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Turkish Journal of Hematology

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ABSTRACTS

POSTER PRESENTATIONS

10th International Congress on Leukemia Lymphoma Myeloma

May 10, 2025 • HYBRID CONGRESS

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AIMS AND SCOPE

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

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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.

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SCIENTIFIC PROGRAM

10 May 2025	
TIME	**HALL A**
08:45-09:00	**OPENING REMARKS** **Muhlis Cem Ar (İstanbul Üniversitesi - Cerrahpaşa, İstanbul)**
09:00-10:00	**ACUTE LYMPHOBLASTIC LEUKAEMIA** **Scientific Chairs: Anthony Moorman (Newcastle University, United Kingdom), Muhlis Cem Ar (İstanbul Üniversitesi - Cerrahpaşa, İstanbul)** - Genetics of B-cell Precursor ALL and Its Therapeutic Implications in Paediatric and Adult ALL: **Anthony Moorman (Newcastle University, United Kingdom)** - T-cell ALL Biology and Its Therapeutic Implications: **Frederik van Delft (Newcastle University, United Kingdom)**
10:00-10:30	**COFFEE BREAK**
10:30-11:30	**ACUTE MYELOBLASTIC LEUKAEMIA** **Scientific Chairs: Lars Bullinger (Charité University Medicine Berlin, Germany),** **Mutlu Arat (Memorial Şişli Hastanesi, İstanbul)** - Molecular Basis of AML – Implications for Routine Diagnostics: **Lars Bullinger (Charité University Medicine Berlin, Germany)** - Current Treatment Standards in AML and New Therapeutic Developments: **Christoph Röllig (Dresden University of Technology, Germany)**
11:30-11:45	**COFFEE BREAK**
11:45-12:25	**PFIZER SATTELITE SYMPOSIUM** **Discover Deep and Durable Responses with Elrexfio in R/R MM Treatment** **- Meral Beksaç (Liv Hospital, Ankara)**
12:25-13:30	**LUNCH**
13:30-15:00	**NON-HODGKIN LYMPHOMA** **Scientific Chairs: Gianluca Gaidano (University of Eastern Piedmont, