CASE OF MULTIPLE MYELOMA?

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Introduction: Multiple myeloma (MM) is a monoclonal plasma cell disease accounting for about 10% of hematological malignancies.The most common causes of admission are anemia (%73) and bone pain (58%).Rarely,bleeding resulted by hemostatic abnormalities due to high serum paraproteinemia may also be the first reason for admission.We present a case diagnosed as MM, who was admitted initially with hematochezia and hematuria.

Case:A 69-year-old male patient was admitted to the emergency department in November 2018 with lower abdominal tenderness,macroscopic hematuria and hematochezia.

Radical prostatectomy was performed in 2007 and in 2014 he receieved 72 Gy RT for relapse disease. In December 2017 prostate specific membrane antigen (PSMA)-PET revealed, multiple lytic lesions in bones. Also MRI revealed 25% height loss in the sacral and lumbar vertebrae.With suspicion

of metastasis he was ordered six courses of docetaxel and zolandronic acid by radiation oncology.

In September 2018,PSMA-PET showed progression with additionally lytic characteristics in new areas.Upon this,abirateron and prednisolone were started in medical oncology,when PSA was 0.003.

When admitted to our emergency room,sonographically there was no ectasia/dilatation in the renal collecting system.Laboratory test results were shown in Table 1.Because of acute postrenal/renal injury and hematuria the patient has been hospitalized.The nephrologist indicated an emergency hemodialysis.Macroscopic hematuria regressed after bladder irrigation. Urine culture was sterile.

Simultaneously the patient underwent colonoscopy due to rectal bleeding,in which giant solitary rectal ulcers were observed.

The patient, whose anemia and thrombocytopenia progressed,had in routine examination: Albumin:2.3g/dL, total protein:9.2 g/dL; M protein in serum protein electrophoresis:3.7g/dL(Figure 1). Monoclonality of IgG Kappa was in immunofixation electrophoresis (Table 1).

The biopsy showed hypercellular bone marrow containing 80% IgG kappa monoclonal plasma cells.CyBorD protocol was started to the patient with MM.The patient did not need routine hemodialysis.

In his second course he developed hematuria,which we considered to be secondary to cyclophosphamide and therefore protocol was changed to VRD(bortezomib-lenalidomide and dexamethazone).

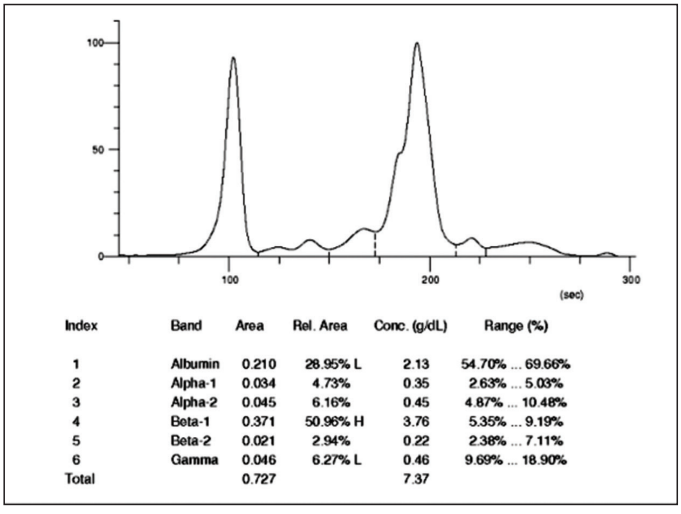
After the second cure with VRD:(Table 1)(Figure 2)

As a result of bone marrow biopsy,the plasma cell ratio was <10% and the patient was directed to autologous stem cell transplantation.

Discussion:MM is associated with bleeding diathesis in about 15% of patients. In our case, aPTT and PT were initially and latterly normal.Thrombocytopenia was not enough to explain spontaneous gross bleeding.Because of the recrren radiotherapyprotocoles ,radiation-related hemorrhagic cystitis was also considered in the differential diagnosis.Gross hematuria after the second course with CyBorD was thought to be associated with cyclophosphamide and hematuria did not recur after the treatment was changed to VRD.He has been referred to autologous stem cell transplantation without complication.

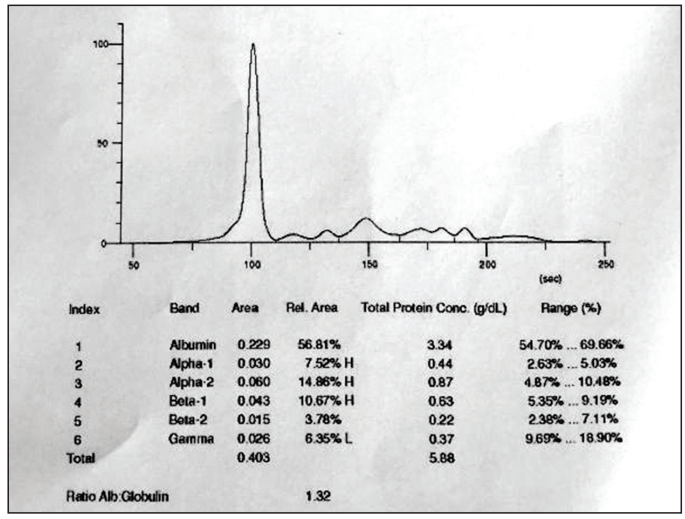
Here we would like to memorize the different spectrum of clinical features for plasma cell neoplasias,presenting with bleeding either from gastrointestinal or urinary system.We should remember the possibility of co-existing malignancies and/or genetical predisposition for malignancies after the first diagnosis in elderly patients.

