Volume 40 Issue 1 Suppl. 1 March 2023

E-ISSN: 1308-5263

Turkish Journal of Hematology

The Official Journal of the Turkish Society of Hematology

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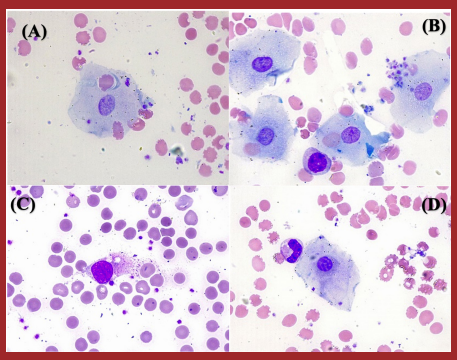
ABSTRACTS

ORAL PRESENTATIONS

POSTER PRESENTATIONS

9th International Congress on Leukemia Lymphoma Myeloma
May 12-13, 2023 • VIRTUAL CONGRESS



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Circulating Histiocytes and Hemophagocytosis in Peripheral Blood

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TURKISH JOURNAL OF HEMATOLOGY

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E-ISSN: 1308-5263

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e-Publication Date

12.05.2023

Cover Picture

Circulating Histiocytes and Hemophagocytosis in Peripheral Blood

Peripheral blood smears showing circulating histiocytes with images of hemophagocytosis affecting red blood cells and platelets (Wright-Giemsa stain, 100^{x} magnification).

International scientific journal published quarterly.

The Turkish Journal of Hematology is published by the commercial enterprise of the Turkish Society of Hematology with Decision Number 6 issued by the Society on 7 October 2008.

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AIMS AND SCOPE

The Turkish Journal of Hematology is published quarterly (March, June, September, and December) by the Turkish Society of Hematology. It is an independent, non-profit peer-reviewed international English-language periodical encompassing subjects relevant to hematology.

The Editorial Board of The Turkish Journal of Hematology adheres to the principles of the World Association of Medical Editors (WAME), International Council of Medical Journal Editors (ICMJE), Committee on Publication Ethics (COPE), Consolidated Standards of Reporting Trials (CONSORT) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

The aim of The Turkish Journal of Hematology is to publish original hematological research of the highest scientific quality and clinical relevance. Additionally, educational material, reviews on basic developments, editorial short notes, images in hematology, and letters from hematology specialists and clinicians covering their experience and comments on hematology and related medical fields as well as social subjects are published. As of December 2015, The Turkish Journal of Hematology does not accept case reports.

General practitioners interested in hematology and internal medicine specialists are among our target audience, and The Turkish Journal of Hematology aims to publish according to their needs. The Turkish Journal of Hematology is indexed, as follows:

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Publisher
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The Turkish Journal of Hematology's editors and Editorial Board members are active researchers. It is possible that they may desire to submit their manuscripts to the Turkish Journal of Hematology. This may create a conflict of interest. These manuscripts will not be evaluated by the submitting editor(s). The review process will be managed and decisions made by the Editor in Chief, who will act independently. In some situations, this process will be overseen by an outside independent expert in reviewing submissions from editors.

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TURKISH JOURNAL OF HEMATOLOGY INSTRUCTIONS FOR AUTHORS

The Turkish Journal of Hematology accepts invited review articles, research articles, brief reports, letters to the editor, and hematological images that are relevant to the scope of hematology, on the condition that they have not been previously published elsewhere. Basic science manuscripts, such as randomized, cohort, cross-sectional, and case-control studies, are given preference. All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a double-blind reviewing system. Review articles are solicited by the Editor-in-Chief. Authors wishing to submit an unsolicited review article should contact the Editor-in-Chief prior to submission in order to screen the proposed topic for relevance and priority.

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Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org/). Original manuscripts require a structured abstract. Label each section of the structured abstract with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page. Technical and other assistance should be provided on the title page.

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Original Manuscripts

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The title page should include the authors' names, degrees, and institutional/professional affiliations and a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to their institution, which is listed separately. Please provide contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

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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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(https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf).

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Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

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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.

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Abstract length: Not to exceed 150 words.

Article length: Not to exceed 1200 words.

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Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported findings/results. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

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.

Discussion: Highlight the new and important findings/results of the study and the conclusions they lead to. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

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SCIENTIFIC PROGRAM

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PROCEEDINGS

Follicular Lymphoma with Focus on Therapy in Advanced Stage Disease

Eva Kimby

Karolinska Institute, Sweden

Follicular lymphoma (FL) is a B-cell lymphoma with mostly an indolent course. Since the introduction of rituximab (R), an anti-CD20 antibody more than 20 years ago, and other new drugs, the current median overall survival (OS) often extends beyond two decades. Today, many FL patients, especially the elderly are more likely to die with, rather than from lymphoma

The biological spectrum of the disease is heterogeneous. The last update of the WHO-classification of lymphomas (WHO-HAEM5) and the International Consensus Classification (ICC) have not changed the diagnostic criteria for the main type of FL, but grading is debated as distinction between grades 1-3A is insufficiently reproducible and the underlying genetic alterations are not distinctive. The WHO-HAEM5 describes a subtype of FL with diffuse growth pattern frequently occuring in the inguinal region, mostly correspnding to the ICC provisional entity BCL2 R-negative CD23positive follicle center lymphoma. According to ICC testicular FL is also a distinct entity.

Around 80-90% of FL show a translocation t(14;18)(q32;q21), which places the B-cell leukemia/ lymphoma 2 (BCL2) oncogene under control of the Ig heavy-chain enhancer. This is no longer thought to be the primary genetic driver, as several recurrent genetic alterations are found, especially in epigenetic regulators (KMT2D, CREBBP and EZH2).

t(14;18)-negative FL often shows a high incidence of CREBBP, STAT6, TNFRSF14 mutations and deletion of 1p36, especially in limited-stage disease.

Epigenetic deregulation may reprogram also the tumour microenvironment. In FL the overall T cell profile differs from normal lymphnodes. Using mass cytometry, several subsets of intratumoral CD4+ T cells have been described, some poorly functional due to loss of co-stimulatory receptor expression. In patients with T-cell depleted tumours there is an association with inferior survival.

The clinical course of FL is variable. Some patients are asymptomatic and present with limited or low tumor burden while others show advanced stage disease at the time of diagnosis.

Risk stratification of FL patients is based on clinically defined indices (FLIPI, FLIPI-2, PRIMA-PI, and FLEX) as well as on m7-FLIPI and PRIMA 23-gene expression, the last two also incorporating biology. Positron emission tomography (PET)-based imaging using maximum standardised uptake value (SUVmax), total metabolic tumour volume (TMTV) and baseline total lesion glycolysis (TLG) can also be used as predictors of clinical outcomes.

Unfortunately there are no validated clinical indices or biomarkers to guide initial therapy. Patients with dissiminated asymptomatic low tumour burden disease is generally recommended a watch-and-wait (W&W) approach as early initiation of treatment has not shown any OS benefit. Morover, a trial comparing R with or without R-maintenance with W&W, showed that 30% of W&W patients had not needed any therapy at 10 years follow-up. R-monotherapy first-line is an alternative also for symptomatic advanced-stage disease as this delays chemotherapy and in "R-sensible" patients leads to long OS without any chemotherapy. R in combination with lenalidomide (R2) is very effective as first-line therapy, with both progression-free survival (PFS) and OS comparable to R-chemotherapy according to the RELEVANCE trial. The GALEN trial showed that obinutuzumab (O) is a good alternative to R, in combination with lenalidomide.

Most patients with symptomatic high tumor burden, according to the GELF-criteria, are still treated with R or O in combination with chemotherapy (CVP, CHOP, or bendamustine). These therapies are effective but relapses are still rather frequent and disease-free periods mostly shorten at relapse and with each new therapy. Still OS is around 80% at 10 years. Patients achieving less than complete metabolic response (CMR) to first-line therapy or showing progressive disease within 24 months from start of therapy (POD24) or with histologic transformation, have an increased risk of death due to lymphoma. The GALLIUM trial showed that O-chemotherapy extends PFS, time to next therapy (TTNT) and reduces early progression (POD24) compared to R-chemotherapy, but with no OS benefit. In a sub-analysis, bendamustine, combined with either anti-CD20 antibody, showed an improved PFS and CMR rates compared to CVP/CHOP, but with excess toxicity and mortality in bendamustine-treated patients, especially age over 70years if maintenance.

In the PRIMA trial using up-front R-chemo, mostly CHOP, R-maintenance prolongs remission with sustained benefit at 9 years follow-up, why maintenance with R is mostly recommended even if no OS advantage. In the GALLIUM trial both arms include maintenance, with more toxicity in the bendamustine arm. Specifically in patients with CR after R- or O-bendamustine maintenance is questioned (due to toxicity). In an ongooing trial PETREA, patients who are PET-negative after induction immunochemotherapy are randomised to standard maintenance for 2 years or no further therapy. PET-positive patients are randomised to standard maintenance or maintenance plus lenalidomide.

Data are lacking on the best way of sequencing therapies and relapse options are many. A non-cross resistant immunochemotherapy or R2 are often used if symptomatic relapse.

R2 is an approved second line and often used due to activity and tolerability in all age groups, and also in patients with early relapse.

Targeteting of the deregulated epigenome is an interesting concept, with tazemetostat as the first-in-class inhibitor of EZH2. In a pivotal phase 2 trial, patients with mutated tumours showed better responses, leading to licensing of the drug. However, tazemetostat has modest activity as a single agent but is well tolerated and combination therapies are under evaluation.

Immune-directed therapies are of great interest in FL and high response rates with durable responses have been shown with bispecific antibodies and CAR-T cells. Trials are ongoing also in the upfront setting (epcoritamab + R2 and mosunetuzumab + lenalidomide).

Cell-therapies will be discussed further in the next talk.

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Marginal Zone Lymphomas

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Marginal zone lymphomas (MZL) are indolent mature B-cell lymphomas with variable epidemiologic, pathologic, and clinical features. Three main subtypes described include extranodal MZL (EMZL), splenic MZL (SMZL), and nodal MZL (NMZL) [1,2].

Extranodal marginal zone lymphoma (EMZL) is a localized disease in most of the cases [3], arising in response to various infectious, autoimmune, or other inflammatory stimuli, which leads to an eventual neoplastic transformation. Typically, gastric EMZL may be related to *Helicobacter pylori,* the paradigm for the association between tumorigenesis and a chronic inflammatory stimulus. However this association has decreased over the past 20 years [4]. The sites involved may arise either from mucosa such as in stomach, intestine, lungs, thyroid, salivary gland (MALT-associated lymphoid tissue (MALT) lymphoma), or from non-mucosa sites such as meninges, skin, orbit. EMZL represents the most common MZL subtype, accounting for 50 to 70% of MZLs and 5% to 8% of all B-cell lymphomas [5-7]. SMZL represents < 2% of all lymphomas, shows a median age of 69 years at first diagnosis. Patients present with splenomegaly and bone marrow and usually blood involvements. Anemia and thrombocytopenia may be present. While splenic hilar nodes may be involved, more distant nodal disease is rare. Nodal MZL is the least common of all the subtypes of MZL, accounting for approximately 10% of MZL and <2% of all non-Hodgkin lymphomas.

Marginal zone lymphoma has a natural indolent course, with many patients surviving beyond 10 years from diagnosis[1]. However, in the approximately 20% of MZL patients who relapse or progress within 2 years, median overall survival (OS) is only 3–5 years [8,9].

The optimal treatment for MZL is not clearly standardized. At diagnosis, the need of treatment to start treatment should be considered. A pathogen-directed therapy in case of association with microbial pathogens may induced long-term control particularly in Helicobacter pylori-associated gastric EMZL. If no association has been diagnosed, the first-line treatment option will consider the type of entities (EMZL, SMZL or NMZL) and the extension of the disease. Local therapy include surgery or involved-site radiation therapy (ISRT) with a dosing between 20–30 Gy in locations such as orbit, skin, or t(11;18) negative gastric EMZL [10]. In SMZL, splenectomy should be reserve only to massive SMZL.

Systemic therapy is based on chemoimmunotherapy rituximab-based approaches for symptomatic, advanced-stage MZL, except SMZL where single agent rituximab is proposed [11]. The association Chlorambucil and rituximab has demonstrated efficacy in advanced symptomatic EMZL in a phase III trial comparing chlorambucil monotherapy or rituximab monotherapy. Complete response rate (CRR) was reported at 79% vs 63% vs 66%, and median progression – free survival (PFS) at 5 years rates of 72% vs 59% and 57%, respectively [12]. The combination of rituximab and bendamustine (BR) has been proposed for only four cycles instead of six to reduce toxicity, without detrimental effects on the outcome [13]; in this report analyzing 57 patients, the CR (CR/uCR) rate after 3 cycles was 75%, and 100% at the end of treatment (4 or 6 cycles). After a median follow-up at 82.7 months (IQ range, 75-90), the estimated PFS was 92.8% (95%CI, 81.9 – 97.2) with no difference according to primary site of disease. The chemotherapy backbone (chlorambucil or bendamustine) is chosen according to the patient's age and status with respect to fitness and organ functions, since older or frail patients receiving bendamustine-rituximab may have high rates of fatal toxic effects.

The benefit for maintenance with Rituximab after R-clb or BR in patients with MZLs is controversial with no evidence with survival benefit. In the IELSG38 where Rituximab maintenance for 2 years was evaluated after R-clb in EMZL patients in first line, 51% (95%CI, 42-61) attained a CR at the end of induction increased over the time, 60% (95%CI, 50-69) after 1 year of maintenance, and 67% (95%CI, 57-76) at the end of the second year [14]. Rituximab maintenance following induction with BR has been reported to induced a superior PFS for rituximab maintenance over observation phase 3 StiL NHL7-2008 MAINTAIN trial (104 randomized patients) (median PFS not reached vs. 92.2 months, HR 0.35, 95% CI 0.17–0.76; p = 0.008) [15]. However, in both studies, no survival benefit was observed. Novel agents, such as Bruton's tyrosine kinase inhibitors including ibrutine, zanubrutinib, lenalidomide, novel celmod agents, bispecific antibodies, CAR T-cells are currently under evaluation alone or in association.

In conclusion, access to novel therapies remains challenging for MZL. International efforts with collaborative groups based on better understanding of tumor biology, microenvironment at different anatomical sites will help with the selection of targeted treatments and up-front identification of biomarkers for early progression.

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PedAL Project

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Pediatric AML is a myeloid diseases that, despite improvements in outcome, requires intensive chemotherapy, with HSCT in selected cases (AML), resulting nowadays in overall survival rates of approximately 75-80%. However, with survival rates of at best 50% at relapse, there is still clear medical need, also because AML treatment is still associated with morbidity and treatment related mortality.

Despite the medical need, almost no new drug approvals occurred in children, although many new drugs were approved in the adult space. There are however some discrepancies between Europe and the US, as FDA approvals exist for Gemtuzumab ozogamicin (relapsed AML) and Vyxeos liposomal (for MDS and therapy-related AML) for use in children with AML.

After the Pediatric Strategy Forum on AML in 2019, and with support from the Leukemia Lymphoma Society and COG and the European AML study groups, a large international project was launched to study new drugs for pediatric AML, and to set new standards of care for 1st and 2nd relapse of AML. This project is referred to as the PedAL (Pediatric Acute leukemia) project, and is implemented in Europe by ITCC and the upfront AML groups collaborating in the EuPAL (European Pediatric Acute Leukemia) foundation, and in the AML-BFM SG. The programs aims not only at studying the safety and activity of the drugs, but aims at obtaining regulatory approval where applicable. Studies may be performed in the context of regulatory commitments of the market authorization holders, such as a PIP or PSP. Scientific advice from EMA was obtained on several topics and resulted in generating a complex clinical trial protocol with subtrials (study ITCC-101).

In this presentation, we will address several new compounds that will be studied either via PedAL or otherwise, including venetoclax, menin inhibitors, FLT3 inhibitors, CD47 inhibition, FOL1R targeting, and CD123 directed compounds. We will also briefly touch upon new developments in immunotherapy in AML, especially regarding an NK-cell engager, which will soon recruit children 12 years of age and older in the first in men phase 1 study, consistent with the FAIR (fostering age inclusive research) principle to drop the age whenever feasible. Of interest, the PedAL/EuPAL project also has resulted in a QA/QC network for MRD assessment in pediatric AML, and in a project to define ELN criteria for pediatric AML.

After the successful introduction of new molecules for ALL over the past decade, the aforementioned drugs may alter the therapeutic armamentarium for pediatric AML, and hopefully contribute to improved outcome with a better risk/benefit balance for children with newly diagnosed and relapsed AML.

Pediatric Studies with Inotuzumab Ozogamicin for B-cell Acute Lymphoblastic Leukemia

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Acute Lymphoblastic Leukemia (ALL) is a malignant disease affecting lymphoid progenitors in the bone marrow, more commonly of the B type (85%), which accumulate in the peripheral blood and extramedullary sites.[1] The estimated incidence in pediatrics is around 4 cases per 100.000 children per year, and it is more frequent among 3-5 year-old children.[1] Thanks to a risk-stratified approach based on rotational multi-agent chemotherapy blocks, the current probability of survival for a child diagnosed with ALL approaches 95% at 5 years, and ranges between 85-90% at 10 years.[2,3] These results have been achieved by refining risk group stratification leading to optimization of chemotherapy, including intrathecal chemotherapy and Hematopoietic Stem Cell Transplant (HSCT) in selected cases.[4,5] Unfortunately, 10-15% of patients relapse or are refractory (R/R), and for them the probability of surviving remained unsatisfactory over the last decades. Indeed, in these cases, the Overall Survival (OS) at 10 years is close to 50%.[6,7] Patients treated in re-induction settings are exposed to high-intensity chemotherapy and most high-risk patients consolidate with HSCT to avoid the risk of subsequent relapse.[2,3] The consequences of this approach can lead to sever adverse events including, among others, osteonecrosis, cardiovascular impairment, infertility, neurological damage, infections and sepsis.[8,9] Therefore, it is necessary to develop innovative therapies which are less toxic and more effective at inducing remission in R/R patients.

Among the new compounds that have been developed in the last decade, Inotuzumab Ozogamicin (InO) has shown a remarkable efficacy in ALL pre-clinical models.[10,11] InO is a monoclonal antibody loaded with calicheamicin and directed against CD22. Calicheamicin is a cytotoxic agent damaging the DNA and causing cell apoptosis.[10] While CD22 is a transmembrane protein involved in the downward regulation of B cell receptors signaling and expressed by 60% to >90% of B-lymphoid malignancies but not by hematopoietic stem cells, non-lymphoid cells, nor memory B cells.[12,13] Therefore, it represents a good target for treating ALL, which cells were already shown particularly sensitive to calicheamicin in both animal models and ex-vivo human models.[10,11,14]

Data from adults with R/R ALL treated with InO, such as the phase 3 INO-VATE ALL study, showed higher remission rates in the InO group compared to chemotherapy (80.7% vs 29.4%), as well as longer duration of response (median 4.6 vs 3.1 months), which led to its approval in 2017.[15] Meantime, InO was shown effective also on pediatric ALL cells in laboratory studies.[14] This evidence supported testing InO also in pediatric B cell CD22+ R/R ALL.

The first experience with InO in pediatric ALL was summarized by Bhojwani et al (2019). The study included 51 R/R children treated on a compassionate use basis and reported that 67% achieved bone marrow remission, of which 71% with Minimal Residual Disease (MRD) negativity.[16] Among the first safety concerns, hepatic toxicities, and particularly hepatic sinusoidal obstructive syndrome (SOS), played a relevant role. In the cohort reported by Bhojwani et al, 52% of patients who underwent HSCT post treatment developed SOS.[16] Another compassionate use series investigating InO in a small French population was published by Calvo et al (2022). Among the 12 R/R patients, 8 achieved remission, of which 2 with MRD negative results after cycle 1.[17]

The first registration trial testing InO as a single agent in pediatric B cell precursor CD22+ ALL, was the ITCC-059 study (EUDRA-CT 2016-000227-71) conducted in Continental Europe and Israel, sponsored by the Erasmus Medical Center in Rotterdam, and financed by Pfizer Inc. The trial enrolled 25 patients aged 1-18, refractory or with second or greater

relapse, or relapsed after HSCT, and used a rolling-6 design to define the Recommended Phase 2 Dose (RP2D). Based on the experience in adults, the treatment was fractionated in 3 doses per cycle (28 days) given on days 1, 8 and 15, with a loading dose on day one until remission. The trial tested doses from 1.4 mg/m^2/cycle (0.6 + 0.4 + 0.4, DL1) to 1.8 mg/m^2/cycle (0.8 + 0.5 + 0.5, DL2). The latter was selected as the RP2D, the same as approved per adult ALL patients. The Overall Response Rate (ORR; <5% BM blasts, with or without the recovery of platelets and absolute neutrophil count, hence CR, CRp and CRi) after course 1 was 80% (95% confidence interval (CI): 59% to 93%), at DL1 the ORR was 75% (95%CI: 43% to 95%), and at DL2 it was 85% (95%CI: 55% to 98%). Of the responders (n=20), 84% (95%CI: 60% to 97%) also achieved MRD negativity, and the 12-month OS probability was 40% (95%CI: 25% to 66%). No cases of SOS were reported while on treatment with InO, but 2 patients developed SOS after receiving further chemotherapy with methotrexate and cyclophosphamide post-InO.[18]

The phase I single agent trial was followed by two phase II trials. One in Europe, as a follow-up of the ITCC-059 study, and the other in the US, sponsored by the Children's Oncology Group (COG). Simultaneously, a phase IB cohort was opened under the umbrella of the ITCC-059 study, testing the combination of InO with chemotherapy based on vincristine, and dexamethasone as a modification of the UKALL-R3 protocol.

The results from the phase II single agent arm of the trial ITCC-059 were published in 2022. The study treated 28 patients at 1.8 mg/m^2/cycle with a median follow-up (FU) of survivors of 16 months. Among the 27 patients evaluable for response, the estimated ORR was 81.5% (95%CI: 61.9-93.7%), and 81.8% (18/22) of the responding subjects was MRD negative, hence the pre-specified response criteria were met. At 6 months, the Event-Free-Survival (EFS) probability was 55.6% (95%CI: 39.6–77.8%) and OS was 66.7% (95% CI: 51.1–87.0). At 12 months, EFS probability was 36.7% (95% CI: 22.2–60.4%) and OS probability was 55.1% (95% CI: 39.1–77.7%). Overall, 7 (25%) cases of SOS were reported, of which 6 after HSCT. Five patients experienced grade 3-4 transaminases elevation and 2 had grade 3-4 bilirubin increase. Five (17.6%) patients had infection of grade ≥3.[19]

In the American COG sponsored AALL1621 trial, InO was tested again at the RP2D of 1.8 mg/m^2/cycle (1.5 mg/m^2/cycle after remission) in 48 heavily pretreated pediatric patients. The estimated ORR was 58.3% (90% CI, 46.5 to 69.3%), and 18 of the 27 (66.7%) responders with available data was also MRD negative. Also in this trial, the risk of SOS post HSCT as consolidation was relevant, with 6 cases of SOS diagnosed among the 21 patients (28.6%) receiving HSCT post InO. Nevertheless, SOS incidence was lower than what anticipated by Bhojwani et al (2019), as also found in the ITCC-059 trial. Despite cases of transaminases elevation (max grade 3), no patients required InO dose modification for hepatic toxicity. In addition, the trial confirmed possible prolonged cytopenia (beyond day 42) among responders which in this case occurred in 1 out of 4 patients.[20]

Overall, the evidence collected by both research groups (ITCC and COG) underscored that InO as a single agent is safe and effective for pediatric R/R patients with ALL at the expenses of a potential increased risk of SOS in those consolidating with HSCT, and rare cases of delayed bone marrow regeneration. In addition, despite relatively common, the cases of transaminases elevation and bilirubin increase appeared transient and not clinically severe.

Following the studies with single agent regimens, InO was also tested in a phase I study combined with chemotherapy, in the context of the trial ITCC-059 (phase IB).[21] R/R subjects with M2 or M3 bone marrow were enrolled. Also in this case a rolling-6 design was used with the first cycle as the Dose-Limiting Toxicities (DLTs) evaluation period. InO (fractionated in 3 doses/cycle, days 1, 8, 15) was combined with vincristine 1.5 mg/m^2 (days 3, 10, 17, 24), two blocks (days 1-5 and 15-19) of dexamethasone 20 mg/m^2 (divided in 2 daily doses), and intrathecal (IT) therapy (methotrexate ± steroids and cytarabine as per local practice, days 1 and 8). After cycle 1, patients could arbitrarily receive additional combination therapy or InO as single agent at the RP2D of 1.8 mg/m^2/cycle.[21] Overall, 30 patients were treated of which 29 were evaluable for DLTs. The initial DL of InO tested was 1.1 mg/m^2/cycle. The Maximum Tolerated Dose (MTD) was already achieved as 2 DLTs occurred (SOS and transaminases elevation). With the aim to reduce liver toxicities and allow higher InO exposure, the protocol was amended to reduce dexamethasone to 10 mg/m^2/day. Post-amendment, it was possible to re-escalate up to 1.8 mg/m^2/cycle as capped per protocol. The RP2D of InO in combination with 1.5 mg/m^2 of vincristine (days 3, 10, 17, 24) and 10 mg/m^2 of dexamethasone (two 5-day blocks) was declared at 1.8 mg/m^2/cycle (followed by a 1.5 mg/m^2/cycle once in remission). Five (16.6%) patients developed SOS of which only 1 during InO treatment and 4 after subsequent HSCT. Alanine aminotransferase increase occurred in 22 cases (73.3%), of which 13 (43.3%) at grade 3-4, and 6 (20%) patients had hyperbilirubinemia, none at grade 3 or 4. Four (13.3%) patients experienced sepsis, and 3 (10%) other grade 3 infections.[22] The ORR was 76.7 % (95%CI: 57.7 to 90.1%), 15 responders (65.2%) were MRD negative by end of study treatment (preliminary data). The estimated OS probability at 6 and 12 months was 73.9% (95%CI: 58.8-92.9%) and 58.1% (95%CI: 40.5-83.4%) respectively, with a median follow-up of 11.7 months (range 1.3-23.7).[21]

Recently, an additional cohort has been opened in the ITCC-059 trial enrolling so-called very-high risk (VHR) patients. Namely, patients with first bone marrow or combined relapse B-cell ALL CD22 + with M2 or M3 marrow status and at least one of the following VHR features (based on IntReALL 2020, Eckert et al, 2021): relapse within 18 months after initial di-

agnosis or genetic mutations such as KTM2A/AF4, E2A/TCF3-PBX1 t(1;19) or E2A/TCF3-HLF t(17;19), severe hypodiploidy (<40 chromosomes), or TP53 mutation and/or deletion.[22] Preliminary response data in this population are limited to the first 13 patients enrolled, of which 10 achieved remission, and 4 were also MRD negative (unpublished data).

This combined evidence corroborate the efficacy of InO against pediatric ALL, while proving the drug tolerable also in heavily pre-treated children. The current dose recommended in pediatrics for the single agent regimen is 1.8 mg/m^2/cycle fractionated in three administrations per cycle and reduced to 1.5 mg/m^2/cycle once remission is achieved. This dose is the same as in adults and it is supported by preliminary pharmacokinetic data which underscore a similar disposition of InO in adults and children.[23]

In upcoming trials, InO will be compared to chemotherapy (UKALL -R3) in a phase III randomized trial for first relapse high-risk ALL children (NCT05748171). The M.D. Anderson Cancer Center is planning to test mini-hyper-CVD (cyclophosphamide, vincristine, and dexamethasone), intensified IT therapy, plus rituximab, InO, and blinatumomab (Pedi-cRIB) in R/I children (NCT05645718).[24] In addition, there are examples of trials testing InO in front-line. For example, in patients > 14 years, the M.D. Anderson Cancer Center is testing hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with sequential blinatumomab with or without InO (NCT02877303) in newly-diagnosed patients. Preliminary results from the latter study showed that all patients in the InO group were alive and in remission at 1 year.[25] In adults, InO is also being tested in newly diagnosed CD22+ ALL young adults (18-39 year-old) combined with chemotherapy (NCT03150693). In older patients, which do not tolerate regular ALL-directed multi-agent chemotherapy, there are attempts to develop "chemotherapy-free" regimens based on InO. Trial NCT03739814 tests InO in induction followed by blinatumomab as consolidation in patients > 60 years.[26] In pediatrics we also have examples of InO used in front-line, despite not in the induction phase which for now remains based on 3 or 4 drug induction chemotherapy regimens. The COG AALL1732 trial is testing InO added post-induction (arm III) to COG-modified BFM chemotherapy versus chemotherapy alone, for high-risk newly diagnosed ALL pediatric patients (NCT03959085) and the ALL Together group is testing InO, in a front-line setting, as additional consolidation treatment (arm R3-InO) before the maintenance chemotherapy block in intermediate-high risk (NCT04307576) patients.

Therefore, Ino, blinatumomab and CAR-T cells therapies have significantly changed the therapeutic armamentarium for ALL, and will impact significantly on current available chemotherapy regimens. InO has a high potential to be used in induction, whereas blinatumomab is more effective as consolidation regimen in the setting of minimal residual disease.

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Studies of Precision Dosing of Hematopoietic Cell Products and ATMPs

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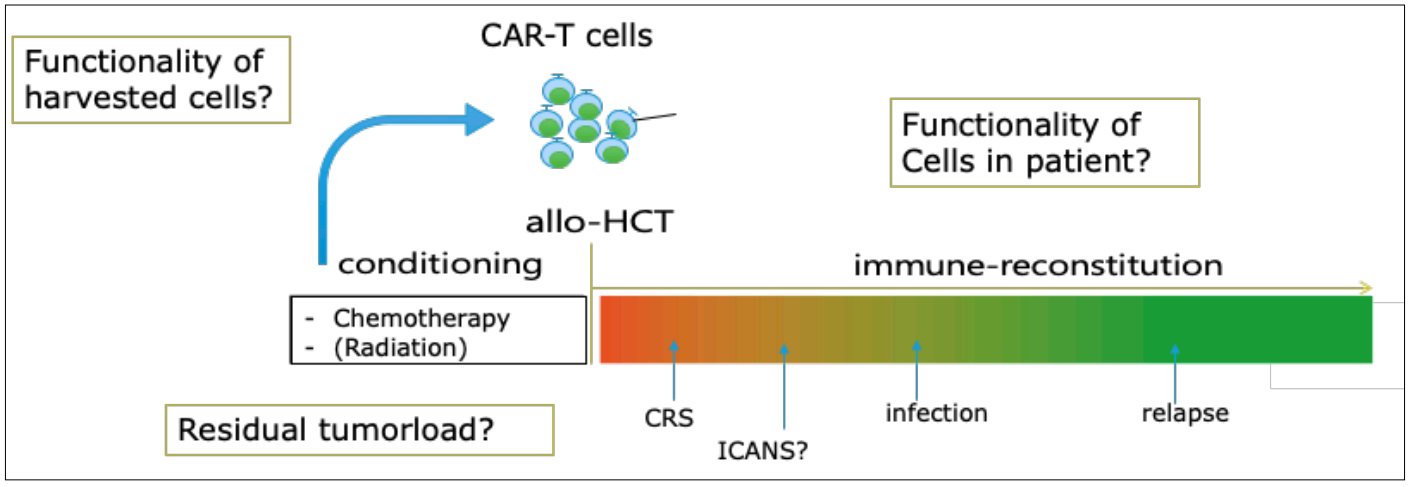
Precision dosing of cell therapy has a history in the transplant setting. Actually, in hematopoietic stem cell transplantation it has not been overt that a particular cell dose is optimal. There are minimal stem cell numbers needed for engraftment but, for instance in sibling transplant, a higher nucleated cell dose is still related to improved outcomes with no clear maximum. Only for T cell numbers it was determined that to completely eliminate the chance of early GvHD, the T cell number should be lower than 5x 10e4/kg. This T cell number is used as the maximum limit in T cell-depleted grafts, but is such a low number that it will, of course, result in a delayed immune reconstitution. On the other hand, a minimum graft T cell dose that will still give the patient a good graft versus leukemia or antiviral immunity has not been determined. However, it seems that very early on, it can already be determined whether a patient has good or poor immune reconstitution, using a CD4 > 50 within 100 days as the predictor (15). And this is not only determined by the graft content or graft type. Because what has been realized is that the precision dosing of drugs of the transplant conditioning determines immune reconstitution, the chance of complications, and survival. These drugs may even affect which organs are "conditioned", as not all drugs for instance cross the blood-brain barrier equally. Busulfan and TBI are considered superior in conditioning the brain and opening for instance microglia niches, which are needed for hematopoietic cell and gene therapy to work for leukodystrophies (19, 6). Busulfan, fludarabine, and thymoglobuline exposure during conditioning and later on, have all been shown to strongly impact hematopoietic cell transplant survival in malignant and non-malignant disease (1,4, 5,7, 11-17). In the seminar, I will go into these details.

For ATMPs, using an escalating dose design, often with 3-5x increases per dose level, minimal dose levels for effect have been determined for different cell products. However, there is no clear linear relation between CART cell dose and effect. There is a lot of interest in the apheresis product used for ATMP and more specifically the phenotypic and functional composition of the cells going in (CD4/ CD8 ratio, naïve/ memory phenotype, exhaustion marker expression etc.) (21,22). For some diseases such as B-ALL, persistence is most important, while for lymphoma peak expansion might be most important. The persistence of some products may be dependent on the expansion of the cells, or may need a treatment strategy with several re-infusions of the ATMPs. But importantly, it might actually be patient characteristics, such as pre-infusion tumorload and also the conditioning regimen exposure, that determines the expansion of the cells.

In analogy with the data from transplant, where a higher fludarabine exposure impacts immune recovery post-transplant (11,12), we studied the relation between CART cell effectivity and Fludarabine exposure. According to the Tisagenlecleucel label we condition children and young adults receiving Tisagenlecleucel with cyclophosphamide (1000 mg/m2) and fludarabine (120 mg/m2 in 4 doses). Surprisingly, we and others found that patients with a fludarabine exposure of > 14 mg*h/L, have a better outcome, with significantly higher chance of persisting B cell aplasia and lower incidence of CD19+ relapse in this pediatric and adolescent B-ALL setting (3,20). This is directly related to a better CART persistence. Based on preliminary data, we hypothesize that the conditioning chemotherapy influences the milieu to an extent that it influences the lymphopenic expansion of the CART cells.

It is therefore likely, that for any cellular ATMP, the drug product should be very well characterized. But as it is a live-expanding product, the recipient's exposure to the ATMP over time should be studied in the context of all drugs given in the procedure that can affect cell expansion and longevity. We can only optimally precision dose our drug, when we know which "buttons to press" and which "knobs to turn".



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Digital PCR and Its Future Role in CML

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Digital PCR (dPCR) is a molecular technology allowing the absolute quantification of targets, both as DNA and RNA molecules. It demonstrated to be accurate, precise and sensitive and to be able to overcome different real-time PCR (RT-qPCR) limits, in particular for the quantification of rare targets [1].

In the CML scenario, the interest among dPCR has been progressively increased in the last years asdemonstrated by the number of publications concerning this topic. dPCR has been tested in different settings, such as minimal residual disease (MRD) quantification, application for liquid biopsy and BCR-ABL1 mutations detection [2].

Very studies demonstrated the capability of dPCR to better detect BCR-ABL1 transcript when compared with RT-qPCR. This improvement has been reported as affecting the selection of patients eligible for TFR, the quantification of the two transcript types (e14a2 and e13a2) and the assessmentof the stability of the DMR [3–9].

In parallel, dPCR resulted able to identify for the first time BCR-ABL1 transcript molecules shuttled by extracellular vesicles (EVs) in patients in chronic phase and responsive to TKI therapy. This evidence open the opportunity to detect leukemic cells resident in the bone marrow and otherwisenot identifiable by conventional MRD monitoring [10].

Last but not least, dPCR has been reported as accurate and sensitive even in the detection and quantification of point mutations affecting the tyrosine kinase domain of Abelson and associated toTKI resistance [11,12].

All together, these interesting applications of dPCR in CML suggest that this technology would be largely used in the next future to support the RT-qPCR gold standard in the estimation of the MRD and in the selection of patients for TKI discontinuation. Moreover, its involvement in TKI resistant or refractory CML patients will be of pivotal importance. In parallel with the clinical applications, itsuse in CML research would be of great interest and could allow the detection and investigation of additional rare markers.

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Chronic Myeloid Leukemia Diagnosed During Pregnancy: How to Manage a Challenging Situation?

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Background Chronic myeloid leukemia (CML) diagnosed during pregnancy is a rare challenging situation for management, considering a potential teratogenicity of tyrosine kinase inhibitors (TKIs).

Aim We aimed to describe therapy and outcomes in patients (pts) with CML at onset during pregnancy.

Methods: Data were obtained both retrospectively and prospectively in the observational trial "CML pregnancy registry" supported by European LeukemiaNet (ELN).

Results: A total of 400 pregnancies in 299 CML women (including consecutive pregnancies) were collected in the period 2001 - 2022. Clinical and demographic data, therapy, pregnancy outcomes and follow-up were analyzed. CML in a chronic phase (CP) was diagnosed during pregnancy in 87 (29%) females with Me CML onset at 11 weeks gestation (range 5-38). Sixty-five (76%) pregnancies ended in childbirth, other outcomes were 18(21%) elective and 3(3%) spontaneous abortion. During pregnancy 23(35%) pts were not treated with anti-leukemic drugs , while 42 (65%) received therapy. In total 28 (43%) pts received interferon (IFN). Six pts were switched from IFN to imatinib (IM). Twenty (31%) pts received imatinib (IM) at late pregnancy: Me start was 18 week (range 16-34). Seven (11%) pts received hydroxycarbamide (HC) as monotherapy or in combination with IFN or IM. Additionally, 5(8%) pts received leucapheresis.

Sixty six children were born (one set of twins). No congenital abnormalities were reported in 64 (97%). One baby had an abdominal skin angioma (exposed to IFN in 2-3 trimester and HC in 3rd trimester). One baby born at 35 w had a patent foramen ovale (IM since 33 week). Seven newborns were of low birth weight (<2500 g), with no definite connection to therapy during pregnancy.

All 86 females received TKIs after pregnancy end: IM 70(81%)/ 2ndgeneration TKI 16(19%). With Me follow-up of 36 months (mo) (range 1 mo–17 years) 23/70(33%) pts on IM were switched to other TKI. The best overall response was at least major molecular response in 65(86%) of 75 evaluable pts with a treatment period >6 months.

No CML progression was observed during pregnancy. However, 3 pts unfortunately died 19, 24 and 119 mo after pregnancy completion, the reasons were not thought to be related to management in pregnancy: non-compliance, progression/resistance (1 case with T315/F359 mutation in the time of pre-ponatinib availability) and death after bone marrow transplantation.

Conclusions: More than 20 years of international efforts of women with CML onset during pregnancy can conclude that there is a real evidence of a normal childbirth in women diagnosed with CP CML during pregnancy. No increased rate of birth abnormalities or life threatening events was observed including cases treated with IM at late pregnancy. It is reasonable to balance the risks for both the safety of mother and infant and the efficacy of treatment. IFN can be used from 1st trimester and may be prolonged in cases of good disease control and good tolerability. IM is probably safe in 2nd- 3rd trimester considering its limited placental crossing. The use of HC has no advantages over IM and passes freely to the placenta and it may be acceptable only of an urgent cytoreduction is needed and no leucapheresis is available.

Therapy, n (%)	Pregnancy trimester		
	1st trimester, n (%)	2nd trimester, n (%)	3rd trimester, n (%)
Interferon	16 (24,5)	18 (28,0)	19 (29)
Imatinib	-	7 (11,0)	17 (27)
Interferon --> imatinib	-	6 (9,0)	1 (1,5)
Interferon and HU	1 (1,5)	1 (1,5)	2 (3,0)
Imatinib and HU	-	-	2 (3,0)
Hydroxyurea	-	1 (1,5)	1 (1,5)
Total number on therapy	**17 (26)**	**33 (51)**	**42 (65)**
No drug therapy	**48 (74)**	**32 (49)**	**23 (35)**

Figure 1. Therapy in females with CML onset during pregnancy (n=86): drugs and dosages

Therapy, n (%)	Pregnancy trimester		
	1st trimester, n (%)	2nd trimester, n (%)	3rd trimester, n (%)
Interferon	16 (24,5)	18 (28,0)	19 (29)
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Imatinib and HU	-	-	2 (3,0)
Hydroxyurea	-	1 (1,5)	1 (1,5)
Total number on therapy	**17 (26)**	**33 (51)**	**42 (65)**
No drug therapy	**48 (74)**	**32 (49)**	**23 (35)**

Figure 2. Therapy by trimester in females with CML onset during pregnancy (n=65)

Pediatric Acute Promyelocytic Leukemia

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Acute promyelocytic leukemia (APL) is characterized by the recurrent translocation t(15;17) resulting in PML-RARa. The use of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) is highly effective making this now the most curable subtype of AML. ATRA therapy was evaluated in pediatric patients enrolled on the first North American intergroup trial (INT0129), and this trial showed improved disease-free survival (DFS) for patients receiving ATRA during induction and/or maintenance therapy. The Children's Oncology Group (COG) AAML0631 trial demonstrated further improvement in cure rates with addition of ATO. Children treated on this trial received two 5-week cycles of ATO during consolidation, and this treatment included a significant reduction in cumulative anthracycline dose compared to prior historical regimens. The 2-year event-free survival (EFS) was 97% for patients with standard-risk APL and 83% for patients with high-risk APL. This use of ATO along with ATRA and traditional chemotherapy resulted in only 4% risk of relapse. The COG trial AAML1331 evaluated an ATO-ATRA chemotherapy-free regimen in children with APL similar to the regimen from the GIMEMA-AMLSG-SAL APL0406 trial for adult patients with standard risk APL. On COG AAML1331, pediatric patients with HR APL were enrolled on a treatment arm that included the anthracycline idarubicin only in induction using a ATO-ATRA based regimen without maintenance therapy. Patients with standard-risk APL had a 2-year EFS of 98% and patients with high-risk APL had a 2-year EFS of 96%. These excellent outcomes establish this approach as a preferred treatment for pediatric APL. Treatment of APL, however, is characterized by unique challenges including an increased risk of early death from coagulopathy and differentiation syndrome. Standard risk APL using a cytotoxic free ATO-ATRA induction also frequently results in hyperleukocytosis (elevated white blood cell count from blast differentiation) requiring cytoreduction. Thus, careful monitoring of these potential complications and aggressive supportive care to correct coagulopathy and treat differentiation syndrome and/or hyperleukocytosis is critical to prevent early death and ensure excellent cure rates.

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Precision Diagnostics and Minimal Residual Disease

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As European Hematology Association (EHA) president (2021-23) and given the longstanding close relationship between EHA and the Turkish Society of Hematology, culminating in partner society status in January 2024, when Elizabeth Macintyre was invited to propose an ALL session at the 9th ICLLM, she chose to showcase EWALL. The EWALL European Working group on Adult Acute Lymphoblastic was created during the European Leukemia Net (ELN) initiative and is one of our 24 EHA Specialized Working Groups (SWG). It includes the leaders of the national ALL study groups in Europe.

EWALLs Major aims are:

- Diagnostics; identification of new genetic markers, particularly to define the new ALL subgroups ETP (Early T-Precursor ALL), bcr-abl-like-ALL
- Minimal residual disease; the EWALL study group is leading in the standardization of the different methods for MRD, particularly immunophenotyping, RT-PCR, and ongoing, NGS
- Treatment and patient care of adolescents and young adults (AYA)
- Focus on the treatment and patient care in older ALL patients:
- Development of joint treatment approaches including prospective clinical trials
- Exploration of targeted therapies; EWALL is preparing in sequential studies 1st, 2nd, and 3rd generation tyrosine kinase inhibitors
- Development of targeted therapies by immunotherapy
- Development of joint meta-analyses
- Cooperation of the pharmaceutical industry for the optimal evaluation of new compounds in ALL, either in company sponsored or investigator initiated trials
- Develop guidelines and consensus recommendations for the management of ALL

Adele Fielding, co-chair of EWALL, will present the current activities of EWALL. Nicola Gökbuget will then present the new EWALL guidelines on management of Adult ALL. Elizabeth Macintyre will address evolution in diagnostic and prognostic biomarkers in ALL and the relative place of oncogenic evaluation and minimal residual disease detection (MRD) in the precision hematology era. The final presentation on precision therapy for relapsed refractory T-ALL will be given by Philippe Rousselot. Relevant references will be specified on the corresponding slides. All speakers have been requested to give short presentations, in order to leave time for a panel discussion with the audience.

EWALL-TARGET for Precision Therapy in Relapsed/Refractory T-ALL

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Depending on protocol and subtype 5-10% of T-ALL patients will be primary refractory, and 30-40% of patients will relapse. A new complete remission is attained in 20-40% of patients, but prolonged disease free survival is observed in around 10-15% of cases only.[1-4] Nelarabine is approved for R/R T-ALL in second relapses and the registration study showed a CR rate of 36%. Overall, survival was 24% at 1 year and 12% at 3 years.[5] (Figure 1). None of the major progress achieved in B-cell ALL such as monoclonal antibodies and CAR-T cells are currently available for T-ALL patients when they fail conventional chemotherapy or hematopoietic stem cell transplantation (Figure1).