Keywords: multiple myeloma, hematuria, lytic bone lesions



Index	Band	Area	Rel. Area	Conc. (g/dL)	Range (%)
1	Albumin	0.210	28.95% L	2.13	54.70% ... 69.66%
2	Alpha-1	0.034	4.73%	0.35	2.63% ... 5.03%
3	Alpha-2	0.045	6.16%	0.45	4.87% ... 10.48%
4	Beta-1	0.371	50.96% H	3.76	5.35% ... 9.19%
5	Beta-2	0.021	2.94%	0.22	2.38% ... 7.11%
6	Gamma	0.046	6.27% L	0.46	9.69% ... 18.90%
Total		0.727		7.37	

Figure 1. Serum protein electrophoresis at admission with monoclonal band in the beta region



Index	Band	Area	Rel. Area	Total Protein Conc. (g/dL)	Range (%)
1	Albumin	0.229	56.81%	3.34	54.70% ... 69.66%
2	Alpha-1	0.030	7.52% H	0.44	2.63% ... 5.03%
3	Alpha-2	0.060	14.86% H	0.87	4.87% ... 10.48%
4	Beta-1	0.043	10.67% H	0.63	5.35% ... 9.19%
5	Beta-2	0.015	3.78%	0.22	2.38% ... 7.11%
6	Gamma	0.026	6.35% L	0.37	9.69% ... 18.90%
Total		0.403		5.88	
Ratio Alb:Globulin			1.32		

Figure 2. Serum protein electrophoresis-the second cure with VRD

Table 1.

	Reference values	*Initial*	*Postchemotherapy*
Hemoglobin (g / dL)	12,9-15,9	7,1	10,7
Leukocytes (10e3/uL)	3,7–10.1	5,9	6,9
Platelets (×109/L)	155-366	75	47
Activated partial thromboplastin time (sec)	31	32,2	30
Prothrombin time (PT) (sec)	11,6	13,2	12,9
Fibrinogen (mg/dL)	200-400	363	385
Urea (mg/dL)	10-50	199	68
Creatinine (mg/dL)	0,7-1,2	12,3	1,07
Calcemia (mg/dL)	8,6-10,6	7,1	7,2
Lactate dehydrogenase (U/L)	135-248	246	204
Albumin (g/dL)	3,5-5,2	2,3	3,6
Total Protein (g/dL)	6,4-8,3	9,2	6,1
AST/ALT (U/L)	0-50	21/16	21/49
M protein (g/L)	0,30-0,74	3,7	0,58
Serum free kappa/lambda light chain(g/L)	1,7-3,7/0,9-2,1	5,45/0,63	1,58/0,48
Urine Immunofixation kappa/lamda light chain(mg/L)	0,012-32,71/<4.9	955,8/6,1	410/6,1

■ Chronic Lymphocytic Leukemia

P-058 Abstract Referance: 147

ATYPICAL PRESENTATION OF MYCOBACTERIUM TUBERCULOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: The main cause of hospitalization in CLL patients is infections, mainly pulmonary and urinary. The causes of infections in CLL patients is multifactorial including immunosuppression mediated by the disease itself as well as the drugs used to treat the disease. Patients with CLL have defects mainly in humoral immunity characterized by defective immunoglobulin synthesis. Here we describe a CLL patient who is followed up without specific therapy and presented with tuberculous peritonitis.

Patient: A 67-year-old male patient with the diagnosis of RAI Stage 1 CLL who had been followed up without any treatment was admitted to hospital with fever, abdominal pain and fatigue. His complete blood count revealed a WBC of 38700 x10^3/uL, consisting of %90 lymphocytes. Hb level was 9,8 g/dl and platelet count was 291000 x10^3/uL . His biochemistry findings were consisted with Lactate Dehydrogenase 219 U/L, Protein/Albumin 6,1/2,7 mg/dl , AST/ALT 265/191 U/L, ALP/GGT 214/157 U/L, Urea/Cre 54/1,0 mg/dl. He had an elevated ESR (104 mm/hr) and CRP (322 mg/L). The patient did not have a past medical history of tuberculosis. He did not report any recent tbc infection in the family. His physical examination showed an elevated body temperature and ascites which was confirmed by an ultrasound exam. Computerized tomography of the abdomen revealed enlarged lymph nodes (paraaortic, hepatogastric, hepatoduodenal, paraceliac, parailiac, pararectal, retrocrural, epicardial areas and at the hilus of the spleen) and a thickened omentum. Ascetic fluid was exudative and cytological exam showed rare atypical cells but no real sign of malignancy. Polymerase chain reaction performed on ascitic fluid sample for Mycobacterium Tuberculosis was negative. However, omentum biopsy showed granuloma formations with necrosis and EZN stain detected bacilli in the necrotic zones. With these findings the patient was diagnosed as tuberculous peritonitis and anti-tbc therapy was started with 4-drug regimen (Isoniazid, Rifampin, Ethambutol and Pyrazinamide). After the start of therapy, the patient's symptoms quickly started to relieve. He has been on anti-tbc treatment for 4 months without symptoms and his ascites also resolved significantly.