The biological landscape of T-ALL is well characterized.[6-9] The immunogenic classification distinguishes immature T-cell leukemias including early T precursors (ETP), early cortical and late cortical or mature T-ALL. The 10 key recurrently mutated pathways include transcriptional regulation (91% of cases), cell cycle regulation and tumor suppression (84%), NOTCH1 signaling (79%), epigenetic regulation (68%), PI3K-AKT-mTOR signaling (29%), JAK/STAT signaling (25%), RAS signaling (14%), ribosomal function (13%), ubiquitination (9%) and RNA processing (9%).[10,11] Furthermore, T-ALL cells are dependent upon BCL-XL and upon BCL-2 especially when the T-ALL blasts bear an ETP phenotype.[12]

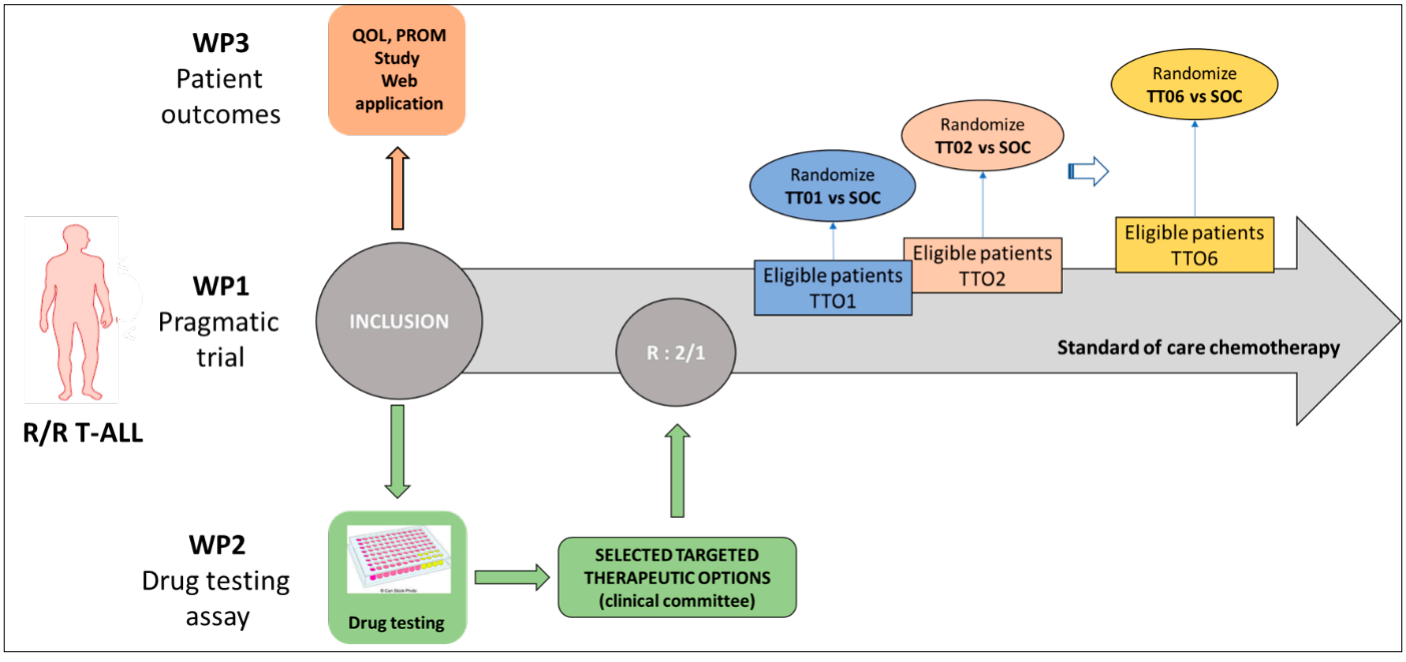

Figure 1. Structure of the EWALL-TARGET study. Laboratory work and clinical validation committee (Green), EWALL-TARGET pragmatic trial (grey), targeted therapeutic options (TTOs) 1 to 6. WP: work package. R/R T-ALL: relapse refractory T-cell Acute Lymphoblastic Leukemia, QOL: quality of life, PROM: patients reported outcomes, Tt: treatment, TTO: targeted therapeutic option, R: randomization.

However, these genomic data do not manage to reliably predict the response of the leukemic cells to a treatment, due to interactions of the different cellular pathways affected in a living leukemic cell. Therefore a in vivo drug testing could overcome this problem. In previous work, using more than 100 patient derived xenograft cells (PDX), we were able to validate the drugs proposed in the trial (V Asnafi, personal data).

The general aim of the EWALL-TARGET proposal is to prospectively evaluate the concept of precision medicine in term of efficacy and feasibility in the real-life context, with the example of relapse/refractory T-ALL. The treatment strategies will focus on validated and predefined targeted therapeutic options (TTO). Eligible Patients with T-ALL in relapse or refractory will be included in the EWALL-Target pragmatic trial. After inclusion of the patient and signed informed consent, fresh leukemic cells samples will be shipped to the reference laboratory to perform the EWALL-TARGET drug testing assay. Patients will then start a pre-phase treatment. After 7 to 10 days, patients with an informative drug testing assay will be randomized 2/1 between the experimental arm (6 targeted therapeutic options, TTOs) and the control arm (SOC). Patients without informative results from the drug testing assay will be registered only. The best TTO for patients in the experimental arm will be selected by the Clinical Validation Committee. The primary endpoint of the ALL-Target pragmatic trial is the complete remission rate (CR) plus CR with incomplete hematologic recovery (CRi) by 3 months post randomization. Responding patients will have the opportunity to continue the selected TTO for a total of 6 months. Non-responding patients in the control arm will be proposed to cross-over to the selected TTO option proposed before randomization.

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Front Line Management of DLBCL – Can we Beat DLBCL?

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Rituximab was introduced into the backbone of diffuse large B-cell lymphoma (DLBCL) in 2002 following a randomised trial in the 60-80 year old age group which demonstrated a progression free and overall survival advantage (Coiffier *et al*, 2002). Since then, rituximab has saved many thousands of patients from an untimely lymphoma death. However progress subsequently slowed. Many trials using R-CHOP as the background failed to show benefit. Examples include the Phoenix study in which ibrutinib combined with R-CHOP was compared with R-CHOP in non-germinal centre derived DLBCL (defined by immunohistochemistry). The GOYA study investigated a more potent anti-CD20 antibody, obinutuzumab, combined with CHOP but again no benefit was seen compared with R-CHOP. The US Alliance group tested the dose intense DA-EPOCH-R regimen against R-CHOP with no benefit but increased toxicity.

Two notable exceptions are worth considering. The French group studied the dose intense regimen R-ACVBP and compared this with R-CHOP in younger patients (18-59y) with low intermediate risk disease (Recher *et al,* 2011). Despite demonstrating both a progression free and overall survival, outside of France the regimen has not widely adopted partly due to the excess toxicity and increased healthcare resource utilisation. Furthermore, the outcomes of the R-CHOP group were surprisingly poor in what is a relatively good risk group. The REMARC study was a phase 3 randomised, placebo-controlled trial in patients aged 60-80y who had achieved a PR or CR to 6-8 cycles of R-CHOP for DLBCL assessing 2 years of maintenance lenalidomide (Thieblemont *et al*, 2017). The progression free survival was prolonged. Again however, this approach has not been widely adopted as there was no overall survival and the lenalidomide treatment significantly prolongs treatment duration and is associated with side effects of, for example, neutropenia and rash.

The supremacy of R-CHOP has however been recently challenged since the publication of the POLARIX trial (Tilly *et al*, 2021). This was a phase 3 randomised, double-blind, placebo-controlled trial in previously untreated patients with diffuse large B-cell lymphoma aged 18-80y and with an IPI of 2-5. 6 cycles of R-CHOP was compared with 6 cycles of Pola-R-CHP (in which vincristine is replaced by the anti-CD79b antibody-drug conjugate polatuzumab vedotin) with both arms containing 2 additional rituximab infusions. The primary endpoint of progression free survival was met with an investigator assessed 2y PFS of 76.7% in the pola-R-CHP arm compared with 70.2% in the R-CHOP arm. A reduction in 2nd line treatments was observed in the experimental arm although to date no difference in overall survival is evidence. Safety was similar between the two groups. This has led to approvals in a number of territories including Europe and USA. With a number need to treat to avoid one relapse of approximately 15, reimbursement across different countries is variable.

Another trial worth mentioning due to a recently presented overall survival advantage is the UK REMODL-B study. This again was a randomised phase 3 trial in previously untreated DLBCL. All patients received R-CHOP as their first cycle, whilst gene expression analysis was performed in real-time, enabling subsequent randomisation to be stratified according to cell of origin. Patients then received 5 cycles of R-CHOP or R-CHOP combined with bortezomib. The hypothesis was that a benefit for bortezomib would be seen in the Activated B-Cell (ABC) subgroup and the trial was powered accordingly. The initial report (with a median follow up of 29.7 months) showed no benefit (Davies *et al*, 2019). With longer follow up (median 64 months) however, both a progression free and overall survival advantage emerged in the ABC subtype only (Davies *et al*, 2023). The OS was 67% with R-CHOP and 80%

with RB-CHOP, HR 0.58 (95% CI 0.35-0.95). It is unclear whether this will impact current standard of care. Bortezomib is not licensed or reimbursed for this indication and without a pharmaceutical company driving the applications, this is unlikely to change. Furthermore, gene expression profiling is not standardised or routinely available and if the backbone in at least some countries is changing to Pola-R-CHP for IPI 2-5, it is unclear what impact bortezomib would have in this group.

Where next from the first line treatment of DLBCL? A number of trials are ongoing although most are using the R-CHOP backbone. Despite the negative Phoenix trial, interest remains in combining a BTK inhibitor with R-CHOP. This is because in the pre-planned subgroup of younger patients within the Phoenix trial, a significant benefit was seen (Younes *et al,* 2019). Benefit in older patients was not evident due to excess toxicities leading to a reduction in the treatment intensity of chemotherapy. This has led investigators to reason that if a better tolerated BTK were used and if primary prophylaxis with, for example, GCSF and co-trimoxazole were instituted for all patients, the benefit seen in younger patients could be seen for all. This is the approach taken in the on-going UK REMODL-A trial, a randomised phase 2 study assessing the addition of acalabrutinib to cycle 2 of R-CHOP again stratified according to gene expression profiling defined cell of origin . Furthermore there is a randomised phase III study (the Escalade trial) comparing R-CHOP with R-CHOP combined with acalabrutinib in patients 70y or younger.

A very interesting novel group of molecules are the bispecific antibodies with a number in development in diffuse large B-cell lymphoma: glofitamab, epcoritamab and odronextamab. These agents are highly active in relapsed / refractory disease with a complete response rate of approximately 40%, many of which are durable (Dickinson, 2022; Thieblemont, 2023; Bennerji, 2022). Trials combining these agents with R-CHOP or Pola-R-CHP are being developed.

A well-defined high-risk patient group are those which harbour a translocation involving *Myc* (with an immunoglobulin gene partner) and *BCL2*, the so-called double-hit lymphomas. Whether an approach different from R-CHOP (or Pola-R-CHP) should be adopted for this patient groups remains highly controversial. A number of retrospective studies have shown the use of more intensive therapies (e.g. DA-EPOCH-R) are associated with better outcomes (Petrich, 2014). However, there are clearly biases associated with these analyses, such as younger and fitter patient being more able to tolerate more intensive chemotherapy. A recent retrospective analysis of 300 patients did show an overall survival better associated with more intensive treatment (Goyal *et al*, 2023). Without a prospective randomised trial, it is difficult to know whether the well described excess toxicity of a more intensive approach is outweighed by the possible improvement in outcome.

Another important group to consider are older patients (defined as 80 and old). With an aging population, there are increasing number of older patients presenting with DLBCL and they pose a specific set of challenges such as co-morbidities, polypharmacy and frailty. Older patients are heterogeneous and a number of tools exist for measuring co-morbidities and frailty although the gold standard comprehensive geriatric assessment is cumbersome and time consuming. The Italian group defined a simplified geriatric assessment and combined this with haemoglobin and IPI at diagnosis, to define the elderly prognostic index or EPI which robustly risk stratifies this patient group (Merli *et al*, 2021). However the patients analysed were not treated in a homogenous way and it is unclear whether such a score can effectively inform the best treatment approach for a given individual.

The French group published a phase 2 trial in patients over 80 using reduced doses of R-CHOP, subsequently termed R-miniCHOP. In this group of patients with median age 83y, the median PFS and OS was 47% and 59% which was regarded as very promising for this cohort. It became widely adopted as a standard for older patients. This has been further reinforced by a number of studies showing the importance of dose intensity of R-CHOP in patients in the 70-80y age group but not in the 80y and older age group . This suggests that the excess toxicity in very old patients outweighs any benefit from increased treatment intensity and underscores the need for a different approach to be taken in older patients (Juul, 2018). Whilst outcomes with R-miniCHOP are encouraging, more work clearly needs to be done in this patient group. One ongoing study to highlight is the POLAR BEAR trial which is a randomised studies comparing R-miniCHOP with R-miniCHP combined with polatuzumab vedotin in patients 80y or older or frail patients 75y or older.

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CLL Targets Beyond BTKi and BCL2i

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The treatment landscape for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has dramatically evolved since the approval of the first in-class covalent Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, in the United States in 2014.

Regulatory approval of venetoclax, a BCL2 inhibitor, in 2016 has continued to change the treatment paradigm. However, resistance to these novel classes of agents due to target mutations or activation of alternative pro-survival pathways has emerged as an unmet medical need. Patients who have been exposed to or refractory to both classes of agents, so called "double-exposed/refractory", represent a particular treatment challenge.

Alternative approaches to target B-cell receptor (BCR) signaling. *Spleen tyrosine kinase (SYK)* is a key kinase indispensable for BCR signaling. We have shown that SYK inhibition with entospletinib leads to downmodulation of MCL1 protein in CLL both in *vitro* and in the clinic.[1, 2] Treatment of CLL cells with entospletinib, but not other BCR-signaling inhibitors, led to a disruption of BAFF-BCR cross-talk and downmodulation of MCL1 mRNA and protein, thus implicating SYK in transduction of multiple pro-survival signals emanating from the tumor microenvironment.[1] Entospletinib has shown promising clinical activity in CLL, alone or in combination with obinutuzumab, including in patients with high-risk diseasesuch as TP53 aberrant.[3, 4] The drug is very well tolerated, however its development in CLL has been halted.

Meanwhile, we have shown that luxeptinib, a dual SYK/BTK kinase inhibitor, has activity in BTK inhibitor-resistant lymphoid models *in vitro.*[5] Luxeptinib is now being investigated in lcinical trials in hematologic malignancies.

Protein kinase C-β (PKC-β) is an immediate downstream target of BTK that is overexpressedin CLL.[6] In B cells, PKC-β is believed to be the chief PKC isoform mediating BCR- dependent NF-κB activation. PKC-β facilitates leukemogenesis in CLL by enhancing BCR- mediated signaling.[7] As such, efforts to inhibit PKC-β are emerging as a novel therapeutic strategy for patients with CLL/SLL. The early results of MS-553, a selective PKC-β

inhibitor, indicates that this agent is tolerable and effective both as single agent and incombination with venetoclax.[8]

Proteolysis-targeting chimeras (PROTACs) are a new class of small molecules with two covalently-linked ligands recruiting target protein and E3 ubiquitin ligase together to trigger and enable proteasomal degradation of the target protein.[9] "BTK degraders", such as NRX- 2127 (Nurix Therapeutics) and BGB-16673 (Beigene), have entered clinical trials in patients with lymphoid malignancies. NX-2127 has shown to degrade both wild-type (WT) and C481- mutated BTK protein *in vitro*, in non-human primate studies and mouse xenograft tumor models expressing either WT or C481-mutant protein. Additionally, NX-2127 has shown preclinical activity similar to immunomodulatory drugs (IMiDs) by catalyzing the ubiquitination of Ikaros (IKZF1) and Aiolos (IKZF3), resulting in increased T-cell activation.[10] Early results of an ongoing clinical trial of NX-2127 demonstrate an ORR of 33% in heavily pre-treated patients with CLL, and overall good tolerability [11].

Novel BH3-mimetics. Engaging the pro-apoptotic or inhibiting the anti-apoptotic apparatus within a cancer cell is a promising treatment strategy that has inspired the development of animportant class of compounds termed "BH3 mimetics".

AZD5991 is a highly selective BH3-mimetic that demonstrates high potency in *MCL1*- dependent cell lines.[12] AZD5991 binds directly to MCL1 and induces rapid apoptosis in cancer cells, most notably myeloma and acute myeloid leukemia, by activating the Bak- dependent mitochondrial apoptotic pathway. The preclinical activity of AZD5991 has shown that selective targeting of MCL1 induced metabolic dysfunction and abrogated survival of diffuse large B cell lymphoma and ibrutinib-resistant mantle cell lymphoma cell lines *in vivo* and *in vitro*.[13] Other BH3-mimetics targeting MCL1 include AMG-176 and S63845.[14-16] In an experimental design testing the effects of AMG-176 on CLL and normal hematopoietic cell death it was demonstrated that AMG-176 is an active agent in inducing CLL cell death while sparing normal blood cells. However, MCL1 targeting agents may be associated with toxicities, including suppression of hematopoietic stem and progenitor cells, potentially leading to cytopenias in the clinic.[17]

Therapeutic antibodies. Targeting surface antigens on B cells and inducing both direct and antibody-dependent cellular cytotoxicity has been a success story in the field of B cell lymphoid malignancies including CLL/SLL. Anti-CD20 monoclonal antibodies – rituximab, obinutuzumab and ofatumumab – have significantly improved the survival outcomes.

The B cell activating factor receptor (BAFF-R) is one of the main pro-survival receptors in B cells.[18] In a preclinical study, ianalumab (VAY-736), a humanized defucosylated engineered antibody directed against BAFF-R, antagonized pro-survival effects of BAFF in CLL cells and showed promising activity both as a single agent and in combination with ibrutinib.[19] A phase 1 study of dose escalation and dose expansion investigated the combination of ianalumab with ibrutinib in 32 patients with CLL with median one prior line of therapy (range, 0-4). Of these 32 patients, total of 14 patients (43.8%) had an acquired BTK inhibitor resistance mutation. In terms of high-risk molecular features, 18.8% harbored del(17p), and 75% had unmutated *IGHV* status. The ORR was 57% with 38% of patients achieving complete response. A total of 13 patients (41%) achieved undetectable minimal residual disease (uMRD) in blood/marrow at the end of treatment. This study showed promising results not expected with ibrutinib alone.[20]

Tafasitamab – a Fc-enhanced, humanized, monoclonal antibody to *CD19* – in combination with idelalisib or venetoclax in 24 patients has been associated with an ORR of 77% and 91%, respectively. The most common severe adverse event in both cohorts was neutropenia.[21]

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is expressed in 95% of cases with CLL. Cirmtuzumab is a humanized monoclonal antibody that targets ROR1. In a phase 1 study involving 26 patients with R/R CLL, cirmtuzumab administered at four biweekly infusions was shown to have a long plasma half-life and did not have dose-limiting toxicity, potentially providing another treatment opportunity for patients with CLL.[22]

Immune Cell Enabling Therapies. Early studies of chimeric antigen receptor (CAR) T cells demonstrated efficacy in patients with CLL, ultimately paving the way for FDA approval of several CAR T-cell products in lymphoid malignancies. A recent report of a phase 1/2 study of lisocabtagene maraleucel, an autologous CD19-directed CAR T-cell therapy (TRANSCEND CLL 004), confirmed efficacy in patients with R/R CLL.[23] In this study, 23 patients with median 4 prior lines of therapy (range 2-11) were enrolled, 10 of whom were considered double exposed/refractory. In terms of high-risk cytogenetic features, 35% of patients had del(17p), 61% had mutated *TP53* and 35% had unmutated *IGHV*. In this heavily pre-treated patient population with frequent high-risk molecular features, the ORR was 83% with 45% of patients achieving CR. At a median follow-up of two years, the median PFS was 18 months for all patients (95% CI, 3-NR) and 13 months for the double exposed/refractory subgroup (95% CI, 2.8-NR). In terms of MRD assessment, 75% and 65% of patients

achieved undetectable MRD state in blood and marrow, respectively. Regarding safety, 74% of all patients experienced cytokine release syndrome (CRS) [high grade CRS 9%] and 39% of all patients developed neurotoxicity [high grade 21%]. In total, 65% of patients required administration of tocilizumab and/or corticosteroids.[23] In addition to the ongoing phase 2 portion of this study, efforts now focus on innovative CAR T-cell designs as well as combination strategies.

As noted in the Transcend CLL 004 trial, CRS and neurotoxicity are common with CAR T- cell therapy. NK cells that express CD19 CAR show promise to become off the shelf therapeutics with potential lower toxicity than CAR T cells. In a Phase 1/2 trial, HLA- mismatched CD19-targeting CAR NK cells induced CRs in three patients with CLL after a single infusion and without CRS or neurotoxicity attributable to the cellular product.[24] Finally, bi-specific antibodies have demonstrated impressive efficacy in non-Hodgkin lymphoma and are also an off-the-shelf product boasting high tolerability. Development of bispecific antibodies in CLL is still in early stages. Epcoritamab (GEN3013; DuoBody CD3 xCD20) is a bispecific antibody that can induce potent activation and cytotoxic activity of CD4+ and CD8+ T cells to target CD20-expressing cells. A phase 1b/2 ongoing trial is currently examining the safety and tolerability of the product in patients with R/R CLL. The early results suggest that epcoritamab administered subcutaneously is well tolerated in a heavily pretreated patient population with multiple high-risk features and shows clinical activity.[25] Furthermore, an ongoing study is demonstrating preliminary efficacy of epcoritamab in patients with Richters transformation, a notoriously difficult-to-treat complication of CLL.[26]

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Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

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NLPHL is a rare subtype of lymphoma accounting for 5 -10 % of all cases of Hodgkin lymphoma (HL) and affecting both children and adults. [1, 2] The median age at presentation is 39 years with a male predominance of 3:1. [3]

Compared with classical HL (cHL), the clinical behaviour tends to more indolent. Patients usually present with early stage disease with peripheral lymphadenopathy and few adverse prognostic factors. Mediastinal involvement is rare. Prognosis is favourable although late relapses may occur.[3,4] NLPHL may transform to high grade B cell lymphoma at a reported rate of 14% and median time to transformation of 8.1 years [5] with risk factors for transformation including advanced stage, splenic involvement and variant patterns. [6] Data from retrospective series and registry data consistently demonstrate 5 year overall survival (OS) of ~ 90-95%. [7,8] A population based study (1988-2010) using SEER data demonstrated superior survival for NLPHL compared with cHL with 10 year OS for NLPHL 83% compared with 74% for cHL [9] although better outcomes for NLPHL are partly due to the majority of patients having early stage, low volume disease. Risk factors associated with inferior progression free survival (PFS) and OS include advanced stage disease, B symptoms, mediastinal disease and variant histology pattern (C, D and E). [1, 10-12] Disease progression < 2 years from diagnosis was a significant predictor for adverse outcome with 10 year OS of 47% in 471 patients enrolled in GHSG trials, HD7-15.[13]

Deaths from NLPHL are uncommon with more patients dying of second malignancies and non-malignant causes, including treatment related, than of NLPHL. [14] Late treatment related toxicity needs careful consideration when determining the optimal management plan.

Pathology and Biology

NLPHL continues to be classified as an uncommon subtype of HL in the most recent WHO classification (WHO Haem5). [15] There are however major biological and clinical differences between NLPHL and classical HL (cHL). The neoplastic cells in NLPHL have a functional B cell program and NLPHL has a close relationship to T cell/histiocyte rich large B cell lymphoma (TCRBCL). In view of this the International Consensus Classification of Mature Lymphoid Neoplasms [16] suggests NLPHL should be renamed nodular lymphocyte predominant B-cell lymphoma (NLPBL).

An excision biopsy is preferred with a full immuno-histochemical panel to enable distinction between NLPHL from other conditions including progressive transformation of germinal centres, lymphocyte rich cHL and TCRBCL.

The malignant cells (LP cells) in NLPHL usually constitute < 1% of the tumour tissue and express some (CD20, CD79a, OCT2) but not all (CD19; CD22 and CD79b) B cell markers. Six histological variants have been described [17] with patterns A and B being typical patterns and patterns C-F variant patterns. Combinations of different patterns can occur within a single lymph node. Increased numbers of genomic aberrations and mutations are observed in LP cells from patients with variant growth patterns. [18]

The typical pattern is more common (~ 75%) and is associated with early stage disease (1.9% stage IV disease) and later relapse (6.5% in 5 years. [12, 19]. The 25% of patients with a variant pattern (C-F) had a higher incidence of stage IV disease (11.4%) and a higher relapse rate (18.1% in 5 years). The majority (67%) remain in the same pattern at relapse. In

a study of 152 patients enrolled in the GHSG trials HD16-18 [20] an incremental increase in the percentage of patients with advanced stage stratified by pattern was noted (30% for typical pattern A/B; 46% for pattern C; 76% for pattern D and 75% for pattern E).

Similar observations are seen in the paediatric population [21] where 78% of 60 patients had a typical pattern with 6% of these patients having stage III disease compared with 23% of those with a variant pattern. Relapse was also more common in patients with a variant pattern (15% versus 4%).

Currently, however, the histological pattern does not influence management.

Treatment

There are no prospective randomized trials in NLPHL and there is no standard treatment approach, especially for advanced stage disease. [22-24] Treatment with standard cHL regimens is effective but toxic (especially anthracycline and bleomycin related toxicities) and the majority of patients with NLPHL do not require intense treatment. In children with early stage disease, the focus has been on de-escalation of treatment with good results. A similar approach has been taken in adults in some centres but data to support this is sparse. A recent UK consensus paper suggests a more uniform management approach across all ages and stages. [25]

1) Early stage patients

Management options for patients with early stage disease (stage I and IIA) include resection followed by observation, radiotherapy (RT), chemotherapy (CT), combined modality treatment (CMT), active surveillance and anti CD20 therapy.

Resection alone is often employed in children with stage IA disease. If complete resection is confirmed by PET scan, many patients have a prolonged disease free survival (DFS) of >75% at 5 years with avoidance of chemo-radiotherapy associated late effects. [26] OS rates of 90-100% have been reported after complete resection with no OS benefit from additional therapy (RT, CT or CMT) although PFS may be improved. [27] Recurrence in children is not associated with significant upstaging or transformation. [28] A similar approach may be followed in adults. [29]

Radiotherapy: RT is very effective treatment in early stage NLPHL but is usually avoided in children due to late toxicities including second malignancies. Most adults (> 16 years) with un-resected stage I/IIA NLPHL are offered radiotherapy. Several retrospective studies with the majority including patients with stage I and II NLPHL, showed freedom from progression (FFP) rates of ~75-95% and OS 90-100% with RT. [30-33]

A single centre experience reported 5, 10 and 15 year PFS of 95%, 89% and 76% respectively with no improvement in outcomes with addition of CT. [31] The GHSG concluded that involved field RT (IFRT) should be standard treatment for stage IA NLPHL due to equivalent disease control but less toxicity than that associated with either extended field RT (EFRT) or combined modality treatment (CMT). [34]

Active surveillance: for adult patients with early stage, un-resected disease who are unsuitable for radiotherapy, an active surveillance approach may be adopted. A number of retrospective studies [6, 8, 35] have reported 5 year PFS between 71.5 and 77%.

In a Memorial Sloan Kettering study, 23 of 37 patients managed by active surveillance had early stage disease. 5 year PFS for those managed by active surveillance was shorter at 77% compared with 87% for those who received active treatment however there so was no significant difference in OS. [35] There is little data to support this approach in children with un-resected disease.

Chemotherapy alone: for some patients, factors such as distribution of disease, age, sex and predicted late toxicity may result in other options being considered. Chemotherapy as a single modality in early stage disease is mainly used in the paediatric setting. Shankar et al [36] reported a 75% freedom from treatment failure (FFTF) and 100% OS at 40 months following 3 cycles of CVinbP (cyclophosphamide, vinblastine and prednisolone).

Results from adult studies are variable. In a single institution study of 113 patients, Chen et al reported 7 patients treated with chemotherapy alone with 6 developing early disease progression requiring salvage therapy. [29] In contrast, CVP was given to 15 patients (11 early stage) in a UK retrospective study [8] with a 5 year OS of 100%. Of note, the majority of patients were young with a median age of 16 years (12-29). In a large, retrospective analysis [6] 47 of 559 patients with stage I/II NLPHL were treated with chemotherapy alone (80% ABVD +/- R and 15% R-CHOP) with 77.8% 5 year PFS and 97.9% OS. The optimal chemotherapy regimen is unknown however patients with early stage disease and no adverse risk factors have a good prognosis providing a rationale for avoiding anthracycline or bleomycin containing regimens with their associated cardiac and pulmonary toxicities. Given NLPHL is a CD20 positive lymphoma, addition of Rituximab to combination chemotherapy is logical akin to management of all other CD20 positive lymphomas.

Combined modality treatment: patients with early stage NLPHL have excellent outcomes compared to patients with early stage cHL and whilst combined modality treatment is an option for early stage NLPHL, excellent outcomes can be obtained in most patients with a less intensive treatment approach. [2, 6, 24, 27, 37, 38]

Rituximab alone is associated with inferior PFS compared with RT, CT or CMT (38.5% 5 year PFS in a cohort of stage I/II patients [6] and 10 year PFS of 51.1% in a cohort of stage IA only patients.[39] It may be considered if patients are not suitable for other approaches.

2) Advanced stage patients

Options for the management of advanced stage patients include active surveillance (akin to patients with other asymptomatic low grade lymphomas) or chemotherapy.

Chemotherapy: the optimal chemotherapy regimen is unclear. Options including cHL regimens such as ABVD or, rarely, escalated BEACOPP or non-Hodgkin lymphoma (NHL) regimens such as CVP or CHOP. ESMO, NCCN and BSH guidelines recommend addition of Rituximab. [22-24]

The data to support CVP (+/-R) in the adult setting is scanty however this may be the preferred option in patients with low volume stage III disease. In patients with stage III or stage IV disease with risk factors including B symptoms, splenic involvement, mediastinal disease or variant histology, most commonly used regimens are ABVD or CHOP +/- R.

Support for a cHL approach mainly comes from GHSG studies. [40] Eichenauer et al reported NLPHL patients managed on HL trials, HD7-15. The majority of advanced stage patients were treated with BEACOPP regimens and had a 10 year PFS ~ 70% and OS of ~87% with the remainder mainly treated with ABVD-like regimens + RT and achieving 10 year PFS of ~ 80% and OS >93%. ABVD was studied in a matched paired analysis of advanced stage patients with cHL and NLPHL, n=42. [1] Time to progression (TTP) including transformation to aggressive lymphoma was inferior in patients with NLPHL treated with ABVD compared with patients with cHL (10 year TTP 63% versus 73%, p=0.04). Non Hodgkin Lymphoma protocols have been used in the treatment of NLPHL in the paediatric and adult settings. R-CHOP was given to 27 patients with NLPHL with good PFS (estimated 5 and 10 year PFS of 88.5% and 59.3% respectively). [41]

Other regimens including Bendamustine-Rituximab [42] and Rituximab and Lenolidamide (R2) [43] may have efficacy in NLPHL but study numbers are small.

Novel Agents: unlike cHL, LP cells rarely express CD30 and therefore there is no role for the anti CD30 antibody drug conjugate, Brentuximab Vedotin in NLPHL. Check point inhibition however may be a successful therapeutic strategy with 96% of NLPHL cases having follicular helper T cell rosettes with the majority showing PD-1 positivity [20] and in addition pre-clinical reports suggesting rationale for CPI. [44]

Future directions: meaningful progress in the investigation and management of this rare condition requires international collaboration. The GLOW consortium has recently published an international survey on practice patterns for the management of NLPHL [45] and will utilise the information gathered to help inform prospective data collection and future clinical trials.

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Relapsed/Refractory Classical Hodgkin Lymphoma

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Recent SEER data for the US show gradual improvements in relative survival over the past several decades for patients with classic Hodgkin Lymphoma (cHL). Nonetheless, over nine hundred individuals with cHL in the US will die each year from relapsed or refractory disease many of them in the prime of life. It has been estimated that as many as 10-30% of all patients with cHL will either fail to respond to frontline therapy or relapse. Although the majority of younger patients who are candidates for aggressive second-line therapy that includes autologous hematopoietic stem cell transplant (auto-HSCT) can be cured in this setting, secondary effects of therapy shorten life expectancy. Moreover, greater than half of all deaths occur in older patients, the majority ineligible for conventional second-line therapy and auto-HSCT. Better frontline therapies with the potential to cure more patients from the start are under investigation and promise to reduce significantly the number of patients requiring salvage therapy. In the meantime, efforts are underway to improve clinical outcomes for relapsed/refractory patients who are candidates for auto-HSCT. In addition, alternative, less toxic therapies with curative potential applicable to the growing elderly demographic with cHL or those who fail auto-HSCT are desperately needed.

To date, much of the effort to improving outcomes for relapsed/refractory cHL has been focused on increasing the fraction of patients who are candidates for auto-HSCT. Response to pre-transplant second-line cytoreductive therapy judged by PET/CT is a strong predictor of outcome with high-dose therapy. Hence, achievement of a negative PET/CT defined according to Lugano 2014 criteria has been one of the primary endpoints of many trials. To date, there have been no randomized clinical trials comparing conventional second-line chemotherapy regimens. Most trials have been small phase II trials with approximately 50-60% of patients achieving complete remission prior to auto-HSCT assessed by gallium scanning, CT or PET/CT. Monotherapy with brentuximab vedotin (BV), an antibody drug conjugate targeting CD30, induced high response rates in heavily pretreated patients including those relapsing post-auto-HSCT. These encouraging results led to a series of trials intensifying therapy through the addition of BV to conventional chemotherapy salvage regimens. Overall2. incorporated into second-line regimens, but with the growing use of BV-AVD as frontline therapy in advanced stage patients as a result of the Echelon-1 trial, an increasing percentage of relapsed/refractory patients will have already failed BV. Checkpoint inhibitors (CPI), notably nivolumab and pembrolizumab (and others) have demonstrated efficacy in relapsed/refractory patients as single agents (Mei et al.; Kuruvilla et al.) and in combination with second-line chemotherapy. Checkpoint inhibitors (CPI) have now been shown to be very effective in the upfront setting either in combination with chemotherapy or as monotherapy followed by chemotherapy. Consequently, a growing number of relapsed/refractory patients will have been treated previously with CPI. It is likely that future frontline regimens will incorporate both CPI and antibody drug conjugates and will cure more patients with initial treatment, thus reducing the need for effective salvage therapy. The ultimate goal is to cure all patients upfront through the incorporation of our most powerful agents into frontline therapy. Reducing late effects including secondary malignancies and cardiovascular disease is also high priority.

For patients who do prove refractory to frontline therapy or relapse and are not transplant eligible by virtue of age or comorbidities, CPI-based monotherapy or some of the novel agents under investigation including new antibody-drug conjugates, cytosine nucleoside analogs, JAK inhibitors, bispecifics and anti-CD30 CAR T-cells, will hopefully be options going forward. Never before has the outlook been so bright for patients with cHL!

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ABSTRACTS

■ Non-Hodgkin's Lymphoma

OP-01 Abstract Referance: 36

THE CIRCULATING EXOSOMAL CD30 AND CD79B IN DLBCL: DOES IT INFLUENCE THE TARGETED THERAPY DECISION IN PRECISION MEDICINE?

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The R-CHOP chemoimmunotherapy is the first-line standard treatment regimen for Diffuse Large B-Cell Lymphoma (DLBCL) patients. Nevertheless, up to 30-40% of the patients do not respond to the therapy or relaps after an initial response (1). Novel therapeutic strategies in relaps/refractory DLBCL has improved outcomes. However, the validated predictive biomarkers have yet to be extensively studied for precision-based care. We aimed to determine the presence of CD30 and CD79B as targets for immunotherapy in plasma-derived exosomes of DLBCL patients. To examine the exosome-tumor relationship, we also explored the profiles of target proteins in primary tumor samples.

Exosome samples isolated from our previous studies of 20 newly diagnosed DLBCL patients and 20 healthy controls were included in the study (2, 3) and re-characterized according to the recent MISEV2018 guidelines, including the density and size of particles (determined by Nanoparticle Tracking Analysis), as well as the expression of exosomal markers (determined by Western Blotting) (4). CD30 and CD79B expression on the exosomes and tumor cells were analyzed by Western Blotting and Immunohistochemistry, respectively.

The exosomes were within the expected size range and positive for exosomal markers (CD63 and CD81), but negative for the endoplasmic reticulum protein, calnexin. Seventeen (85%) patients had CD30-positive exosomes in their blood, while tumor cells expressing CD30 were found in only 2 (10%) patients. We evaluated CD79B expression in tumor cells of 6 patients because of insufficient tissues available for the testing. CD79B-positive exosomes were detected in 4 patients and there was complete agreement between exosomes and tumor cells in terms of CD79B positivity.

Recently completed a clinical study of Hodgkin Lymphoma (5) and a pre-clinical study of DLBCL (6) have demonstrated that the toxicity of CD30 antibody-drug conjugate Brentuximab Vedotin (BV) in CD30-negative tumor cells is dependent on CD30-positive exosomes. Our data suggest that clinical studies are needed for the anti-tumoral efficacy of BV in the presence of CD30 positive plasma exosomes, regardless of CD30 status in tumor cells of patients with DLBCL. Similarly, a possible function of CD79B-positive exosomes in the therapeutic efficacy of the anti-CD79B antibody-drug conjugate Polatuzumab Vedotin have not yet determined. Identifying characteristics of tumor cells as well as targeting different supporters contributing to tumor microenvironment will improve the therapeutic strategy of precision medicine.

Keywords: Diffuse Large B-Cell Lymphoma, Exosome, CD30, CD79B

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Acknowledgments: This study was supported by a grant from The Scientific and Technological Research Council of Turkey, TUBITAK (Grant No. 321S005).

■ Other

OP-02 Abstract Referance: 9

IS TGF-β1 AND SMAD-7 PREDICTIVE OF TREATMENT RESPONSE IN PATIENTS WITH LOW-RISK MDS AT THE TIME OF DIAGNOSIS?

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Introduction: Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disease with varying degrees of ineffective hematopoiesis secondary to cytopenias, morphological dysplasia, and risk of transformation into acute myeloid leukemia (AML). In low-risk MDS patients, supportive treatments such as blood transfusion, iron chelation, erythropoiesis-stimulating agents (ESA), granulocyte colony-stimulating factor, and thrombopoietin are given. In this study, we aimed to retrospectively examine the effects of bone marrow SMAD-7 and TGF-β1 protein expressions on the prognosis and response of erythropoiesis-stimulating agent (ESA) treatment in patients with low-risk MDS.

Material and Method: Patients with low-risk MDS diagnosed by the adult hematology department of Bursa Uludağ University Hospital between 2016-2021 were retrospectively analyzed. The study included 56 low-risk MDS patients.

Results: In the immunohistochemical examination of the bone marrow specimens at the time of diagnosis, only 5 (9.8%) of the patients showed low staining with SMAD-7, while 51 (90.2%) did not. According to TGF-β1 staining, 18 (32.1%) of the patients showed moderate/high staining, while 38 (67.9%) had either low staining (36/38) or no staining (2/38). When the TGF-β1 and SMAD-7 expression levels were compared according to ESA treatment given or not, no statistical significance was found according to the SMAD-7 status (p=0.571), while statistical significance was found according to the TGF-β1 status (p=0.011). Moderate and high staining with TGF-β1 suggests that patients are candidates for ESA therapy. TGF-β1 and EPO levels were compared, and the relationship between low EPO levels and medium/high staining of TGF-β1 was found to be statistically significant (p = 0.04). However, when the TGF-β1 staining status was compared with the 1st and 3rd-month treatment responses in those receiving ESA treatment, no significant difference was found between the two groups.

Discussion and Conclusion: In conclusion, it is important that TGF-β1 and EPO levels were compatible with initiating ESA treatment in our study. Multicenter studies with a large number of patients with the TGF-β pathway should be increased, and the results should be supported.

Keywords: Transforming growth factor-β, Myelodysplastic syndrome, erythropoietin

■ Other

OP-03 Abstract Referance: 16

INFECTION FREQUENCY AND DISTRIBUTION IN CASES USING KINASE INHIBITORS IN HEMATOLOGY: RETROSPECTIVE REAL-LIFE EXPERIENCE

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Introduction and Aim: Although the infection risk of conventional chemotherapies in hematological diseases is known, the safety profile of treatments targeting different intracellular signaling pathways, such as kinase inhibitors in terms of infections, is not fully understood. For this purpose, in our study, patients using kinase

inhibitors targeting different intracellular signaling pathways were evaluated for bacterial, viral, fungal, and opportunistic infections.

Methods: The patient registry system was reviewed retrospectively. Between 2005 and 2022, 544 patients receiving kinase inhibitors for CML, CLL, AML, NHL, MPN, and GVHD were included in the study. The following parameters were evaluated: bacterial infection; evidence of culture growth or response to started antibiotic therapy, CMV/BKV/HBV; positive PCR result, fungal infection; evidence of culture growth, galactomannan positivity or response to antifungal treatment, PJP (Pneumocystis jirovecii pneumonia); Demonstration of PJ antigen, tuberculosis infection; ARB positivity was defined as culture growth or response to anti-TBC treatment. The available kinase inhibitors were ruxolitinib, imatinib, dasatinib, nilotinib, bosutinib, ponatinib, ibrutinib, midostaurin, sorafenib, and gilteritinib.

Results: Of the 544 patients included in the study, 69% had chronic myeloid leukemia (CML), 14% had chronic lymphocytic leukemia (CLL), 8% had graft versus host disease (GVHD), 6% had polycythemia vera (PV), 3% had acute myeloid leukemia (AML), 2% non-Hodgkin lymphoma (NHL), 2% Waldenström macroglobulinemia (WM). The distribution of infections by diseases is summarized in Table 1. Tuberculosis and PJP were not seen when the whole cohort was examined. HBV reactivation; It was seen in 2 PV patients using ruxolitinib and 4 CLL patients using ibrutinib. The only patient group in which CMV reactivation was not observed is WM cases using ibrutinib. In addition to bacterial infections, CMV viremia was seen in 11% (n=2) of AML patients using FLT3 inhibitors. Fungal infection was not seen in AML patients receiving FLT3 inhibitors. The frequency of infection by drugs is summarized in Table 2.

Discussion and Conclusion: Treatment with Janus kinase inhibitors increases the incidence of both viral and bacterial infections. The incidence of infection with ibrutinib varies according to the underlying disease, the combined use of ibrutinib with other drugs, and in which step it is used. While there was no increase in the frequency of infection when used as a single drug in patients with Waldenström macroglobulinemia, the frequency of infection increased when combined or with advanced treatment steps in NHL. The absence of fungal infection in AML patients using FLT3 inhibitors may be due to antifungal prophylaxis. Given the increased risk of infection associated with some of the drugs studied, it is clear that the infection frequency is related to the kinase itself and the host condition. The frequency of infection in different hematological disease groups of the same drug is also different. The frequency of infection varies according to the step in which the drug is used in a single disease group, as well as the medications used. In the use of oral kinase inhibitors, viral reactivations such as CMV and HBV are seen together with bacterial infections. Although viral reactivation is well followed in certain drug groups, especially in terms of HBV, it may be missed in patients using kinase inhibitors, and patients may be lost due to reactivations. In this regard, there is a need for multicenter studies that present real-life data.

Keywords: TKI;BTK inhibitors;FLT3 inhibitors;infection; JAK inhibitors

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Table 1. Infection frequency by diseases

	CML N=377	PV N=35	NHL N=16	WM N=13	CLL N=80	AML N=17	GVHD N=46
Bacterial inf.	23(6.8%)	12(34.28)	6(37.5%)	2(15.3%)	20(25%)	12(70%)	8(17%)
HBV react.	0	2(5.71%)	0	0	4(5%)	0	0
TB	0	0	0	0	0	0	0
PJP	0	0	0	0	0	0	0
Fungal inf.	0	1(2.85)	4 (25%)	0	0	0	1(0.2%)
CMV	2(0.59%)	3(8%)	14(25%)	0	10(12.5%)	2(11%)	19(41%)
BKV	-	-	-	-	-	-	4(0.08%)

PJP: Pneumocystis jirovecii p. CMV: Cytomegalovirus inf., TB: Tuberculosis, BKV: BK virus, CML: Chronic myeloid leukemia, PV: Polycythemia vera, NHL: Non-Hodgkin lymphoma, WM: Waldenströmemia macroglobulinemia, CLL: Chronic lymphocytic leukemia, AML: Acute myeloblastic leukemia, GVHD: Graft versus host disease

Table 2. Infection frequency by drugs

Table 1.Patient characteristics

Center	İnh	28	40,0%
	Aufl	27	38,6%
	medicana	15	21,4%
Tx-year	era1	16	22,9%
	era2	54	77,1%
Age		35 (18-62)	
Median follow-up time, month		64,0 (46,7-87,3)	
Age-40	≤40	49	70,0%
	>40	21	30,0%
Gender	M	41	58,6%
	F	29	41,4%
Pre-allo PS	≤70	25	35,7%
	>70	45	64,3%
Stage	Early	24	34,3%
	Advance	46	65,7%
Pre-allo treatment	≤3 sıra	26	37,1%
	>3 sıra	44	62,9%
Conditioning regimen	MA	23	32,9%
	RIC	47	67,1%
Stem cell source	PKKH	62	88,6%
	KI	7	10,0%
	kordon	1	1,4%
ATG use	No	57	81,4%
	Yes	13	18,6%
TBI	No	49	72,1%
	Yes	19	27,9%
Acute Gvhd	N/A	1	1,4%
	Yes	29	41,4%
	No	40	57,1%
Chronic Gvhd	N/A	1	1,4%
	Yes	17	24,3%
	No	52	74,3%
PostBr_BV	Yes	11	15,7%
	No	59	84,3%

■ Stem Cell Transplantation

OP-04 Abstract Referance: 14

ALLOGENEIC STEM CELL TRANSPLANTATION FOR RELAPSED AND/OR REFRACTORY HODGKIN LYMPHOMA:A MULTICENTER REAL WORLD EXPERIENCE

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Introduction: Relapsed and/or refractory (R/R) Hodgkin Lymphoma (HL) after autologous stem cell transplantation (ASCT) is associated with poor outcomes and nearly 50% of patients (pts) will ultimately relapse. Novel therapeutic agents such as immune checkpoint inhibitors (CPI) (nivolumab, pembrolizumab) and brentuximab vedotin (BV) have both shown considerable activity in this pt population, but the risk of relapse is still high. Allogeneic stem cell transplant (allo-SCT) maintains its curative potential also in the era of new drugs, but it is associated with significant morbidity and mortality. Herein we report on our multicenter experience with allo-SCT for R/R HL.