Conclusion: Patients with CLL may experience a variety of infections due to profound immunosuppression. Tuberculosis should be considered in any CLL patient who has fever of unknown origin and atypical presentations. Sometimes, molecular investigation of the ascetic fluid may fail to demonstrate the bacillus DNA and a tissue biopsy may be required for definitive diagnosis.

Keywords: Chronic Lymphocytic Leukemia, CLL, TB, Mycobacterium Tuberculosis, Peritonitis, Ascites

■ Other

P-059 Abstract Referance: 114

WHAT IS THE BEST TREATMENT OPTION IN A LYMPHOMA PATIENT WITH CARDIAC THROMBUS: THROMBOLYTIC THERAPY OR SURGERY?

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Introduction: The basis for the strong association between cancer and trombosis is a well known issue. Primary mediastinal large B-cell lymphoma (PMBCL) is the most common type of B cell lymphoma leading to thrombosis. Some risk factors may potantiate the development of thromboemboli such as central venous catheters (CVC). Catheter-related right arterial thromboiss (CRAT) is a rare but potentially life-threatining complication of CVC.

Case : A 32-year old woman with PMBCL and on chemotherapy(R-EPOCH) through an-indwelling catheter was referred for echocardiograpy due to dyspnea and tachikardia at the end of the fourth cycle. Echocardiograpy revealed 27 X28mm and 17X14mm in diameter, mobile thrombus. Thorax CT also supports .Shown in the Picture(pic 1)

Treatment: This mass was removed by videoassisted surgery without any complications. The patient has been on LMWH and antiaggregan therapy for 6 months.

Conclusion: Minimally invasive surgery and anticoagulation is a safe alternative option when compared to thrombolitic therapy. The patient is in methobolic complete remission at the end of one year without any comorbidity.

Keywords: lymphoma, cardiac thrombus, surgery

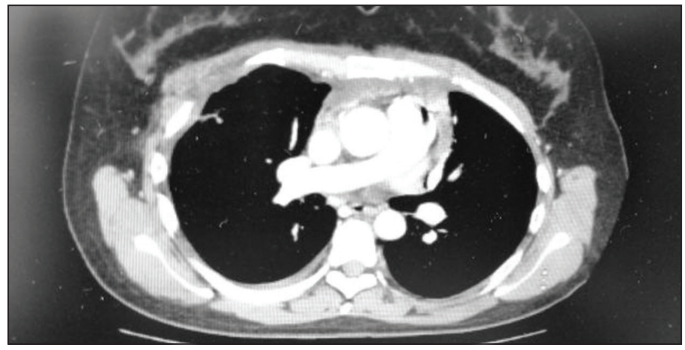

Figure 1. Cardiac thrombus

■ Other

P-060 Abstract Referance: 71

COEXISTENCE OF INTRAABDOMINAL AND INTRATHORACIC MASS DUE TO EXTRAMEDULLARY HEMATOPOIESIS IN A PATIENT WITH BETA THALASSEMIA INTERMEDIA

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Extramedullary hematopoiesis is an uncommon condition characterized by the formation of blood cells outside the bone marrow as a compensatory process in several hematological diseases such as thalassemia. EMH is common in non-transfusion-dependent thalassemia patients. In patients with thalassemia intermedia, the incidence of EMH increases up to 20% while the incidence is below 1% in patients with multiple blood transfusion thalassemia major. The most common sites of EMH are liver and spleen, Less frequently the retroperitoneal, and mediastinal regions may be involved. We report a 48-year-old woman with beta-thalassemia intermedia who coexistence of intra-abdominal and intrathoracic extramedullary hematopoietic masses due to poor clinical follow-up. Imaging workup showed intrathoracic and intra abdominal masses. The extramedullary hematopoietic focus was confirmed by biopsy from the thoracic mass. Radiotherapy planned for extramedullary masses. The patient refused radiotherapy treatment. Hydroxyurea was started. This case raises the question of whether or not blood transfusion can be performed in some patients with non-transfusion-dependent beta thalassemia intermedia. We want to emphasize the importance of blood transfusion replacement in case of need and close clinical follow-up in patients with beta thalassemia intermedia by presenting a patient who developed multiple extramedullary hematopoietic foci.