Methods: Seventy pts with R/R HL who underwent allo-SCT between 2004 and 2021 in three transplant centers were included. Pts were included between 2010 and before (era1) in one centre, 2011 and after (era2) in all centers. The response was assessed with according to the Lugano criteria before allo-SCT. Primary end point was post-transplant (post-tx) overall response rate (ORR). Secondary endpoints were overall survival (OS), progression free survival (PFS) and response rates according to parameters especially tx-years, pre/post-tx use of CPIs and/or BV.

Results: Pt characteristics are summarized in the Table 1. Median follow-up time was 64 months (range, 40.7-87.3). Post-tx disease relapse or progression occurred in 23 pts (33%). The median time to disease relapse was 6.3 months (range, 1-24.5). Twenty-nine pts were alive at the analytic date (41%); 23 in complete response CR (79%), 4 partial response (PR) (14%), 2 stabl disease (SD) (7%). The 3-year OS, PFS were 39% (95% CI 27.2–50.8) and 28% (95% CI 16.2-39.8), respectively; the day 100 and 1-year non-relapse mortality (NRM) rates were 26% (95% CI 16.2–35.8) and 37% (95% CI 25.2–48.8), respectively (Figure 1).

According to tx-year, the pre-tx response rates were not statistically different between the two eras (p=0.46) but post-tx CR rates were significantly (sgnly) higher in era2 (p=0.01). The survival and NRM rates were not statistically sgn between the two eras, but PFS was sgnly longer in 2016 and after (p=0.03) (Figure 2). Patients were included in era1 in the one and only centre, the survival rates were not statistically sgn between the two eras.

The pts with chemosensitive disease (CR, PR) at the time of allo-HCT had more common the use of BV, RIC conditioning regimens (cr), high HCT CI score but less common the use of ATG. Pre-tx CR showed a better OS, PFS, NRM (p>0.05), patients in CR at the time of post-tx showed sgnly better OS, PFS (p<0.001).

Pre-tx and post-tx, the use of BV and CPI showed a sgnly better OS, PFS but not statistically sgn (p>0.05). Pre-tx the use of BV and CPI did not have a sgn impact on NRM, post-tx the use of BV (p=0.06) and CPI (p=0.08) showed a reduction NRM but not statistically sgn (Figure 3). Pts who received ATG had sgnly worse OS (p=0.04), NRM (p=0.01), but similar PFS (p=0.28). Pts who received post-tx cyclophosphamide (cy) had sgnly better OS (p=0.04) and PFS (p=0.05) but similar NRM (p=0.19). Cr did not show a sgn difference in OS, PFS and NRM (p>0.05).

According to donor types; the use of pre-tx CPI (p<0.05), TBI (p<0.001) in cr and post-cy (p<0.001) were common for haploidentical (haplo) tx. ATG was used more commonly for matched unrelated donor (MUD) when compared with matched related donor (MRD) (p<0.001). The incidence of acute GVHD (p=0.09) and chronic GVHD (p=0.002) were higher with MRD. Haplo pts had superior OS (p=0.015) and PFS (p=0.03) compared to MUD and MRD. NRM was comparable between haplo and MRD, but lower than in MUD (p<0.05).

Conclusions: Our results suggest that allo-SCT is a viable therapeutic option in pts with R/R HL. An improvement in supportive care, better pt selection and the common use of novel therapeutic agents, likely contributing to the improved tx outcomes. Future studies are needed to explore the role of allo-SCT in pts with R/R HL.

Keywords: R/R HL, allo-SCT, CPI

Table 1. Patient characteristics

Center	fnh	28	40,0%
	autf	27	38,6%
	medicana	15	21,4%
Tx-year	era1	16	22,9%
	era2	54	77,1%
Age		35 (18-62)	
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Gender	M	41	58,6%
	F	29	41,4%
Pre-allo PS	≤70	25	35,7%
	>70	45	64,3%
Stage	Early	24	34,3%
	Advance	46	65,7%
Pre-allo treatment	≤3 sıra	26	37,1%
	>3 sıra	44	62,9%
RT	No	38	54,3%
	Yes	32	45,7%
Preallo-BV	No	30	42,9%
	Yes	40	57,1%
Preallo-CPI	No	58	82,9%
	Yes	12	17,1%
Preallo_disease	CR	11	15,7%
	PR	18	25,7%
	SD/PD	41	58,6%
Conditioning regimen	MA	23	32,9%
	RIC	47	67,1%
Stem cell source	PKKH	62	88,6%
	KI	7	10,0%
	kordon	1	1,4%
ATG use	No	57	81,4%
	Yes	13	18,6%
TBI	No	49	72,1%
	Yes	19	27,9%
Acute Gvhd	N/A	1	1,4%
	Yes	29	41,4%
	No	40	57,1%
Chronic Gvhd	N/A	1	1,4%
	Yes	17	24,3%
	No	52	74,3%
Posttx_BV	Yes	11	15,7%
	No	59	84,3%
Posttx_CPI	Yes	8	11,4%
	No	62	88,6%
Posttx disease	CR	27	50,0%
	PR	13	24,1%
	SD/PD	14	25,9%
NRM	No	41	58,6%
	Yes	29	41,4%
Postallo100 mortality	Yes	18	25,7%
	No	52	74,3%

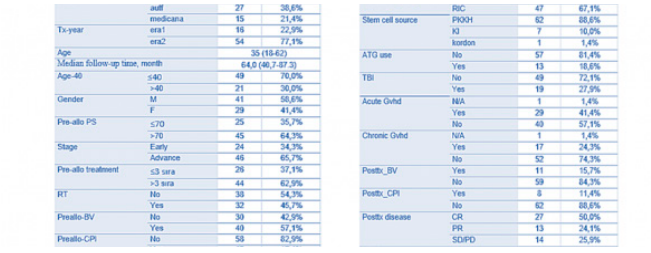

Figure 1. Survival and NRM

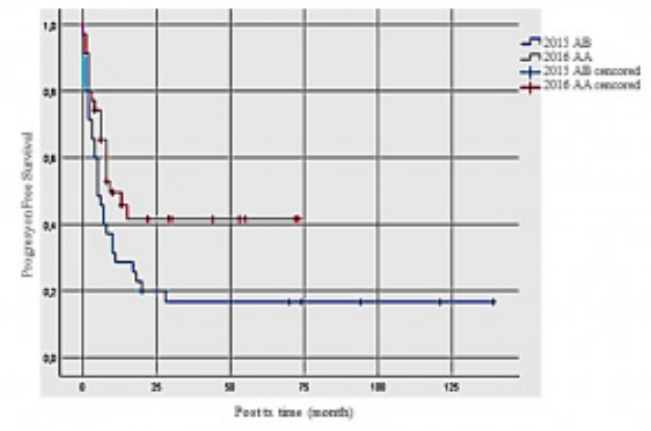

Figure 2. Survival according to tx-year

■ Multiple Myeloma

OP-05 Abstract Referance: 28

THE EFFECT OF INTERLEUKIN-2 GENE POLYMORPHISMS (IL-2 RA, -330 T/G,+166 T/G) ON MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is a plasma cell dyscrasia that accounts for 1% of all cancers and approximately 10% of hematological malignancies. There are defined genetic anomalies with known effects and importance such as trisomies and immunoglobulin heavy chain translocations on MM pathology. Interleukin 2 (IL-2) is a cytokine secreted by T helper type 1 cells, released after induction of T helper cells with antigens or major histocompatibility complexes presented by antigen presenting cells. The relationship between hematological malignancies and IL-2 is more complex than in solid tumors. IL-2 supports B cell differentiation and plasma cell formation, therefore plays an important role in B cell and plasma cell derived diseases. It can be accepted theoretically that increased IL-2 level is associated with increased plasma cell differentiation, but the current literature data is quite limited for plasma cell-derived malignancies. In our study, we aimed to investigate the effects of IL-2 RA (rs2104286), -330 T/G (rs2069762), +166 T/G (rs2069763) gene polymorphisms on MM disease susceptibility, progression-free survival (PFS) and overall survival (OS).

Material and methods: Patients with diagnosed with MM in our clinic between January 2010 and December 2022 and healthy individuals to form a control group were included in the study. For all patients, the same first-line treatment (VCD regimen: Bortezomib, cyclophosphamide, dexamethasone; bortezomib 1.3 mg/m2 D1,8,15,22; cyclophosphamide 300 mg/m2 D1,8,15,22; dexamethasone 40 mg/m2) week) was utilised. Autologous stem cell transplantation (ASCT) was preferred for patients who had at least a response of partial remission after four cycles of treatment and were eligible for stem cell transplantation; lenalidomide-dexamethasone (LD) was preferred as maintenance therapy. Patients who did not undergo an ASCT received also LD maintenance therapy.

Results: A total of 300 patients and 170 healthy controls were included in the study. The number of patients who underwent an ASCT was 196 (73%). Gene variants were shown to have no effect on disease susceptibility. It was revealed that both median PFS and OS of patients with IL-2 -330 TG genotype were significantly shorter compared to others(p=0.019 for PFS, p=0.027 for OS). The median PFS of patients with the IL-2 +166 GG genotype were significantly shorter compared to others, there was no significant difference in terms of OS between subgroups (p=0.017 for PFS, p=0.412 for OS).

Conclusion: Literature data supports that IL-2 level is found to be low in patients with MM. Genotypes shown to be associated with significant shorter survival in our study, are also associated with low expression in literature. The relationship between IL-2 and MM plays an important role among cytokines and will shed light for the future studies.

Keywords: Multiple myeloma, interleukin-2, prognosis, survival

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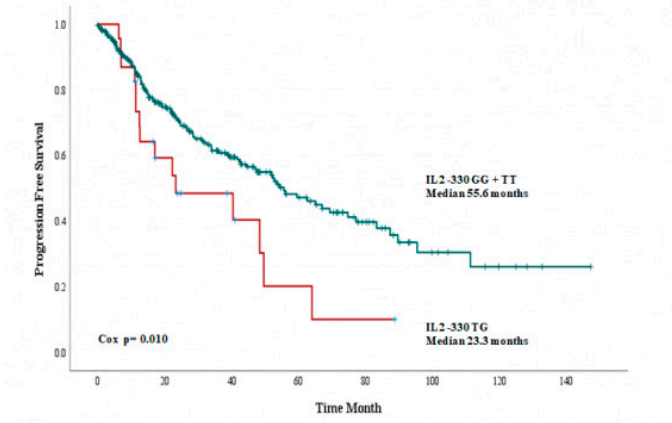

Figure 1.

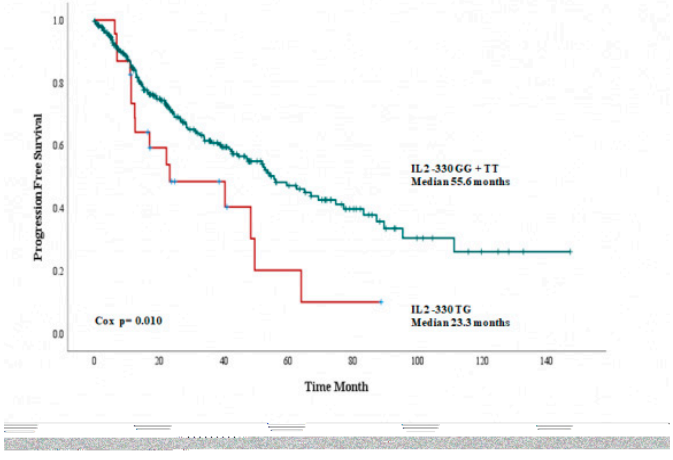

Figure 2.

Table 1. Clinical features and treatment regimens of MM patients

		Multiple Myeloma		Control
		median	n[a] (%)	n[b] (%)
Age		58 (29-84)		56 (29-78)
Gender	Female/Male		131/169 (43/57)	87/83 (51/49)
Ig subtypes	□/□		180/93 (70/30)	
	G/A		159/47 (60/18)	
	Light chain		58 (22)	
Stage (Salmon-Durie)	I-II		56/35 (20/13)	
	III		184 (67)	
	A/B	Light chain	227/48 (82/18)	
IPI	I		101 (37)	
	II/III		65/106 (24/39)	
ECOG	>1		50/224 (18)	
Hemoglobin	gr/dL	10.7 (5.8-16.1)		
Leukocyte	mm^3	6770 (2000-54560)		
Thrombocyte	x10^3/ mm^3	203 (69-788)		
C-reactive protein	mg/dL	3.5 (2.1-352)		
LDH	IU/L	195 (52-1037)		
b2-microglobulin	mg/L	4.4 (0.4-48.1)		
Albumin	gr/L	3.7 (1.1-5.1)		
Treatment	VCD, ASCT, LD		196 (73)	
	VCD ± LD		104 (27)	
OS		100 months		
PFS		53 months		
Mortality			73 (24.3)	
Follow-up (months)		32 (1.4-147)		

n[a] = 300; n[b] = 170; VCD: Bortezomib, cyclophosphamide, dexamethasone; LD: Lenolidomide, dexamethasone; ASCT: Autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group performance status; LDH: Lactate dehydrogenase; IPI: International Prognostic Index; PFS: Progression-free survival, OS: Overall survival
* = median.

Table 2. Comparison of PFS and OS with prognostic factors of patients diagnosed with MM

		N	PFS Median Mo*	Log Rank p-value	OS Median Mo*	Log Rank p-value
		300	53		100	
IL-2 RA	AA	39	67		90	
	AG/GG	261	48.4	0.242	99	0.123
IL2 -330	TT/GG	277	55.6		111	
	TG	23	23.3	**0.019**	71	**0.027**
IL2+166 G/T	GG	168	36.2		99	
	TG/TT	132	65	**0.017**	90	0.412

PFS: Progression-free survival, OS: Overall survival
* = median.
*Median(months)

■ Acute Lymphoblastic Leukemia

OP-06 Abstract Referance: 29

INFECTIOUS COMPLICATIONS OF PEDIATRIC ALL PATIENTS IN A SINGLE CENTER WITH COMPARISON OF 2 TREATMENT PROTOCOLS

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Introduction: The most common malignancy among children is leukemia, and the overall survival rates raised in ALL and AML patients upto 90% and 60%, respectively. However, infections continue to be among the leading causes of death in these patients.

Methods: In this study, we retrospectively analyzed the infection episodes of patients during induction, consolidation, reinduction phases of treatment. A total of 242 ALL patients were included who were diagnosed between 2008 and 2019. The patients who relapsed or undewent hematopoietic stem cell transplantation or as an underlying immune deficiency were excluded. Additionally, a comparison of the infectious complications among the two different treatment protocols (St Jude Total XV (n=181) vs BFM ALL-IC 2009 (n=61)), that ALL patients received was made.

Results: Among the patients with ALL who received St Jude Total XV treatment protocol, a total of 402 and among the patients who received BFM ALL-IC 2009 treatment protocol a total of 173 infection episodes were encountered. The infection episodes per patient were similar in two different treatment protocols (p=0.261). At least once a microbiologically proven infection was seen in 53% and 62.3% of St Jude protocol and BFM protocol receivers, respectively. Of the infections developed in patients with ALL, 38.4% were micobiologially verified, 27.3% were cilinically defined infections and 34.3% were fever of unknown origin. The number of microbiologically verified infections ere higher in BFM ALL-IC 2009 group, compared to St Jude Total XV protocol (p=0.004). Infection episodes during prolonged neutropenia period were higher in BFM Protocol (p<0.001). In the ALL group, having ANC < 100/mm3 (OR 41.53; CI 95%; p=0.001), ANC 100-500/mm3 (OR 74,03; CI 95%; p<0.001) during the infection episode, presence of central venous catheter (OR 176.46; CI 95%; p<0.001) were found to increase the risk of infection rates.

Of the infection episodes, 77.4% were neutropenic fever, 21.9% were catheter infections, 12.9% were viral infections, 5.9% were fungal infections. BFM ALL-IC 2009 treatment protocol (OR 4.75, CI 95%, p<0.001) and prolonged neutropenia (OR 3.95, CI 95%, p<0.001) were related with increased rate of neutropenic fever episodes. Of the invasive fungal infections, 23.5% were proven, 76.5% were probable infection. Patient age below <3.5 year-old (OR 0.87; CI95%;p=0.006), prolonged neutropenia (OR 2.01; CI 95%;p=0.002) were found to be related with increased risk of invasive fungal infections. The rates of neutropenic fever, catheter infections and viral infections were higher in BFM ALL-IC 2009 protocol receivers, and invasive fungal infections were higher in St Jude Total XV Group; however these differences were statistically insignificant, except for viral infections.

Discussion: Although, the study design is retrospective, since the comparison of the infection episodes in two different protocols were summarized, study is original.

Keywords: ALL, infections, BFM, St Jude

■ Chronic Myeloid Leukemia

P-01 Abstract Referance: 15

EVALUATION OF CHRONIC MYELOID LEUKEMIA PATIENTS' APPROACHES TO TREATMENT-FREE REMISSION

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Objectives: Chronic myeloid leukemia(CML)is a stem cell disease characterized by abnormal clonal proliferation of myeloid precursor cells and accounts for 15% of adult leukemias.With the effective use of tyrosine kinase inhibitors(TKIs)in the treatment of CML,survival rates of CML patients have become closer to the general population.Although lifelong treatment of CML patients with TKIs is recommended,this treatment approach has been questioned and treatment-free remission(TFR)has become one of the treatment targets in CML.For TFR,the criteria set out in the ELN2020 guidelines should be followed(Table-1).The patient's approach to this issue is very important for the results of TFR studies to be applied in daily life.In our study,we aimed to evaluate the approaches of CML patients followed in our center regarding treatment-free remission.

Methods and Materials: Patients aged 18 years and older who were followed up in ESOGU Hematology Department with a diagnosis of chronic phase CML and who had been using a TKI for at least 3 months were included in the study.The study was a questionnaire study and the questions asked to the patients are given in Table-2.Clinical and laboratory data were obtained from patient files and hospital records.

Results: The mean age of 105(51 female,54 male)patients was 55.8 years. The most recently used TKI was imatinib in 68 patients(64.8%),dasatinib in 12(11.4%),nilotinib in 20(19%)and bosutinib in 4(3.8%).31(29.5%)patients were very satisfied with treatment,68(64.8%)were satisfied,2(1.9%)were dissatisfied and 4(3.8%)patients were undecided about treatment satisfaction.14(13.3%)patients thought of discontinuing the treatment and 80(76.2%)patients never thought of discontinuing the treatment.71(67.6%) patients stated that they would discontinue treatment if the doctor deemed it appropriate,17(16.2%)would not discontinue treatment and 17(16.2%)were undecided.Among those who wanted to discontinue treatment,21(22.1%)patients stated side effects,3(3.2%)patients stated difficulty in accessing the drug,1(1.1%)stated drug cost,2(2.1%)stated pregnancy plan,7(7.4%)stated difficulty in use,2(2.1%)stated social security problem, 5(5.5%, 3)patients stated that they wanted to discontinue treatment due to compliance problems,12(12.6%)patients due to multiple drug use,4(4.2%) patients due to work environment,2(2.1%)patients due to home environment,2(2.1%)patients due to dissatisfaction with the medication and 34(35.8%)patients due to other reasons.Of those who wanted to continue treatment,11(28.9%)stated that they would continue treatment because of the risk of disease recurrence, 7(18.4%)because they found the drug effective,7(18.4%)because they found the drug safe,9(23.7%)because they were satisfied with the drug and 4(10.5%)because the doctor recommended it.The number of patients who knew that there are studies showing that treatment can be discontinued in CML was 18(17.1%).78(32%)of the patients stated that they would discontinue treatment if the disease did not recur,9(3.7%)if they could use the same drug again,74(30.3%)if the doctor recommended it,49(20.1%)if there was no risk to life,3(1.2%)in case of pregnancy planning,4(1.6%)if their family supported them and 27(11.1%)if there were drugs that would improve their disease again.4(3.8%)patients stated that they could stop the medication despite the risk of relapse.Frequent follow-up visits after discontinuation affected the decision of 55(52.4%) patients.In the case of restarting the discontinued drug,the improvement in the disease was found to affect the decision of 77(73.3%)patients.

Conclusion: There are very few studies about the patient approach to treatment-free remission.Patients' willingness to discontinue the drug is as important as the results of TKI discontinuation studies.Since most of our patients were satisfied with treatment and never thought discontinuation it is concluded that we need time to encourage our patients for treatment discontinuation

Keywords: CML,tyrosine kinase inhibitors,treatment-free remission

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Table 1. Requirements for tyrosine kinase inhibitor discontinuation (ELN2020)

Mandatory	*Minimal (stop allowed)*	*Optimal (stop recommended for consideration):*
• CML in first CP only (data are lacking outside this setting)	• First-line therapy or second-line if intolerance was the only reason for changing TKI	• Duration of TKI therapy >5 years
• Motivated patient with structured communication	• Typical e13a2 or e14a2 BCR–ABL1 transcripts	• Duration of DMR >3 years if MR4
• Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results	• Duration of TKI therapy >5 years (>4 years for 2GTKI) • Duration of DMR (MR4 or better) >2 years	• Duration of DMR >2 years if MR4.5
• Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter	• No prior treatment failure	

Table 2.	
1) Are you satisfied with your treatment?	a) Very satisfied b) I'm satisfied c) I'm not satisfied d)Undecided
2) Have you ever thought about stopping treatment?	a) Yes. b) No. c) Sometimes
3) Would you be willing to stop taking your medication if your doctor agrees?	a) Yes b) No. c) Undecided
4) What is your reason for wanting to stop treatment? (For patients who answered yes to question 3, more than one option can be selected)	a) Side effects b) Problem of access to medicines c) Cost d) Pregnancy plan e) Difficulty of use f) Dissatisfaction with the medicine g) Family influence h) The problem of social security i) Compliance problem j) Taking too many medications k) Work environment l) School environment m) Home environment n) Others
5) What is your reason for wanting to continue treatment? (For patients who answered no to question 3, more than one option can be selected)	a) Concern about recurrence of the disease b)Family influence c) Finding the medicine effective d) Finding the medicine safe e) Satisfaction with medicine f) My doctor's advice g) Others
6) Do you know that there are studies showing that treatment can be stopped in CML?	a)Yes b)No
7) Under which conditions would you consider stopping treatment (more than one option can be selected)?	a) If my disease does not recur b) If I can use my same medicine again c) If my doctor recommends d) If there is no risk to life e) If my family supports me f) If I plan a pregnancy g) If there are medicines that can make me well again
8) Would you consider stopping the medication despite the risk of relapse?	a) Yes b) No c) Undecided
9) Will the fact that you will have more frequent check-ups after stopping the medication affect your decision?	a) Yes. b) No c) Undecided
10) Would the fact that almost all patients improved again when you restarted the medication you stopped affect your decision?	a) Yes b) No c) Undecided

■ Chronic Lymphocytic Leukemia

P-02 Abstract Referance: 10

THE EFFECT OF T-LYMPHOCYTE SUBGROUPS AT DIAGNOSIS ON CHRONIC LYMPHOCYTIC LEUKEMIA PROGNOSIS

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Introduction: Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in western countries. Although an increase in CD4 and CD8 T-lymphocyte counts is seen in CLL patients, it is controversial whether T-lymphocytes have a stimulating or anti-tumoral effects on leukemic B-lymphocytes. The purpose of this study was to examine the prognostic significance and effects on survival of T-lymphocyte subgroups in flow cytometry at diagnosis of CLL patients.

Material and methods: Eighty-three previously untreated CLL patients who were followed between September 1998 and September 2019 at our center were enrolled retrospectively into the study after obtaining ethics committee approval in line with the principles of the World Medical Association's Declaration of Helsinki. Patients with secondary malignancies at diagnosis were excluded. Patient age, sex, disease stages, laboratory values, and flow cytometry results at diagnosis were examined. Patient progression-free-survival (PFS), overall survival (OS) and treatment times were determined. Malignant B-Cells (MBC) were defined as CD5+CD19+ B-lymphocytes. T-lymphocyte ratios to MBC ratios were calculated from these results. Continuous parameters were analyzed with Kruskal-Wallis and Mann-Whitney U tests. Categorical parameters were analyzed using the Chi-squared test. Spearman analysis was used for correlation. Cox regression models were used to determine the factors affecting survival times. IBM SPSS version 27.0 was used and a p-value < 0.05 was considered statistically significant in all analyses.

Results and discussion: There was no difference in T-lymphocyte parameters according to age, gender, or modified Rai and Binet stages. The CD7 percentage (p: 0.026), CD4/MBC (p: 0.033), CD8/MBC (p: 0.027), and CD7/MBC (p: 0.036) values at diagnosis were significantly lower in patients who required multiple treatment regimens; however, no correlation was found with Time-To-First-Treatment. The CD4 percentage (p: 0.048), CD7 percentage (p: 0.020), CD4/MBC (p: 0.021), CD8/MBC (p: 0.035), and CD7/MBC (p: 0.012) values at diagnosis were significantly lower in patients with a progressive disease. Correlation analysis revealed a positive correlation between CD3 (r: 0.257, p: 0.019), CD4 (r: 0.249, p: 0.023), CD7 (r: 0.247, p: 0.024), and CD8 (r: 0.286, p: 0.017) percentages at diagnosis and PFS. In the multivariate regression model, the Rai stage (intermediate + high risk), CD7/MBC ratio, and treatment status (yes) had a significant effect on PFS (χ^2=41.470, p < 0.001). A single unit of increase in the CD7/MBC ratio decreased the risk of progression by 93.1 % (95% CI: 0.005-0.881, p: 0.040). CD3 (p: 0.001), CD4 (p: 0.001), CD8 (p: 0.005), and CD7 (p: 0.007) percentages were significantly lower in deceased patients. However controversially, CD4/MBC (p: 0.011), CD8/MBC (p: 0.019) and CD7/MBC (p: 0.032) were significantly higher in deceased patients. Correlation analysis revealed a positive correlation between CD3 (r: 0.286, p: 0.009), CD4 (r: 0.262, p: 0.017), CD8 (r: 0.310, p: 0.004) percentages; absolute CD8 value (r: 0.233, p: 0.048), CD4/MBC (r: 0.273, p: 0.023), CD8/MBC (r: 0.305, p: 0.011), CD7/MBC (r: 0.270, p: 0.035) parameters at diagnosis and overall survival time (OS). In the multivariate regression model, the Rai stage (intermediate + high risk) and CD8/MBC ratio had a significant effect on OS (χ^2=9.237, p: 0.010). A single unit of increase in the CD8/MBC ratio decreased the mortality risk by 99.99 % (95% CI: 0.001-0.001, p:0.002). Our study has shown that low T-lymphocyte percentages and low T-lymphocyte/MBC ratios at diagnosis are associated with poor prognosis, progressive disease, and decreased survival.

We think that the role of T-lymphocytes in CLL prognosis could be revealed in more detail with prospective studies evaluating naive T-lymphocyte and differentiated T-lymphocyte subgroups, as well as functional T-lymphocyte markers such as HLA-DR, PD-1.

Keywords: cll, T-lymphocytes, B-lymphocytes

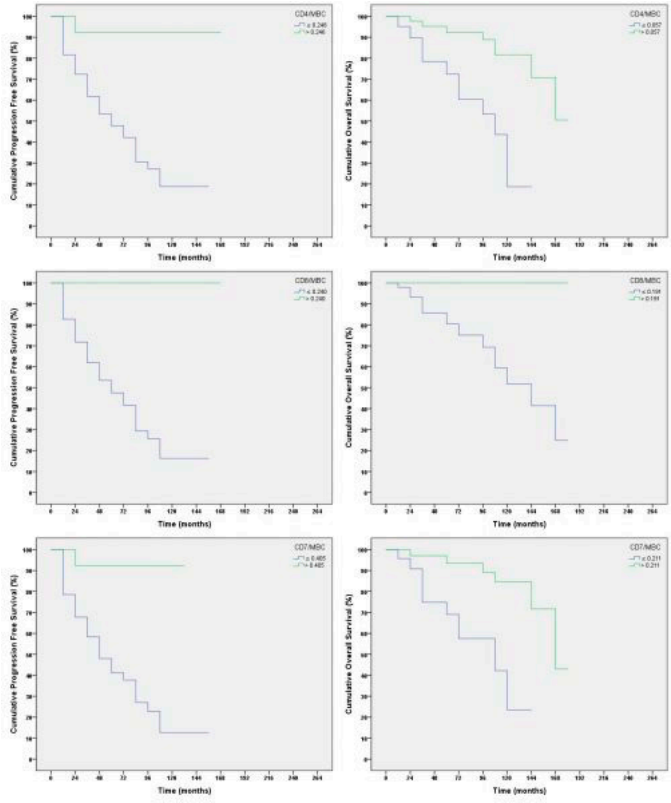

Figure 1. PFS and OS using cut-off values for T-lymphocyte/MBC ratios determined with ROC analyses and Kaplan-Meier tests.

■ Myeloprofilerative Disorders

P-03 Abstract Referance: 19

COMPARISON OF POLYCYTHEMIA VERA PATIENTS DIAGNOSED BEFORE AND AFTER UPDATED DIAGNOSTIC CRITERIA

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Introduction and purpose: PV is a chronic, clonal and progressive myeloproliferative disease characterized by leukocytosis, thrombocytosis and splenomegaly with an increase in the erythroid series, in which JAK2 V1617F mutation is the most common(1). In its natural course, there is an increased risk of thromboembolic and hemorrhagic complications and predisposition to the development of MF, MDS and AML(2, 3). The incidence is estimated to be 2.3-2.8 per 100,000 person/year, with a median age at diagnosis of approximately 60 years and a male to female ratio of 1.2:1. With the 2016 WHO diagnostic criteria for the diagnosis of PV, the hgb threshold was lowered to 16.5 g/dL in men and 16 g/dL in women, and the hct threshold was updated to 49% in men and 48% in women. These changes were made due to retrospective studies showing the presence of patients with JAK2-V617F mutation positive myeloproliferative neoplasia and hemoglobin levels below 18.5 g/dL in men and 16.5 g/dL in women with an increased risk of thrombotic complications during follow-up and a worse prognosis, mostly diagnosed with ET but with bone marrow characteristics consistent with PV(4-7).In our study, we aimed to compare the clinical and laboratory characteristics of patients diagnosed with PV according to the 2008 and 2016 WHO diagnostic criteria in terms of clinical and laboratory features as well as complications during follow-up and to evaluate the effects of the change in diagnostic criteria on real life.

Material and method: In our study, patients aged 18 years and older who were diagnosed with PV and followed up in Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Hematology between January 2011-December 2015 and January 2016-December 2020 were evaluated in two groups. Data were obtained from the hospital automation system and by examining the files of patients diagnosed with PV who came to the hematology outpatient clinic for follow-up.

Results: In our study, 50 (50%) patients were diagnosed between January 2011-December 2015 and 50 (50%) patients were diagnosed between January 2016-December 2020. Demographic characteristics of the patients are summarized in Table 1. In our study, no significant difference was found when the patients before and after 2016 were compared in terms of age at diagnosis, gender, smoking, symptoms and findings at diagnosis, comorbidities, bone marrow pathology findings at diagnosis, cytoreductive, antiaggregant, anticoagulant therapies received. Complete blood count parameters of the patients at the time of diagnosis are summarized in table 2. JAK2-V617F mutation was positive in all (100%) patients.No significant difference was found between MCV, uric acid, CRP, LDH, D-dimer, EPO levels. The treatments administered to the patients during the follow-up period are shown in table 3. Phlebotomy was performed in 98 (98%) patients. 2016 When the two groups diagnosed before and after 2016 were compared in terms of the total number of phlebotomies in the first year and at the last visit, it was found that the numbers were higher in the pre-2016 group (p=0.01 and p=0.00). Complications developed in 19 (38%) patients in the pre-2016 group and 4 (8%) patients in the post-2016 group during follow-up (p=0.001).The distribution of complications is shown in table 4.

Discussion: Although the number of patients who developed complications was higher in the pre-2016 group, a statistically significant difference was found only in the development of MF. We think that this was due to the longer follow up period for patients before 2016 and the limited number of patients included in our study, and we think that significant differences may occur for other complications with larger studies. We think that the higher number of complications in the pre-2016 group is related to both the high hgb, htc, erythrocyte count at the time of diagnosis and the longer follow-up period.

Keywords: Polistemia vera, diagnosis, treatment, complications

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Table 1. Demographic features

Parameters	*Before 2016*	*After 2016*	*p value*
Erkek/Kadın oranı	1,5	1,7	(p=0,837)
Age at diagnosis(mean±sd)	58,5±12,25	62±13,8	(p=0.96)
High risk group	28 (%56)	33 (%66)	0.412
Follow-up period(mean±sd)	95,5±36,4	29±19,3	(p=0,000)
Cigarette smoking	28 (%56)	26 (%52)	(p=0.84)

Table 2. At diagnosis Complete Blood Count Parameters

Parameters	*Before 2016*	*After 2016*	*p value*
Hgb (gr/dl) (mean±sd)	18,6±1,03	17,1±1,16	0.000
Hct (%)(mean±sd)	58,1±4,1	52,2±4,2	0.000
Erythrocyte /µl (median)	7.262.800	6.433.200	0.000
Leucocyte /µl (median)	16.990	11.424	0.056
Platelets /µl (median)	489.520	442.580	0.34
MCV (fl) (median)	94,3	83,3	0.34

Table 3. Treatment

Treatment	*Before 2016*	*After 2016*
Phlebotomy+HU	39	34
Phlebotomy+HU+Anagrelide	7	0
Phlebotomy+HU+Interferon	0	2
Phlebotomy only	4	12
Only HU	0	1
HU+Anagrelide	0	1

Table 4. Complications

Complications	*Before 2016*	*After 2016*	*p value*
Thrombosis	9(%18)	2(%4)	(p=0.055)
Bleeding	6(%12)	1(%2)	(p=0.110)
Myelofibrosis	11(%22)	1(%2)	(p=0.006)
Acute myeloid leukemia	1(%2)	1(%2)	(p=1.000)
Myelodysplastic syndrome	0 (%0)	0 (%0)	(p=1.000)

■ Non-Hodgkin's Lymphoma

P-04 Abstract Referance: 21

EVALUATION OF THE EFFICACY AND SAFETY RITUXIMAB, LENALIDOMIDE,AND IBRUTINIB IN RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

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Background: Relapsed or refractory (R/R) Non-Hodgkin Lymphoma (NHL) is associated with poor outcomes and the therapic options are limited. Recently, the combination of rituximab, lenalidomide, and ibrutinib (RLI) suggest promising efficacy in some clinical studies. Consequently, we evaluated the RLI in a real-life setting.

Methods: This retrospective, single-center study analyzed the outcomes of RLI as an off label salvage theraphy in patients (pts) with R/R NHL from June 2020-April 2022. All pts received L 10-25 mg po daily on days 1-21 every 28 days and I 560 mg po daily on days 1-28. Pts with diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), marginal zone lymphoma (MZL) received 375 mg/m2 iv R on day 1 of cycles (cys) 1-6 every 28 days, pts with mantle cell lymphoma (MCL) received the same dose of R once a week for 4 weeks during cy 1, then on day 1 of cys 1-12 every 8 weeks. I and/or L was administered until progression or unacceptable toxicity. The response was assessed with according to the Lugano criteria. The primary end point was overall response rate (ORR). Secondary endpoints were complete response (CR), partial response (PR), time to response (TTR), duration of response (DoR), overall survival (OS), progression free survival (PFS) and safety.

Results: We analyzed 21 pts including DLBCL (n = 16), PCNSL (n = 2), MCL (n = 2), MZL (n = 1) (Table 1). The median age was 60 years (range, 24-84); 53% had advanced disease stage; 57% were refractory to their last therapy; 67% had non-GCB DLBCL and PCNSL, and 56% with DLBCL had MYC and BCL2 and/or BCL6 rearrangements. Median number of prior therapies was 3 (range, 2-6). Eleven pts had prior auto/allo transplant. Median follow-up time was 6.6 months (range, 0.4–22.3). Eleven pts (52%), 6 pts (29%) and 2 pts (10%) received RLI for ≥ 3, 6 and 12 months respectively. Pts had received a median of 3 (range, 1-19) cys of RLI. Progressive disease (PD) was the most common reason for treatment discontinuation (53%). One (5%) patient discontinued therapy due to adverse events (AEs) (sepsis). The most common non-hematologic AEs were fatigue (48%), infection (33%), diarrhea (24%). AEs were frequently reported at the 25 mg L dose, and the majority (77%) of pts experienced a grade 1-2 AEs. The hematologic AEs were neutropenia (48%) (grade 3-4; 100%), thrombocytopenia (19%) and anaemia (14%). All of the pts were evaluable for response. The median TTR was 2 months (range, 1.7-3.8). The ORR was 38% (95% CI 15%-61%) with 29% CR and 9% PR (Figure 1). The median DoR was 12.8 months (range, 4.4-19.5+). Deaths were reported for 13 (62%) pts (n = 10 PD, n = 3 AEs). The median OS was 7.9 months (95% CI 2.2-13.5) and median PFS was 3.5 months (95% CI 0.0- 8.3) (Figure 2).

Conclusions: Our results suggest that RLI is a viable therapeutic option with promising activity and favorable toxicity profile in pts with R/R NHL.

Keywords: R/R Non-Hodgkin Lymphoma, RLI

Age, median (min-max)		60 (24-84)
NHL subtype	DLBCL	16 (76)
	MCL	2 (9.5)
	PCNSL	2 (9.5)
	MZL	1 (5)
Stage at diagnosis, n (%)	Stage 1	7 (33)
	Stage 4	11 (53)
	Unknown	3 (14)
Previous treatment lines before RLI	2	8 (38)
	3	8 (38)
	4	2 (9.5)
	5	2 (9.5)
	6	1 (5)
Bulky Disease before RLI		8 (38)
SCT, Ibrutinib, Lenalidomide therapies before RLI	ASCT	11 (53)
	ASCT+Allo-HCST	2 (9.5)
	Ibrutinib	3 (14)
	Lenalidomide	3 (14)
Bone narrow involvement at diagnosis		4 (19)
DLBCL/PCNSL subtype	GCB	4 (22)
	ABC	7 (39)
	NOS	5 (28)
	N/A	2 (11)
Disease status before RLI	Primary Refractory	7 (33)
	Relapsed	9 (43)
	Relapsed/ Refractory	5 (24)

Figure 1. Response to RLI

	MCL	2 (9.5)
	PCNSL	2 (9.5)
	MZL	1 (5)
t diagnosis, n (%)	Stage 1	7 (33)
	Stage 4	11 (53)
	Unknown	3 (14)
is treatment lines before RLI	2	8 (38)
	3	8 (38)
	4	2 (9.5)
	5	2 (9.5)
	6	1 (5)
Disease before RLI		8 (38)
	ASCT	11 (53)
rutinib, Lenalidomide therapies before	ASCT+Allo-HCST	2 (9.5)
	Ibrutinib	3 (14)
	Lenalidomide	3 (14)
arrow involvement at diagnosis		4 (19)
/PCNSL subtype	GCB	4 (22)
	ABC	7 (39)
	NOS	5 (28)
	N/A	2 (11)
status before RLI	Primary Refractory	7 (33)

Figure 2. Survival

Table 1. Patient characteristics

Sex, n (%)	Male	10 (48)
	Female	11 (52)
Age, median (min-max)		60 (24-84)
NHL subtype	DLBCL	16 (76)
	MCL	2 (9.5)
	PCNSL	2 (9.5)
	MZL	1 (5)
Stage at diagnosis, n (%)	Stage 1	7 (33)
	Stage 4	11 (53)
	Unknown	3 (14)
Previous treatment lines before RLI	2	8 (38)
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Bulky Disease before RLI		8 (38)
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	ASCT+Allo-HCST	2 (9.5)
	Ibrutinib	3 (14)
	Lenalidomide	3 (14)
Bone narrow involvement at diagnosis		4 (19)
DLBCL/PCNSL subtype	GCB	4 (22)
	ABC	7 (39)
	NOS	5 (28)
	N/A	2 (11)
Disease status before RLI	Primary Refractory	7 (33)
	Relapsed	9 (43)
	Relapsed/ Refractory	5 (24)
Median time between the last theraphy and RLI, day (min-max)		56 (0-1731)

■ Other

P-05 Abstract Referance: 25

FACTORS AFFECTING THE INCIDENCE OF COMPLICATIONS AND MORTALITY OF FEBRILE NEUTROPENIA IN CHILDREN WITH ACUTE LEUKEMIA

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Background: Febrile neutropenia (FN) is an important and common complication that causes high morbidity and mortality in patients with malignancy. Epidemiological data and agents causing infections in FN can change in each region and over time, which affects the management and outcomes of the patients.

Objective: We aimed to investigate the etiology, epidemiological distribution and its change over the years, clinical course, and factors affecting the incidence of severe complications and mortality of FN in children with acute leukemia.

Methods: We retrospectively analyzed the demographic data, foci of infection, etiological pathogens, laboratory parameters, treatments, severe complications, and mortality of patients with acute leukemia under the age of 18 who were diagnosed with FN between January 2010 and December 2020. FNs occurring in bone marrow transplant recipients were excluded.

Results: In 153 patients, a total of 450 FNEs occurred, 84 (54.9%) were male and the median age of the patients at the first FNE was 6.5 years (3-12.2). 127 patients (83%) were diagnosed with ALL and 26 patients (17%) with AML. The median number of FNE per patient was 2 (1-11). The median duration of fever was 2 days (1-5), and the median duration of post-fever neutropenia was 7.5 days (5-13). Fever focus was found in approximately half of the patients, and etiology was found in 38.7% of the patients. The most common focus of fever was bloodstream infection (n=74, 16.5%), upper respiratory tract infection (n=43, 9.6%), low respiratory tract infection (n=34, 7.6%), and urinary tract infection (n=25, 5.6%). In etiology, bacterial infection was identified in 22.7% (n=102), viral infection in 13.3% (n=60), and fungal infection in 6.7% (n=30) of the episodes. More than one etiologic pathogen was detected in 18 (4%) FNEs. Of the 112 bacteria identified, 72 (64.3%) were gram-negative pathogens. While 26 (23.2%) of a total of 112 bacteria were antibiotic resistant, 33.3% of gram-negative bacteria were found to be resistant. Monotherapy was used in the empirical treatment of 182 (40.4%) of FNEs. The median treatment duration of FNEs was 10 (7-17) days. The severe complication rate was 7.8% (n=35) and the mortality rate was 2% (n=9). Prolonged duration of fever and prolonged neutropenia after fever, high CRP level, and having refractory/relapsed malignancy increased the frequency of serious complications and mortality. In logistic regression analysis, refractory/relapsed malignancies and high CRP at first admission were found to be the most important independent risk factors for mortality.

Conclusion/Application to practice: We showed that the most common etiologic cause was bacterial infections due to gram-negative pathogens and the most common focus of FN was bloodstream infections in our center in the last ten years. Prolonged duration of fever, relapsed/refractory malignancies, presence of fever focus, and high CRP level were significant poor risk factors on clinical course and outcome. Evaluating the etiological and epidemiological data and outcomes of patients regularly is important to better manage FNE, improve quality of life, and reduce complication and death rates in children with acute leukemia. For this purpose, each region should closely monitor its etiological distribution, epidemiological characteristics, and changes over time.

Keywords: Acute leukemia, children, febrile neutropenia, prognosis

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■ Stem Cell Transplantation

P-06 Abstract Referance: 26

THE LDH LEVEL AFTER THE INFUSION OF FRESH OR CRYOPRESERVED HEMATOPOIETIC PROGENITOR CELLS HAS NO IMPACT ON THE OUTCOME

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Background: The aim of this study was to evaluate the LDH (Lactate *dehydrogenase*) levels after the infusion of fresh or cryopreserved hematopoietic progenitor cells (HPC) and their effect on allogeneic hematopoietic stem cell transplant outcomes (Allo-HSCT).

Methods: In this cross-sectional retrospective study, 40 patients with acute leukemia who underwent Allo-HSCT in our center between 30.05.2017-01.02.2023 were included. We evaluated the impact of fresh (n=20) or cryopreserved (n=20) stem cell grafts on LDH level, engraftment, acute graft-versus-host disease (GVHD), chronic GVHD, relapse, and survival. We also considered evaluating the effect of LDH level on HPC viability, however, evaluation of cell viability after melting is usually checked under the microscope with acridine orange staining in our center and unfortunately, it cannot be done routinely. Most of the patient's product viability couldn't be performed because of the distance between the transplant unit and the hematology laboratory where the microscope is settled. So, we try to find another parameter that can predict HPC viability and retrospectively evaluated the LDH levels. Categorical variables were compared with the use of Fisher's exact test or the $\chi 2$ test. Survival probabilities were estimated by the Kaplan-Meier method, and the Log-Rank test was used for univariate comparison. All analyses and graphs were obtained using the statistical software SPSS Statistics 26 (SPSS; IBM Corp., Armonk, NY, USA).