Keywords: extramedullary hematopoiesis, thalassemia, intrathoracic and intraabdominal mass, blood transfusion

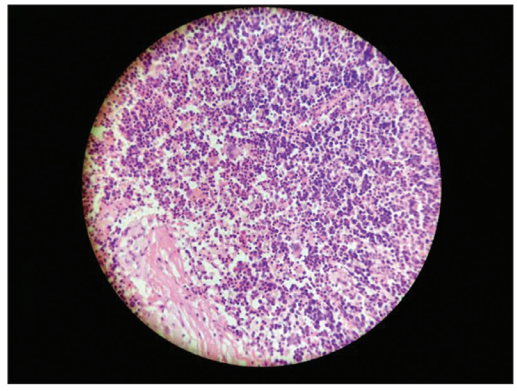

Figure 1. An extramedullary hematopoetic focus. This micrograph shows megakaryocytes and the other hematopoietic cells (HE × 100)

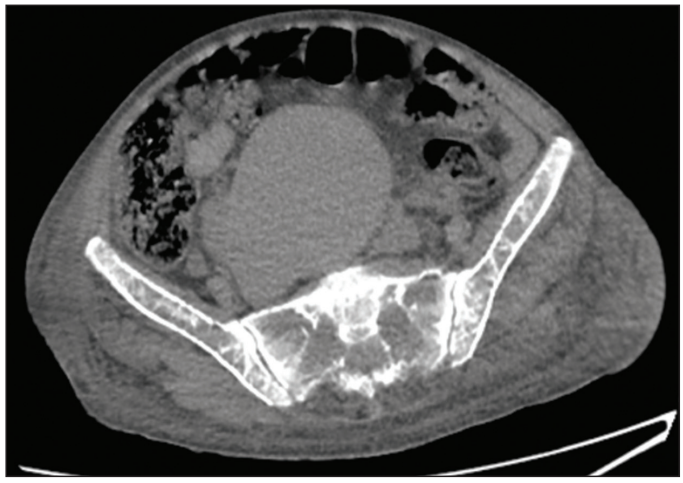

Figure 2. Abdominal computed tomography shows a mass of 155 x 85 mm in the abdomen.

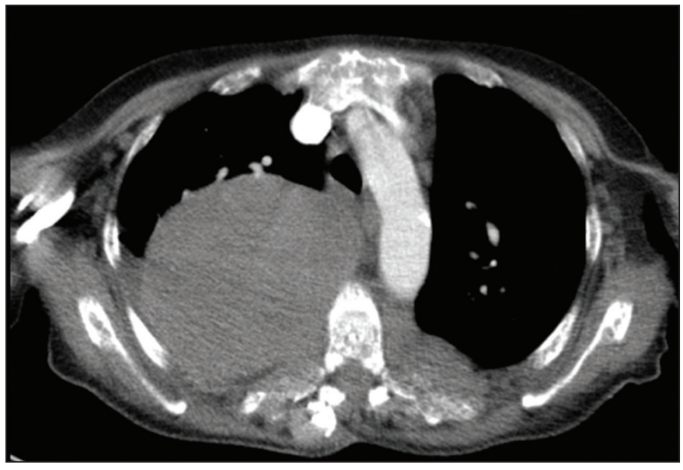

Figure 3. Thoracic computed tomography shows homogeneous mass with anterior-posterior diameter of approximately 100 mm and a lateral diameter of 110 mm in the right thoracic region.

■ Chronic Myeloid Leukemia

P-061 Abstract Referance: 70

SUCCESSFUL TREATMENT OF A CHRONIC MYELOID LEUKEMIA PATIENT WITH INTRACRANIAL HEMORRHAGE

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Introduction: Bleeding and thrombosis are frequent complications in myeloproliferative disorders (MPD) and are associated with severe organ damage and a high mortality.A patient with CML who has a bleeding complication will be presented.

Case report: 33 years old male patient was refferred to our clinic as leucocytosis on complete blood count 8 years ago. Bone marrow aspiration biopsy was performed that reported as hypercellular bone marrow compatible with myeloproliferative neoplasia with showing an increase basophils and megakaryocytes. Bone marrow examination showed a positive BCR-ABL/t(9;22)(q34;q11) chromosomal translocation detected by FISH and RT-PCR and he was diagnosed as chronic myeloid leukemia (CML) in the chronic phase (CP).

Imatinib therapy was started as 1x400 milligram.After about 6 years of regular follow-up, the patient has not come to visit for the last 1 year. The patient was brought to the emergency clinic 1 month ago by his relatives with syncope and a change in consciousness.it was learned that the patient did not use the treatment regularly. The brain MR showed focal intracerebral hemorrhage of the frontal, temporal, and parietal regions . On CBC, haemoglobuine 6.7 mg/dl ,leukocyte 409.000 neutrophile 353.000 and thrombocyte 140.000. The differential counts tested in our hospital were blasts 2%, promyelocytes 5%, myelocytes 15.5%, metamyelocytes 8.5%, bands 14.5%, segments 40%, eosinophils 2%, basophils 4%, lymphocytes 7%, and monocytes 1.5%. dasatinib was started as 2x70 mg, hydroxyurea 2x1000 mg. Leukocyte apheresis was performed.Emergency surgery was not performed by the neurosurgeon. He was followed up in the intensive care unit. it was observed that the intracerebral hematomas resolved in the control computerized tomography of the patient 1 week later . Patient's consciousness and orientation improved .The patient was discharged with a 1x100 mg dasatinib treatment.

Discussion: Hyperleukocytosis is associated with an early morbidity and mortality due to potential complications, including intracranial haemorrhage, pulmonary leukostasis syndrome, and tumour lysis syndrome. Leukostasis can affect every organ or system, symptoms generally arise from the involvement of pulmonary and cerebral microvasculature, and most early deaths are due to the intracerebral haemorrhages. Although complications of leukostasis-associated haemorrhage are common in acute leukemia and chronic myeloid leukemia accelerated and blastic phase, they can be observed in the chronic phase.It should be kept in mind that haemorraghe may develop without thrombocytopenia on patients with leukocytosis.Early leukocyte apheresis and cytotoxic treatment can be life saving for these patients.

Keywords: Chronic, myeloid, leukemia

■ Non-Hodgkin's Lymphoma

P-062 Abstract Referance: 77

ILEUM INVOLVEMENT IN DIFFUSE LARGE B-CELL LYMPHOMA: AN ATYPICAL EXTRANODAL PRESENTATION

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Introduction: Diffuse large B-cell lymphoma (DBBHL) is an agressive lymphoma which is originated from B cell lymphocytes. Although DBBHL usually presents as lymphadenopathy (LAP), the involvement of extranodal organs can also be seen. The most common areas of extranodal disease are stomach, skin, small intestine and tonsil. In this report, we wanted to present our case who was diagnosed with DBBHL from ileum.

Case: A 56-year-old male patient was admitted to the emergency department with nausea, vomiting, abdominal pain and jaundice. In the examinations of the patient who had no stool discharge for 3 days, elevation of cholestasis enzymes, air fluid levels on the abdominal X-ray of the abdomen, and 8x10 cm mass in the mesentery of the abdominal CT were detected. He was operated for ileus. Intraoperative examination showed that the mass originated from the small intestine mesentery and invaded the surrounding tissues and superior mesenteric artery. The mass was accepted as unresectable. Palliative operation was completed and wedge biopsy was performed for diagnostic purposes. Pathology result was reported as DBBHL. KI 67 was detected 80%. PET-CT for staging showed increased FDG involvement in the neck, bilateral axillary, mediastinal, hilar, intraabdominal, pelvic, inguinal lymph nodes, consistent with lymphoma infiltration. Bone marrow biopsy revealed no lymphoma infiltration. There was no atypical cell in the cerebrospinal fluid in the patient who underwent lumbar puncture. Patient was diagnosed as stage 3EB and was evaluated as medium-high risk. The IPI score was calculated as 3. As the patient had stage III EB and the IPI score was 3, prophylactic intrathecal chemotherapy (methotrexate + ARA-C + dexamethasone) was planned in each cure with R-EPOCH (rituximab + etoposide + vincristine + adriamycin + cyclophosphamide + prednisolone) chemotherapy regimen. In the evaluation of the disease after the third cycles of chemotherapy, significant regression was detected and treatment continued.

After the fifth cure, the patient developed LAP in the left inguinal region. Lymph node excisional biopsy was performed considering the disease progression and the pathology result was reported as DBBHL. R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) chemotherapy regimen was planned as rescue chemotherapy because of refractory disease. Also autologous bone marrow transplantation was planned if full remission can be achieved. The patient is currently taking the first course of R-DHAP chemotherapy.

Discussion: DBBHL is the most common lymphoid malignancy in adults. Although these high-grade lymphomas usually show aggressive course, but they are also curable malignancies. Extranodal involvement is also common in this disease with rapidly developing LAP. It should be kept in mind that lymphomas should be considered in the differential diagnosis of intraabdominal masses and may be aggressive.

Keywords: extranodal, ileum, lymphoma

■ Non-Hodgkin's Lymphoma

P-063 Abstract Referance: 115

ANAPLASTIC LARGE T CELL LYMPHOMA ARISING FROM CASTLEMAN DISEASE IN A PEDIATRIC PATIENT: CASE REPORT

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A nonclonal lymphoproliferative disorder, Castleman disease is not a malignant condition, and is very rare in childhood. These condition is usually a great mimic of both benign and malignant abnormalities, because of its diverse manifestations and ability to affect any body region. But also an association with concurrent or subsequent malignancy may occur in CD. In this case report, we describe a pediatric case developing anaplastic large cell lymphoma three years after diagnosis of a hyalin vascular type unicentric Castleman's disease.