Results: All patients in both groups were transplanted from a relative donor. Of the patients who used cryopreserved grafts, 10 were male and 10 were female and the median age was 45 years (range: 24-68 years), 18 were diagnosed with AML and 2 were diagnosed as ALL. Of the patients who were transplanted using fresh grafts, 11 were male and 9 were female. The diagnosis of 18 patients was AML, 2 of them was ALL, and the median age of the patients was 32.5 years (min:22 max:58). LDH levels of patients who used cryopreserved grafts were significantly higher than those who used fresh graft (p:0.000). The median LDH for cryopreserved graft was 416.5 (min:132 max:638) and median LDH for fresh graft was: 163.5 (min:120 max:308) (p=0.000). There was no difference between fresh vs cryopreserved grafts for acute and chronic graft-versus-host disease (aGVHD) (p:0.744 and p:0.723). Patients who had received cryopreserved graft prolonged OS compared to fresh (NR vs 28.6 mos (95% CI 21.9-35.2); p=0.1) (Figure-1). Eight (40%) of 20 acute leukemia patients who had received fresh grafts had active disease at the time of Allo-HSCT (p=0.028), and as expected relapse was found higher in the fresh group (fresh:40% vs cryopreserved:10%; p=0.028). There was no statistically significant difference between the groups in terms of neutrophil engraftment (p:0,311), and platelet engraftment (p:0,548). However, the median time to engraftments was prolonged in the cryopreserved group than in the fresh group. Respectively for the cryopreserved and fresh group, the median time to neutrophil (>0.5 × 10^9/L) was 19.5 days (range:14-27) and 17.5 days (range:12-20) days (p = 0.001), and platelet engraftment (>20 × 10^9/L) 14.5 days (range:9-26) and 11 days (range:8-20) (p=0.029).

Conclusion: From the prognostic point of view, our results based on real-world experience showed an increase in serum LDH levels following stem cell infusion in cryopreserved versus fresh grafts. Based on the results of our study, graft cryopreservation does not significantly increase the risk of GVHD, relapse, or survival. But it is important to highlight that the median time to engraftment was prolonged in the cryopreserved group than in the fresh group.

Keywords: Lactate dehydrogenase, cryopreservation, bone marrow transplantation

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3-Impact of Cryopreservation of Peripheral Blood Stem Cells (PBSC) in Transplantation from Matched Unrelated Donor (MUD) Gabriele Facchin 1,2,*, Chiara Savignano 3 , Marta Lisa Battista 1 , Miriam Isola 2,4 , Maria De Martino 2,4 , Giuseppe Petruzzellis 1,2, Chiara Rosignoli 1 , Umberto Pizzano 1,2, Michela Cerno 1 , Giulia De Cecco 3 , Antonella Bertone 3 , Giovanni Barillari 3 , Renato Fanin 1,2 and Francesca Patriarca 1,2,*

4-Efects of freezing rate on structural changes in l lactate dehydrogenase during the freezing process Haena Park1 , Jun Young Park1 , Kyung Min Park2,5 & Pahn Shick Chang1,3,4,5*

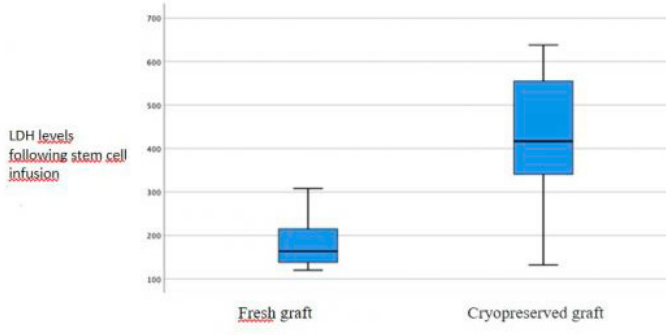

Figure 1. The LDH (Lactate dehydrogenase) levels after the infusion of fresh or cryopreserved hematopoietic progenitor cells (HPC)

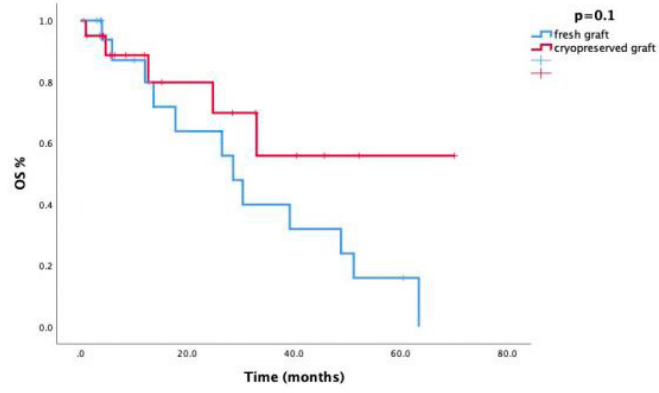

Figure 2.

Table1. Descriptive statistics

	Product		Statistic
AGE	Fresh graft	Median	32.50
		Minimum	22
		Maximum	58
	Cryopreserved graft	Median	45
		Minimum	24
		Maximum	68
Followup (month)	Fresh graft	Median	7.25
		Minimum	.6
		Maximum	51.2
	Cryopreserved graft	Median	10.25
		Minimum	4.1
		Maximum	52.2
LDH levels following stem cell infusion	Fresh graft	Median	163.50
		Minimum	120
		Maximum	308
	Cryopreserved graft	Median	416.50
		Minimum	132
		Maximum	638
neutrophil engraftment (>1 × 109/L)	Fresh graft	Median	19
		Minimum	12
		Maximum	29
	Cryopreserved graft	Median	24.50
		Minimum	15
		Maximum	32
neutrophil engraftment (>0.5 × 109/L)	Fresh graft	Median	17.50
		Minimum	12
		Maximum	20
	Cryopreserved graft	Median	19.50
		Minimum	14
		Maximum	27
platelet engraftment (>20 × 109/L)	Fresh graft	Median	11
		Minimum	8
		Maximum	20
	Cryopreserved graft	Median	14.50
		Minimum	9
		Maximum	26
platelet engraftment (>50 × 109/L)	Fresh graft	Median	14
		Minimum	12
		Maximum	24
	Cryopreserved graft	Median	17.50
		Minimum	13
		Maximum	32

	Fresh Graft (n=20)	*Cryopreserved graft (n=20)*	*P value*
Median Age (years)	32.5	45	
Gender (M/F)	11/9	10/10	0.752
Diagnosis (AML/B-ALL/T-ALL)	18/2/0	18/1/1	0.513
Disease status at the time of Allo-HSCT(1. CR/2.CR/Active disease)	10/2/8	14/6/0	0.005
Alive/dead	8/12	15/5	0.025

Acute Myeloid Leukemia

P-07 Abstract Referance: 40

INVASIVE FUNGAL INFECTION (IFI) PROPHYLAXIS AND FREQUENCY OF IFI IN PATIENTS WITH AML RECEIVING LOW-INTENSITY INDUCTION

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Introduction: Invasive fungal infections (IFIs) significantly causes mortality and morbidity in hematological malignancies. The use of antifungal prophylaxis is recommended in high-risk patients[1]. It is unknown whether antifungal prophylaxis is required in patients receiving a non-intensive treatment such as a combination of hypomethylating agents and venetoclax recently used to treat acute myeloid leukemia and whether dose adjustment is required for some antileukemic drugs due to drug-drug interactions [2]. In this study, we aimed to determine the frequency of invasive fungal infection in acute myeloid leukemia patients receiving low-intensity induction.

Methods: The patient registry system was reviewed retrospectively between January 2021. Eleven patients diagnosed with acute leukemia who received azacitidine (AZA) and venetoclax (VEN) therapy for induction, reinduction, and salvage therapy were evaluated. The study period was between the onset of AZA/VEN therapy and the second course of treatment. During this period, the duration of VEN, daily and cumulative VEN dose, antifungal agent for prophylaxis, dose modifications of VEN for drug interactions, and adverse events ie, neutropenia, were recorded. The definition of fungal infection was determined as possible, probable, and proven according to the EORTC-MSGERC 2020 revised criteria[3] .

Results: 11 patients (n:11), 5 females (45.4%) and 6 males (54.5%), were included in this study and the median age was 62 years (range: 33 - 85). Demographic data and characteristics of the patients are given in Table 1. İn this period, the median follow-up duration was 28 days (range: 24 - 71). The patients who received AZA/VEN were 6 (54.5%), 2 (18.1%), and 3 (27.2%) as induction, reinduction, and salvage, respectively. The median onset day of VEN with AZA was 1 st day (range: 1 - 7). The VEN duration was 28 days (range: 22 - 32), and the cumulative VEN dose was 2800 mg (range: 2200 mg - 11400 mg). The median daily VEN dose was 100 mg (range: 100 – 400 mg). Nine patients (81.8%) had an absolute neutrophil count below $0.5x10^9$/L and all patients were lymphopenic at the end of the period. Median hemoglobin level was 8.7 g/dL (range: 7.1-10.8), median thrombocyte level was $64x10^9$/dL (range: 8-680), and febrile neutropenia episode was 2 (range: 1-2). Eight patients received posaconazole for primary antifungal prophylaxis and 2 patients for secondary antifungal prophylaxis. One patient did not receive antifungal prophylaxis. One patient was empirically switched to caspofungin due to refractory febrile neutropenia on the 11th day of treatment. In this patient, facial swelling occurred on the 18th day, and liposomal amphotericin b was used due to possible IFI. Mucor spp. was demonstrated on nasopharyngeal operation material, and IFI proved. Neither possible nor probable invasive fungal infection was observed in other patients during this period.

Of the 11 AML patients treated with AZA/VEN included in this study, 1 (%9) was diagnosed proven IFI and our incidence rate was similar to recent studies[4] . At the end of the study period, nine patients (81.1%) were neutropenic, and only one had a fungal infection. The dose and duration of venetoclax in this patient were similar to other patients. In addition, the patient who developed a fungal infection had secondary AML and received AZA/VEN treatment as salvage therapy.

Discussion: The VEN/AZA as a non-intensive, well-tolerated treatment provides patients compatibility to the therapy and outpatient administration. However, long-lasting neutropenia, which is not even seen in intensive treatments, is a handicap. Fortunately, antifungal prophylaxis can prevent the IFI risk. Dose modifications are needed to prevent drug interactions. This is a pilot study showing that "non-intensive" combinations for AML are as intensive as "intensive chemotherapies"; the management of these therapies should be the topic of prospective trials.

Keywords: Acute myeloid leukemia, Azacitidine, Venetoclax, Antifungal prophylaxis

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Table 1

Characteristic	All patients (n:11)
Age, median (range)	62 (33-85)
Sex, male (%)	6 (54.5%)
Follow-up duration, day (range)	28 (24-71)
Treatment Line (%)	
İnduction	6 (54,5)
Reinduction	2 (18,1)
Salvage	3 (27,2)
Onset day of VEN, median (range)	1 (1-7)
Duration of VEN, median (range)	28 (22-32)
Daily VEN dose, mg, median (range)	100 (100-400)
100 mg, n	6
200 mg, n	2
300 mg, n	0
400 mg, n	2 and 1*
End of the during,	
ANC, n	2
>0.5x10^9/L	9
<0.5x10^9/L	8.7 (7.1-10.8)
Hgb, median, g/dL	64 (8-680)
Plt, median, 10^9/dL	
Febrile neutropenia, n	9
None, n	2
Febrile neutropenia episode, median	2 (1-2)**
Posacanazole prophylaxis, n	
Primary	8
Secondary	2
None	1
IFI, n	
Proven	1
Probable	0
Possible	0

* The dose was changed according to the antifungal because of drug-drug interaction in the patient who developed proven IFI.
**One patient had a refractory fever.

■ Other

P-08 Abstract Referance: 6

EVALUATION OF SERUM IRON PARAMETERS AT THE TIME OF DIAGNOSIS IN HEMATOLOGICAL NEOPLASIA

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Introduction: Transfusional and non-transfusional iron overload (IO) is a common issue in benign and malignan hematological disorders. Iron homeostasis is strictly regulated in physiological conditions due to its potential toxicity. Main actor is the hepcidin-ferroporin axis [1].

The IO and its clinical associations in hematological neoplasias other than myelodysplastic syndrome (MDS) were studied poor. In this study, we aimed to determine the serum iron test status and the frequency of iron overload pattern at the time of diagnosis of the hematological neoplasia.

Patients and Methods: In this retrospective study, the data obtained from the medical charts and electronic records of 376 patients with hematological neoplasia who were diagnosed and treated in the Adult Hematology Department between February 9, 2000 and October 10, 2012. Patients who were 17 years of age or older, had serum iron tests without any specific

treatment before the diagnosis of the hematological neoplasia were included in the study. Patients were classified as pure inflammation pattern, pure iron deficiency (ID) pattern, inflammation-ID indistinguishable pattern, IO pattern, non-specific iron test disorder, and non-impaired condition according to the status of serum iron tests (Table 1). This study was approved by the Local Institutional Ethics Committee.

Results: There were 73 acute myeloid leukemia (AML), 20 acute lymphoblastic leukemia (ALL), 24 chronic lymphocytic leukemia (CLL), 13 chronic myeloid leukemia (CML), 122 myelodysplastic syndrome (MDS), 90 multiple myeloma (MM), 7 Hodgkin lymphoma (HL), 10 peripheral T-cell lymphoma (PTCL), and 17 diffuse large B-cell lymphoma (DLBCL) cases. Abnormality of iron tests is observed in 83.5% of patients and 61.4% of the patients were classifiable according to their serum iron tests. A serum iron test abnormality was highest in HL (100%), NHL (100%) and ALL (95%). ID pattern was observed in 23.1% of CML patients, and in 14.3% and 11.1% in HL and NHL, respectively. The frequency difference between the disease groups of the ID pattern is statistically significant ($p< 0.001$). When patients with lymphoproliferative diseases and MM under the title of mature lymphoid neoplasia (MLN) were compared together with other hematological neoplasms, the pattern of pure inflammation was found to be 23% and 8.8%, respectively. The difference between two groups was statistically significant ($p< 0.001$). When patients with MLN were compared together with other hematological neoplasms, the inflammation-ID indistinguishable pattern was found to be 14.9% and 4.4%, respectively. The difference between two groups was statistically significant ($p< 0.001$). The IO pattern was observed in 60% in ALL, 53.4% in AML, 53.3% in MDS, 18.9% in MM, 8.3% in CLL and 3.7% in NHL. No patients IO pattern were seen in CML and HL patients. The difference between the groups was statistically significant ($p< 0.001$).

Discussion: Abnormalities in serum iron tests at the time of diagnosis and its effect on survival in hematological neoplasms is a current curiosity. Many studies have been conducted about IO and its consequences especially in MDS [2, 3]. We observed that serum iron test abnormalities at the time of diagnosis were very common in hematological neoplasms. Inflammation pattern was frequently observed in MLN, while it was rarer in other cases. ID pattern was observed less frequently. Inflammation-ID indistinguishable pattern showed a distribution similar to the chronic inflammation pattern and was observed especially in MLN. The IO pattern, which is the main subject of interest of the study, was frequently observed in AML and MDS patients, as expected [4, 5]. Surprisingly, however, IO pattern was not uncommon in patients with ALL and myeloma. Its prognostic significance should be investigated in more detailed studies with more patients. Investigation of iron status may bring many innovations to the treatment of MM.

Keywords: Hematologic neoplasia, serum iron parameters, iron overload

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Table 1. Iron status according to interpretation of serum iron tests

Serum Iron (N= 59-158 mcg/dL males, N=37-145 mcg/dL females)	*TIBC (N= 228-448 mcg/dL)*	*Ferritin (N= 24-336 ng/mL males, 11-307 females)*	*Transferrin saturation (N= 15-45%)*	*Interpretation*
Decreased	Decreased	Normal or increased		Pure inflammation
	Normal or increased	Decreased	Decreased	Pure iron deficiency
Not pure inflammation pattern or pure iron deficiency	Not pure inflammation pattern or pure iron deficiency	Not pure inflammation pattern or pure iron deficiency	Decreased	Inflammation-iron deficiency indistinguishable
Normal or increased			Increased	Iron overload
Normal	Normal	Normal	Normal	Non-impaired condition
Others				Non-specific

Myeloprofilerative Disorders

P-09 Abstract Referance: 7

DIAGNOSIS AND MANAGEMENT OF BCR-ABL1-POSITIVE AND BCR-ABL1-NEGATIVE CHRONIC MYELOPROLIFERATIVE NEOPLASMS IN ELDERLIES

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Background: Chronic myeloproliferative neoplasms (CMPN) are characterized in the advanced stages by the recurrent evolution, increased disease burden and negative socio-economic impact[1,2,4-7]. CMPN, thus, may be considered as a challenging issue of public health and hematologic oncology due to the increased incidence, disability rates and disease burden. The objectives of the study were the diagnosis assertion and management evaluation of BCR-ABL1-positive and BCR-ABL1-negative CMPN in elderly patients.

Materials and Methods: We performed a descriptive and observational study, which enrolled 91 elderly patients with chronic myeloid leukemia (CML), primary myelofibrosis (PMF) and polycythemia vera (PV). They were followed up and treated at the Institute of Oncology between 1995 – 2022. The diagnosis was proved by histopathological, cytological, cytogenetic and molecular examinations of the bone marrow and peripheral blood[3,5,6,7]. The quantitative RT-PCR was accomplished with the aim to determine the expression of the BCR-ABL p210 and p190 transcripts in CML[2,3]. The quantitative detection of JAK2 V617F mutation, detection measurement of MPL mutation provided positive diagnostic criteria for BCR-ABL1-negative CMPN. The type of hematological malignancy was distinguished according to the 2018 Revision of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. The life-table method was used for Kaplan-Meier Survival Analysis with the aim to evaluate the long-term results of treatment.

Results: Thirty-four (37.3%) patients with PMF, 26 (28.6%) – with CML and 31 (34.1%) – with PV were diagnosed in the elderly age groups and followed up by our study. The age group of 60-69 years dominated in CML (22 cases or 84.6%), constituting 25 (80.6%) cases in PV, and 25 (73.5%) - in PMF. The duration of the disease from the onset to diagnosis ranged in PMF between 1.4-7 months (median – 3.7±0.63 months), in CML between 1.5-12 months (median – 2.1±0.37 months) and in PV between 1-7 months (median – 3.8±0.54 months). One- and 5-year overall survival (OS) of CML patients aged greater than or equal to 60 years old was 97.6% and 79% under the

treatment with tyrosine kinase inhibitors (TKIs), being lower as compared with the same indicators in the totality of CML. Under the combination of chemotherapy and phlebotomies the complete remission was achieved in all 31 PV patients. The duration of response ranged from 3 to 9 months (median – 5.8 months). The disease relapsed in all cases with plethoric syndrome and thrombocytosis, which required the restart of chemotherapy with busulfan, hydroxycarbamide, with regaining remissions. In elderly patients the OS over one year constituted 100%, over 5 years – 93.5%, over 10 years – 76.4% , being lower than those registered in all patients with PV (over one year – 100%, 5 years – 98.6%, 10 years – 85.9%). Although the relapse rate was lower in patients treated with busulfan as compared to those managed with hydroxycarbamide, there was no significant difference in the OS of the elderly PV patients undergoing chemotherapy with these antineoplastic agents.

Conclusions: The long-term results of treatment in elderly CMPN patients proved to be inferior to those in CMPN totality because of the development of age-related diseases, vascular accidents on the account of leuko-, thrombocytosis. The targeted treatment with TKIs remains the management option of choice for elderly CML patients regardless of the gender and blood count values. Imatinib may be used as a front-line treatment in Socal low and intermediary risk patients. In PV patients no significant difference was revealed in short- and long-term outcomes of chemotherapy with busulfan and hydroxycarbamide in combination with phlebotomy, being totally superior to those in PMF patients.

Keywords: myeloproliferative neoplasms, elderlies, BCR-ABL1, diagnosis, management

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Acknowledgments: The study was supported by the State University of Medicine and Pharmacy "N. Testemitanu" and Institute of Oncology. RT-PCR was commonly performed at the Laboratory of immunology and molecular genetics from the Institute of Oncology. The author has no conflict of interests to declare.

■ Acute Lymphoblastic Leukemia

P-10 Abstract Referance: 30

ACUTE LYMPHOBLASTIC LEUKEMIA WITH CHROMOSOMAL T(2,4)(Q31;Q32) AND HYPEREOSINOPHILIA: CASE REPORT

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Background: Hypereosinophilia is a condition in which the eosinophil count is >1500/µL and may develop due to primary or secondary causes. Some hematological malignancies and solid organ tumors may cause hypereosinophilia. However, acute lymphoblastic leukemia with hypereosinophilia is rare and usually associated with chromosome 5 abnormalities. A case of acute lymphoblastic leukemia with t(2,4) positive hypereosinophilia has not been reported before in the literature.

Case presentation: A 51-year-old male patient presented to our clinic with complaints of fever, cough, and shortness of breath for a month. He had no history of systemic disease, allergy, atopy, or parasitic infection. There were no notable features in his family history. On physical examination, he had petechial lesions on the anterior surface of both lower extremities. The complete blood count at the time of admission was leukocyte: 57.5300/µL, eosinophil: 6000/µL, lymphocyte: 4200/µL, monocytes: 2450 / µL, hemoglobin:12.6 g/dL, platelet: 32.000/µL, LDH: 708 U/L, uric acid: 7.5 mg/dl, troponin I: 667.9 pg/mL, ALP: 259.6 U/L, GGT: 840.9 U/L, ALT: 72. 9 U/L, albumin: 3.4 g/dL; CRP: 72.3 mg/L; while other laboratory findings were normal. In the peripheral blood smear, 25% of the cells were eosinophils and 5% were blasts. Bone marrow aspiration was performed due to the preliminary diagnosis of acute leukemia. Morphological examination revealed 30% eosinophil and 25% blast morphology cells (Figure 1). In the bone marrow flow cytometric examination, 31% of cells in the blast region of CD45-side scatter, cyt79A: 77%, CD19: 84%, CD22: 77%, HLA-DR: 94%, CD10: 83%, CD34: 86%, CD38: 59% were positive and he was diagnosed with B- ALL. In the cytogenetic analysis, 46,XY, der(4) and t(2,4)(q31;q33) were positive. T(9,22) and JAK2V617F mutation were negative.

Conclusions and discussion: The mechanism of hypereosinophilia accompanying some neoplastic diseases has not been fully known yet. It has been suggested that antigens expressed by tumor cells or exogenous factors such as viral infections may cause T-cell stimulation and increased production of eosinophilopoietic growth factors. However, the development of hypereosinophilia in patients with acute lymphoblastic leukemia is likely the result of a mixture of clonal and reactive processes. It has been shown that in the majority of patients with hypereosinophilia and ALL, abnormal lymphocytes produce significant amounts of Th2 cytokines (IL-3, IL-4, IL-5, IL-13) that induce eosinophil proliferation. Acute lymphoblastic leukemia is one of the possible causes of hypereosinophilia. In a few cases with hypereosinophilia associated with acute lymphoblastic leukemia, genetic abnormalities such as t(5; 14) (q31; q32) and del (5) (q15q33) have been shown to increase IL-3 gene activation and eosinophilopoietic cytokinin production. Acute lymphoblastic leukemia with t(2,4) positive hypereosinophilia is a case that has not been reported before in the literature and is presented to contribute to the literature.