Case Report: A 11 years old healthy female was admitted with a painless right axillar mass. At presentation she had no major health complaints or disease history and has been in good general condition. On the physical examination, there was right axillar lymphadenopathy. It was firm, nontender, mobile and was of 3x2 cm in its maximum diameter. Clinically there was no palpable lymph node enlargement in any of the various lymph node sites. In addition, she had no significant abnormalities detected by blood tests, included complete blood count, C-reactive protein, erythrocyte sedimentation rate, serum biochemical analysis, serum viral analysis . Ultrasonography of the right axillar region confirmed the adenopathy of 32x18 mm diameter. A chest computed tomography scan revealed that the paratracheal lymph nodes sized 1 cm in diameter. An excisional biopsy of the axillary lymph node showed morphological features suggestive of hyaline vascular type of CD. Serological test for HIV was negative in this patient. The patient received no further treatment and remained under follow-up care with no signs of recurrence for three years after her operation. After three years she admitted to our clinic because a supraclavicular mass. Physical examination revealed an adenopathy in the supraclavicular area of up to 4x3 cm in size. Complete blood count, CRP, serum biochemical and viral analysis were normal. Radiological examination of neck with ultrasound showed conglomerate nodal mass in the supraclavicular area with a round configuration of several lymph nodes (2 cm in size). Chest X-ray and abdominal ultrasound were all normal. An excisional biopsy was performed from the cervical lymph node. The pathological diagnosis was identified as anaplastic large cell lymphoma (ALK+). A staging with 18FDG-PET/CT scan showed metabolically active lymph node enlargement, especially in right supraclavicular, bilateral jugular, axillary, iliac regions, and detected 15 mm sized lymph node that abnormal high uptake in medial side of the ascending colon. Bone marrow aspiration and biopsy had no evidence of lymphoma cell infiltrate. Finally, we diagnosed our patient with stage III ALCL, associated with Castleman disease in unicentric hyaline vascular variant. She was treated with ALCL-99 protocol. She had been followed up without any complications after the treatment

Result: Although Castleman disease is not a malignant condition, an association with concurrent or subsequent malignancy may occur in both types of CD. Lymphoma may have been present all along, or the CD may transform into lymphoma. This occurs most often with the multicentric/ PC variant, and is exceptionally rare in unicentric/ HV variant in general, and in childhood CD in particular. A regular medical surveillance is necessary in patients with Castleman's disease, because they are at a high risk for the development of malignant lymphomas.

Keywords: Anaplastic Large T cell Lymphoma, Castleman Disease, childhood

■ Chronic Myeloid Leukemia

P-064 Abstract Referance: 141

NEUTROPHILIC LEUKOCYTOSIS IN A PATIENT WITH LIVER TRANSPLANTATION: DIAGNOSED AS CHRONIC NEUTROPHILIC LEUKEMIA; A RARE CASE REPORT

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Chronic neutrophilic leukemia (CNL) is a rare, BCR-ABL1-negative myeloproliferative neoplasia with a poor prognosis. It is characterized by peripheral neutrophilic leukocytosis, hepatosplenomegaly and hypercellular bone marrow with less than 5% myeloblast, predominant neutrophilic maturation without dysplasia. In 2016, the World Health Organization (WHO) recognized the CSF3R T618I mutation of the colony-stimulating factor 3 receptor (CSF3R) as one of the diagnostic criteria. We report a rare case of CNL with CSF3RT618I positive, 65-year-old patient with liver transplantation due to hepatocellular carcinoma (HCC).

A 65-year-old male patient with a history of liver transplantation due to HCC secondary to chronic hepatitis C was evaluated because of neutrophilic leukocytosis. On his laboratory examination; WBC: 93,7 x 10^3/uL, Neutrophil: 89 x 10^3/uL, platelet: 218 x 10^3/uL Hb: 6,1 g/dL MCV: 91,3 fL. Peripheral smear was revealed mature neutrophils as 90%, 5% metamyelocyte, 5% lymphocytes. There was no dysgranulopoiesis and blast. His bone marrow was hypercellular with granulocytic proliferation and minimal dysplasia at erytroid and myeloid series that may be due to liver cirhosis, HCC and older age. Conventional cytogenetic was normal. To exclude myeloproliferative neoplasia, we studied JAK 2 mutation and bcr/abl (p210,230) from peripheral blood by PCR. All were negative. But we started hydroxyurea due to rapidly progresive neutrophilic leukocytosis. Then CSF3R mutational analysisis by NGS was studied in another center. NGS analyisis was revealed CSF3R T618I mutation. The patient was diagnosed as CNL. At the second month of hydroxyurea, malleolus ulceration was developed while hematological remission was got. Therapy was changed to ruxolitinib. At the 6.month of ruxolitinib, the patient transformed to acute myeloid leukemia.

In case of neutrophilic leukocytosis , CNL should be in mind and CSF3R mutation should be studied also. Molecular data are very important to decide the therapeutic interventation. But unfortunately still prognosis is very poor and there is no standart therapeutic algoritym.

Keywords: Neutrophilia, chronic neutrophilic leukemia, liver transplantation, CSF3R

■ Multiple Myeloma

P-065 Abstract Referance: 108

PLASMA CELL LEUKEMIA: A CASE REPORT

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Seventy years old male patient admitted to our hospital with worsening back pain and difficulty in walking. On physical examination there was a mass settled on the back in the midline. Blood tests revealed anemia, leucocytosis and renal insufficiency. Also serum lactate dehydrogenase and uric acid levels were very high. The patient diagnosed with spontaneus tumour lysis syndrome and serum protein electrophoresis revealed monoclonal M spike. Plasma cells were detected on peripheral blood smear, and bone marrow aspiration and biopsy was performed. Bone marrow aspirate specimen showed 100% atypic plasma cell infiltration. The spinal mass was compatible with extramedullary plasmocytoma on MRI scanning and PET/CT revealed multiple extramedullary masses. The patient was diagnosed with plasma cell leukemia and PAD/VCD regimen was started concurrent with irradiation of spinal mass. During the first course of treatment the patient worsened with newly generating skin lesion on the chin and biopsy from skin revealed plasma cell infiltration. No response to treatment achieved and the patient died on the 47th day of diagnosis.