Keywords: Acute lymphoblastic leukemia, hypereosinophilia, t(2,4)

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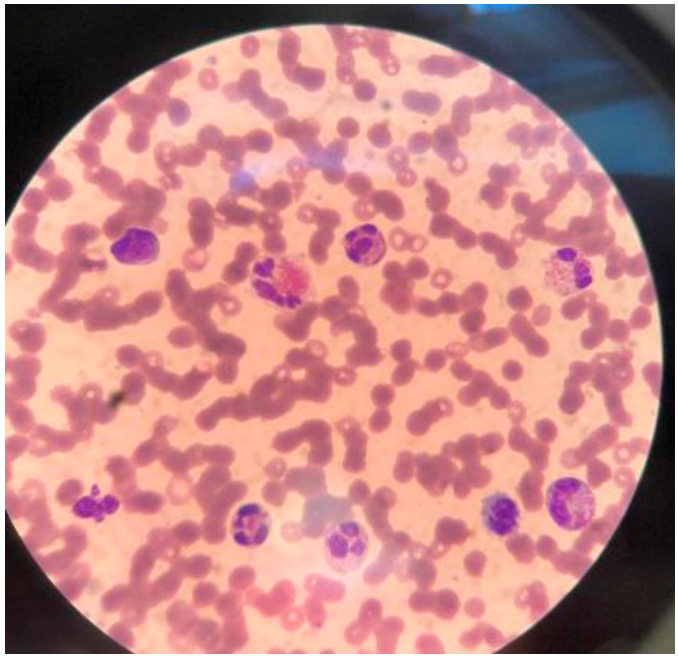

Figure 1. Hypereosinophilia and blasts in bone marrow smear

■ Multiple Myeloma

P-11 Abstract Referance: 32

A CASE OF MULTIPLE MYELOMA WITH EXTRAMEDULLARY OCULAR INVOLVEMENT

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Abstract: Multiple myeloma is a hematological neoplasia that occurs as a result of the neoplastic proliferation of plasma cells, often with extensive bone lesions and pathological fractures. Extramedullary involvement is present at the time of diagnosis in 7% and occurs during the follow-up process in 6% of cases and it is associated with poor survival. We report a case of extramedullary involvement with orbital mass in a multiple myeloma patient because of rarity.

Case: A 51-year-old female patient applied for an orthopedics clinic in April 2021 with pain in the right hip. A spontaneous fracture of the right femur was detected in the patient, and the biopsy result was reported as plasma cell neoplasia. The patient was referred to the hematology clinic and was diagnosed with lambda light chain type multiple myeloma. Three cycles of bortezomib, cyclophosphamide, and dexamethasone (VCD) chemotherapy protocol were applied. The patient's treatment was changed to bortezomib, thalidomide, and dexamethasone (VTd) with a stable disease response after the VCD chemotherapy protocol. Carfilzomib, lenalidomide, and dexamethasone (CRd) chemotherapy protocol was started because of after 4 cycles of VTd, the patient still had a stable disease response. Since stem cell mobilization was planned for autologous stem cell transplantation, lenalidomide treatment was discontinued and carfilzomib, thalidomide, dexamethasone combination treatment was started in the patient who had a very good partial response after 3 cycles of CRd treatment. However, stem cell mobilization was not performed because the patient's ECOG score was 3. Progressive disease was detected in the PET-CT of the patient, which was performed because of widespread body pain after 3 cycles of CTD treatment. Therefore, daratumumab, thalidomide, and dexamethasone combination treatment were started (DTd). The patient, who developed double vision and proptosis on the right eyelid after 2 courses of DTd, was consulted with the ophthalmology clinic. On the orbital computed tomography (CT) of the patient, a homogeneous solid lesion with dimensions of approximately 28*16 mm was detected in the axial plane in the extraconal distance at the superolateral level of the right orbit (figure 1). VDT-PACE treatment was started for the patient who was considered to have multiple myeloma-related extramedullary involvement by the ophthalmology clinic and was not suitable for biopsy. The patient's double vision improved after the treatment and a significant reduction in the mass in the right eye was detected. The patient died of neutropenic fever and septic shock during the follow-up period.

Conclusion and discussion: With the more accessible and frequent use of imaging methods, extramedullary involvement can be detected more frequently in patients with multiple myeloma. Orbital involvement is very rare in multiple myeloma. Proptosis, eye pain, red eye, diplopia, and decreased visual acuity are the most common clinical findings. Systemic chemotherapy and radiotherapy are recommended for its treatment. Although it is rare, orbital involvement of myeloma should be considered in the differential diagnosis of orbital lesions in patients with multiple myeloma.

Keywords: Keywords: Multiple Myeloma, Orbital mass, Extramedullary involvement

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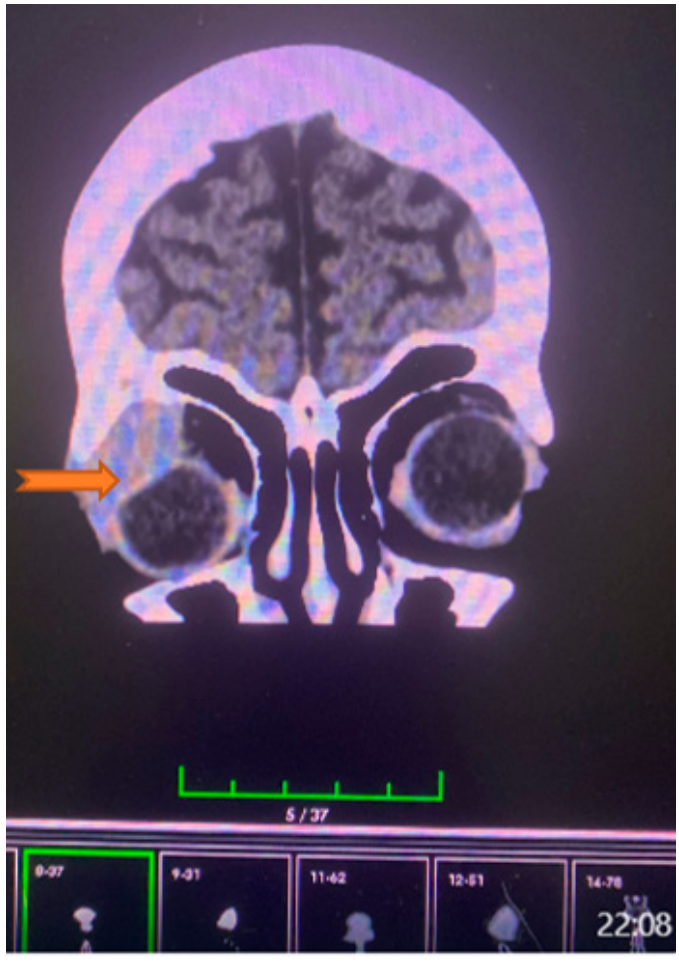

Figure 1. Solid lesion detected in the right orbit

■ Chronic Lymphocytic Leukemia

P-12 Abstract Referance: 37

A CASE OF CHRONIC LYMPHOCYTIC LEUKEMIA PRESENTING WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

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Introduction: Chronic lymphocytic leukemia is a mature B-cell neoplasm characterized by the accumulation of monoclonal B lymphocytes. Rarely, skin, lung, pleura, kidney, and gastrointestinal system involvement may occur in these patients. Central nervous system involvement is seen with a rate of 1-2% in chronic lymphocytic leukemia patients and is usually leptomeningeal rather than parenchymal. We present our patient, who presented with neurological symptoms and was diagnosed with chronic lymphocytic leukemia, due to its rarity.

Case Report: A 67-year-old male patient was admitted to our clinic with complaints of tingling in the hands and legs for the last 10 days, difficulty in walking, and loss of strength in the legs for the last week. Physical examination revealed no other pathology except a 6x4 cm lymphadenomegaly in the left axilla. In laboratory evaluation, it was leukocytes: 45000/µL, hemoglobin:15.9 g/dL, lymphocytes: 12320/µL, lactate dehydrogenase: 437 U/L, and uric acid: 6.93 mg/dL. Atypical large lymphocytes were observed in the peripheral smear (Figure 1). Flow cytometric examination of the bone marrow aspiration sample revealed that atypical lymphocytes were CD5, CD20, CD23, CD79a positive, CD10, and Tdt negative (Figure 2). The patient was diagnosed with chronic lymphocytic leukemia with the present findings. Since the patient had neurological findings, no signs of increased intracranial pressure syndrome were found in the eye fundus evaluation. No mass lesion was found on cranial imaging. Therefore, a cerebrospinal fluid examination was performed. Diffuse atypical lymphocytes were observed in the cerebrospinal fluid smear (Figure 3). Microprotein was 105.3 mg/dl, glucose was 92.9, Na was 146 mmol/L, CI was 133 mmol/L, and bacteria and viruses were reported as negative in the cerebrospinal fluid evaluation. Genetic tests of the patient revealed that the TP53 mutation was positive and the IgHV (immunoglobulin heavy chain) mutation was not detected.

Containing Methotrexate 1 g/m^2 and cytarabine* 3 g/m^2 chemotherapy regimen and intrathecal administration of methotrexate and cytarabine were administered alternately. Improvement was observed in all central nervous system symptoms.

Discussion and Conclusion: Central nervous system involvement of chronic lymphocytic leukemia is a rare condition in the literature. In patients with chronic lymphocytic leukemia with neurological symptoms, central nervous system involvement should be kept in mind as well as infectious and inflammatory causes. These cases can be treated by administering chemotherapy regimens containing methotrexate and cytarabine, which cross the blood-brain barrier well

Keywords: CLL, TP53 mutation, Central Nervous System Involvement

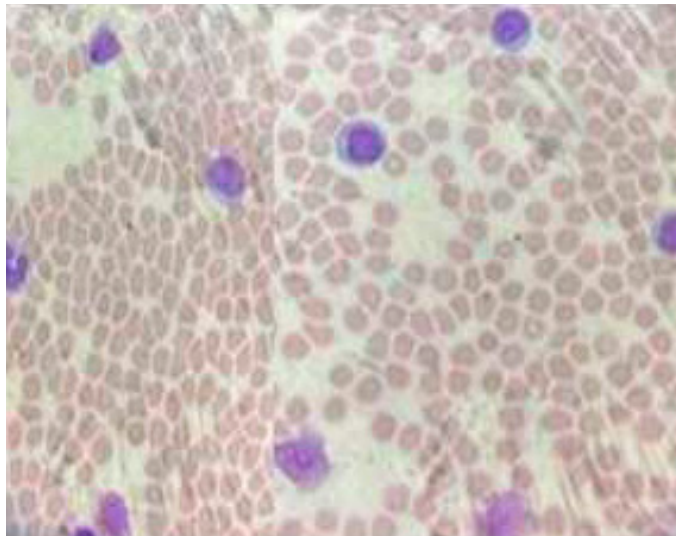

Figure 1. Peripheral smear at diagnosis

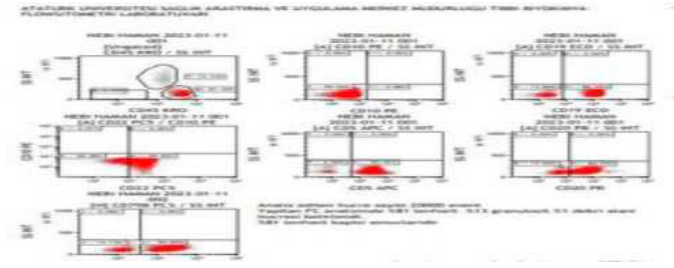

Figure 2. Flow cytometry findings

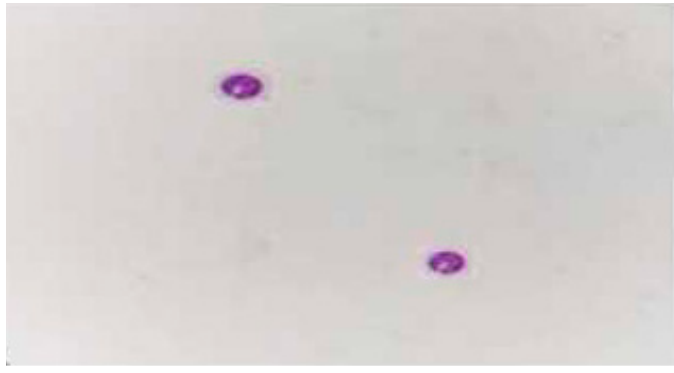

Figure 3. Cerebrospinal fluid smear

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■ Acute Myeloid Leukemia

P-13 Abstract Referance: 31

COEXISTENCE OF HEMATOLOGIC MALIGNANCIES; MDS AND MM; CASE REPORT

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İntroduction: The simultaneous occurrence of myelodysplastic syndrome and multiple myeloma in patients is a rare. We aimed to present our rare case of coexistence of MDS and MM.

Case presentation: We reported the case of a 67-year-old man, no known history of additional disease. He applied with complaints of weakness and fatigue. The patient had a white blood cell count of 5.4×10^9 per liter, hemoglobin level of 10.2 g/dL, platelet count of 92 × 109 per liter, and erythrocyte sedimentation rate of 71 mm/h. He had splenomegaly of 5 cm under the ribs. Serum M-protein by electrophoresis test is the presence of monoclonal immunoglobulin M. IgA; 14.4 g/L and κ (kappa) light chain 46 g/L , λ (lambda) light chain;11 g/L. Although sufficient particles and bone marrow tissue were not seen in the bone marrow biopsy, CD38 and CD138 positivity were observed. Then flow cytometric analysis of peripheral blood was performed. A 13% blastic cell population with CD34, CD117, MPO, CD33 positivity was detected. The patient was diagnosed with concurrent MDS and MM. Fluorescent in-situ hybridization (FISH) analysis showed that 7% monosomy 7, (del 7q). He was initially treated with VCD regimen (1.3 mg/m2 bortezomib for days 1, 4, 8, and 11 , cyclophosphamide 50 mg oral daily, and dexamethasone 40 mg weekly) and Decitabine 20 mg/m^2 ,5 days. After 2 cycles of VCD+Decitabine no blasts were observed in the peripheral blood examination. And IgA level returned to normal. However, deep neutropenia was observed during the treatment process. In the third cycle of treatment, the patient died due to sepsis with the febrile neutropenia.

Discussion: In the literature, 14 cases with the coexistence of MM and MDS have been reported before. It has been shown to be associated with poor prognosis, especially in these cases. The median overall survival (OS) was only 8 months for patients with MM and MDS. Almost all (85.7%) patients had severe anemia or pancytopenia, and nearly half (42.9%) of the cases developed into acute myeloid leukemia.

Coclusions: The coexistence of MDS and MM is a very rare condition. Standard treatment methods are still absent, generally have low response rates to treatment and show a poor prognosis.

Keywords: MDS, MM

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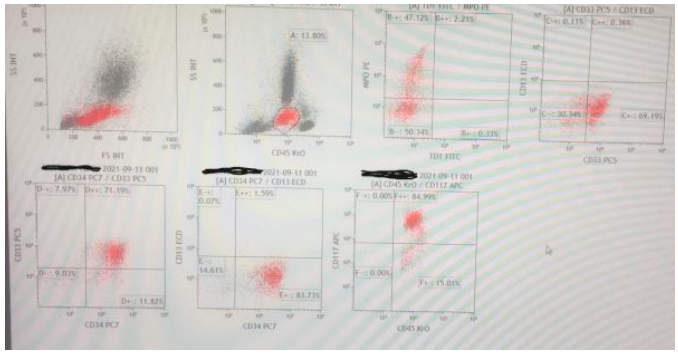

Figure 1. Peripheral blood flow cytometric analysis

■ Chronic Myeloid Leukemia

P-14 Abstract Referance: 35

PERIORBITAL EDEMA SECONDARY TO DASATINIB TREATMENT: A RARE CASE REPORT

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Introduction: Dasatinib is a widely used oral short-acting tyrosine kinase inhibitor. Although it has acted in many other kinases, including as c-KIT, PDGFR-, PDGFR-, and ephrin receptor kinases, it was developed to inhibit ABL and SRC. BCR-ABL is a constitutively active tyrosine kinase, and the illnesses chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (Ph+ ALL) are driven by BCR-ABL. Dasatinib is a very strong inhibitor of BCR-ABL and an effective therapy for both diseases. Dasatinib's frequent but mainly mild and tolerable side effects include cytopenias and pleural effusions (1). Imatinib mesylate has a reasonably frequent adverse effect known as periorbital edema (2). However, this side effect is rare with dasatinib. In this case, we presented a patient who developed isolated periorbital edema with dasatinib, which is very rare in the literature.

Case report: A 65-year-old man on treatment for CML with dasatinib presented with bilateral severe periorbital edema (Figure 1). He was diagnosed with CML 1 year ago. The patient was started on imatinib at a dosage of 400 mg per day. He achieved a major molecular response (MMR) with imatinib treatment. The patient developed diffuse peripheral edema that did not respond to diuretics under imatinib treatment. The drug was discontinued due to widespread edema. After the drug was stopped, the patient's edema regressed. The patient was started on Imatinib again. However, the patient's edema increased again after imatinib treatment. Since the patient could not tolerate imatinib treatment, imatinib treatment was discontinued 8 months after the diagnosis, and dasatinib treatment was started. Periorbital edema developed in the patient approximately 10 days after starting dasatinib treatment. The patient's bilateral periorbital edema was thought to be due to dasatinib. The patient did not have any other drugs or comorbidities. Pretibial edema was not detected in the patient. Chest X-ray was normal, and no effusion was observed. The patient's dasatinib treatment was interrupted for 1 week and diuretic therapy was started. The patient's complaints regressed after 1 week. The patient's dasatinib treatment was started at 50 mg. The continuation of the treatment was planned according to the patient's follow-up and complaints.

Discussion: Patients with CML receiving imatinib treatment frequently have ocular adverse effects (2-4). As far as we know, some rare dasatinib-related periorbital edema has been published in the scientific literature. Periorbital edema due to nephrotic syndrome was observed in most of these cases (5-7). Nephrotic syndrome was defined as urinary protein >3 g/day, hypoalbuminemia (≤ 25 g/L), and edema (8). Nephrotic syndrome patients may also develop pleural effusion. Rapid clinical remission with cessation or dosage reduction of dasatinib indicated its immediate and reversible renal damage. Dasatinib frequently causes pleural effusion, which affects 30% or more of patients in phase 3 studies (9). The case we presented had no signs of nephrotic syndrome. No proteinuria was detected in the urine and the serum albumin level was 4.7 g/dL. The patient also had no signs of peripheral edema or pleural effusion. As far as we know, no case of dasatinib-related isolated periorbital edema has been published in the scientific literature.

Keywords: Dasatinib, Periorbital edema, Imatinib

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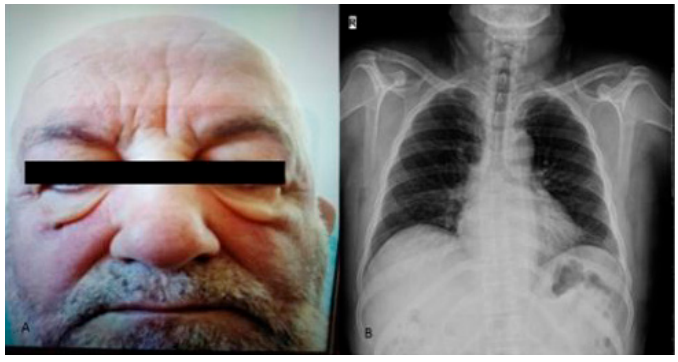

Figure 1. (A) Dasatinib-related periorbital edema in a 70-year-old patient with chronic myeloid leukemia, (B) There are no signs of pleural effusion.

Non-Hodgkin's Lymphoma

P-15 Abstract Referance: 2

CISPLATIN INDUCED CARDIOMYOPATHY AFTER SALVAGE CHEMOTHERAPY FOR NON-HODGKIN LYMPHOMA

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Introduction: Cisplatin is a platinum-based antineoplastic agent used in the treatment of many malignancies. Nephrotoxicity, neurotoxicity, ototoxicity and myelosuppression are among the major adverse effects. The prevalence of cisplatin-induced cardiotoxicity is unknown. However, arrhythmias, myocarditis, cardiomyopathy, and congestive heart failure attributed to cisplatin have been reported. We describe a relapsed non-Hodgkin lymphoma (NHL) patient who developed cardiomyopathy following cisplatin based salvage chemotherapy.

Case Report: A 29-year-old woman was diagnosed with Stage IVB T-cell/Histiocyte-rich B-cell lymphoma (TC/HRBCL) with bone marrow involvement at initial diagnosis. After 3 cycles of R-CHOP, disease progression was demonstrated on PET CT scan, which showed new lesions in the liver and spleen. Concurrently, the patient developed exceeding 39°C. The laboratory tests showed significant direct hyperbilirubinemia (total bilirubin 20.58 mg/dl, direct bilirubin 19.53 mg/dl). Complete blood count and coagulation studies showed the following: leukocyte: 1100/mm3, neutrophil 700/mm3, lymphocyte 100/mm3, HB 7.8 g/dl, PLT 59.000/ mm3, PT: 18.7 sec, aPTT 37 sec, fibrinogen: 113 mg/dl, findings compatible with pancytopenia and disseminated intravascular coagulation (DİC). No sign of extrahepatic cholestasis or infection were evident. Liver biopsy and bone marrow biopsy were not performed due to the risk of bleeding due to DIC. With a presumptive diagnosis of HFS related to TC/HRBCL progression, it was decided that urgent salvage chemotherapy with RDHAP is initiated. By the 4th day of R-DHAP, fever completely defervesced, laboratory findings of DIC resolved and bilirubin levels showed a tendency to decrease. On the 19th day after R-DHAP, bilateral +3 pretibial edema, facial edema, and pleural effusion were observed. Renal function tests were normal. Intensive diuretic therapy was started. Prior to R-DHAP, ejection fraction (EF) on echocardiography (EKO) was 65% and left ventricular (LV) systolic functions were normal. Yet a repeat EKO after R-DHAP showed an EF of 54%, a moderate decrease in LV systolic functions and a 8 mm pericardial effusion. Serum PRO BNP was significantly elevated (13618 ng/l). EKO and ECG showed no sign of cardiac ischemia. With the presumptive diagnosis of cisplatin-induced cardiomyopathy, ACE-İ, betablocker and diuretics were initiated.

Conclusion: Patients receiving a cisplatin-based chemotherapy regimen should be carefully monitored for cardiovascular adverse effects. Adverse effects can be seen even in patients without cardiovascular risk factors. Acute left ventricular dysfunction and heart failure are important causes of mortality and morbidity. It is often reversible with discontinuation of treatment. Basic and regular electrocardiographic and echocardiographic studies, and measurement of cardiac enzymes are of prognostic value.

Keywords: cardiotoxicity, cisplatin, lymphoma

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