Keywords: Plasma cell leukemia, tumour lysis syndrome

■ Other

P-066 Abstract Referance: 148

AN UNUSUAL CAUSE OF SPLENOMEGALY IN A THROMBOCYTOPENIC ADULT PATIENT: NIEMANN-PICK DISEASE

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Izmir Katip Celebi University Ataturk Research and Training Hospital, Hematology Department

Introduction: Niemann-Pick disease (NPD) is a rare autosomal-recessive lysosomal storage disorder characterised by the deficiency of acid sphingomyelinase activity resulted in the accumulation of sphingomyelinase in hepatocytes, reticuloendothelial cells and neurons. Types A and B are associated with mutations in the ASM gene (*SMPD1*) while type C results from mutations in either the NPC1 and NPC2 gene. The age of presentation ranges from the neonatal period to adults over 50 years with an extreme clinical heterogeneity. Here we report an adult patient who presented with thrombocytopenia and splenomegaly and diagnosed with NPD with the typical findings of bone marrow examination.

Case: A 34-year-old female patient who was scheduled for operation due to nasal septum deviation by ENT (ear-nose-throat) department was consulted us due to thrombocytopenia. She did not have any clinical complaints and no previous medical history. Complete blood count and peripheral smear did not show any pathological findings except moderate thrombocytopenia and leukopenia (WBC:3870/mm3, Neu:2250/mm3, Hb:14.3 gr/dl, PLT:87000/mm3). All biochemical parameters and coagulation tests were normal. On physical examination spleen was not palpable but percussion of Traube's space was dull. In abdominal ultrasound, liver craniocaudal length was 160 mm and echogenicity was normal. The spleen length was approximately 200 mm, and a 30 mm accessory spleen was present. Bone marrow aspiration and biopsy were planned for the patient to clarify the current findings. In the bone marrow aspiration, significant increase in macrophages including dense basophilic granulation like sea-blue histiocytes and a number of foam-cells were noted. The appearance was consistent with the typical morphology for hereditary lysosomal storage disease, Niemann-Pick. Biopsy was also revealed hypercellular (%70) bone marrow with marked hyperplasia of histiocytes and grade 2 reticulin fibrosis. Blood samples of the patient were sent to the laboratory to measure the acid sphingomyelinase activity. It was decided to investigate the possible gene mutations as the next step. Cranial MRI and EEG were planned to evaluate the neurological involvement although the patient has normal neurological examination without any neurological complaints. HRCT and ecocardiography were also planned to evaluate the possible lung and cardiovascular involvement. The patient's investigations and follow-up are still continuing in our clinic.

Conclusion: This is an unusual case of a young adult woman with NPD with striking bone marrow findings, suggesting the diagnosis. Although sea blue histiocytes can be found in bone marrow that is rapidly turning over, typical morphological appearance of intense sea blue histiocyte infiltration suggests the diagnosis of NPD, which should be confirmed by demonstrating the enzyme deficiency and/or gene mutations. It should be kept in mind that the cause of splenomegaly may be an inherited lysosomal storage disease like NPD in an asymptomatic adult patient and may be recognized clearly from bone marrow examination.

Keywords: Niemann-Pick Disease, splenomegaly, thrombocytopenia

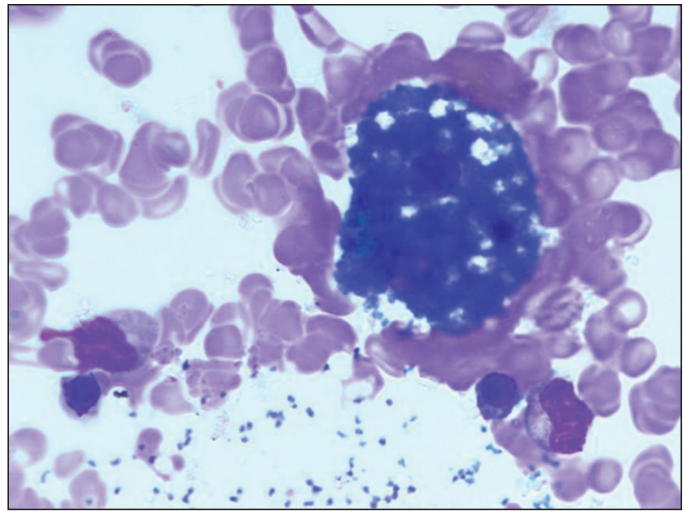

Figure 1. Sea-blue histiocytes in bone marrow aspiration

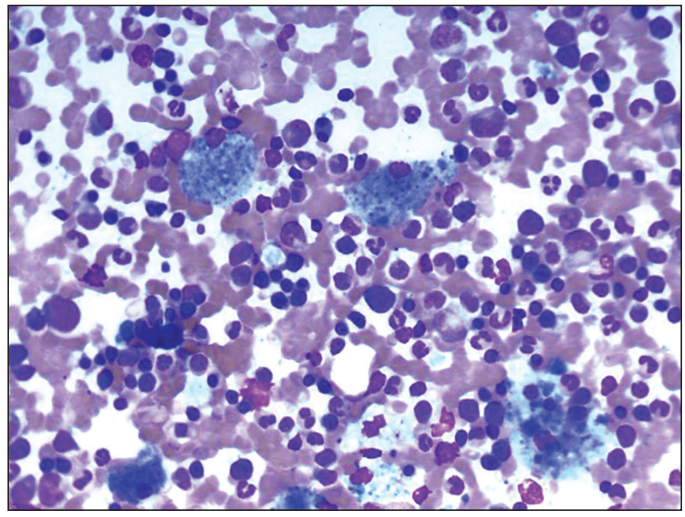

Figure 2. Sea-blue histiocytes in bone marrow aspiration

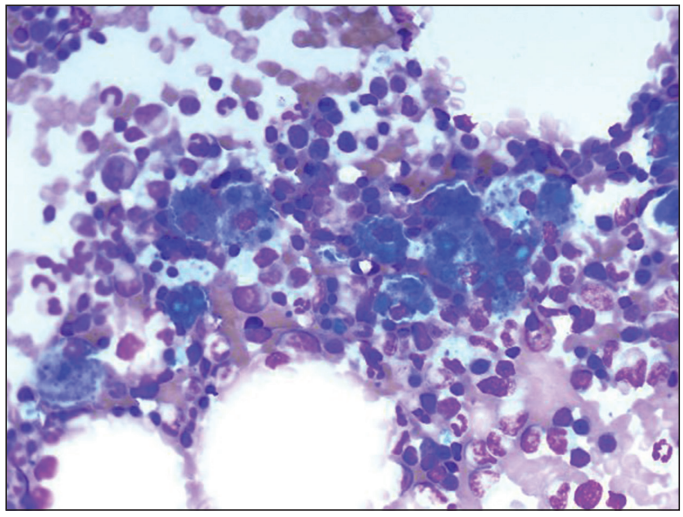

Figure 3. Sea-blue histiocytes in bone marrow aspiration

■ Multiple Myeloma

P-067 Abstract Referance: 146

SUCCESSFUL TREATMENT OF POEMS SYNDROME WITH COMBINATION BORTEZOMIB ,LENALIDOMIDE AND DEXAMETHASONE THERAPY.

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İntroduction: POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal [M] protein and skin changes) syndrome is a rare plasma cell disorder .The standard therapy for patients with POEMS syndrome is high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). But still has no standart treatment for relaps after ASCT. Combination Bortezomib ,Lenalidomide and Dexamethasone therapy is one of the treatment option for relaps patient.

Case presantions: A 47-year-old manwith history of type 2 diabetes mellitus who was admitted to the neurology department with a complaint of inability to walk ,muscle weakness erectile dysfunction. Results from electrodiagnostic studies were compatible with sensorimotor polyneuropathy with predominantly demyelinating features and severe degree of secondary axonal loss.Endocrine evaluation revealed hypothyroidism, hyperpigmentation and hypogonadism. He was diagnosed with partial empty sella syndrome in pituitary MRI. At the moment of admission, the laboratory tests displayed the presence of IgG λ monoclonal gammopathy. Bone marrow aspiration and biopsy revealed normocellular marrow with 2% plasma cells. Morphological examinations by computer tomography (CT) detected osteosclerotic bone lesions of the left femur and right iliac bone at the same time hepatosplenomegaly. This findings including polyneuropathy, monoclonal gammopathy, organomegaly, endocrinopathy, monoclonal protein and skin changes led to the diagnosis of (POEMS) syndrome. The patient was started therapy with dexamethasone and cyclophosphamide for 4 cycles followed by autologous stem-cell transplantation after Melphalan 200 mg/m2 as conditioning regimen.we obtained a hematologic partial remission. with the persistence of serum M-protein detected by immunofixation and a consistent improvement of the neuropathy with ability to walk.He was followed for 3 years as outpatient. Then he relapsed with complaints of inability to walk , loss of libido and erectil disfonction.We started Bortezomib - Lenalidomide –Dexametasone , with Len administered at a dose of 25 mg per day on 21 consecutive days of a 28-day cycle and Dex administered at 40 mg weekly, bortezomib administerd 1,3 mg/m2,together with a thromboembolism prophylaxis therapy. He has received 8 months therapy anda Within months, could walk comfortably. At last follow-up, he was well and continued improvement and haemotologic partial remission with absence of monoclonal protein (M-protein) detectable by serum and urine protein electrophoresis sPEP.

Result: There are currently no standard treatments for patients with POEMS syndrome. there are several options for treatment of POEMS syndrome including melphalan, lenalidomide. bortezomib and transplantation. ASCT eradicates the underlying plasma cell clones more completely than Lenalidomide plus Dexamethasone or Melphalan plus Dexamethasone for first-line treatment regimens(1). Novel regimens including daratumumab may become the treatment options for relaps and multıdrud resistans patients (2). We believe that Bortezomib,lenalidomide and dexamethsone combination therapy is good option for relaps POEMS, however, more research is needed to understand to define best options of thretments.

Keywords: POEMS, M protein

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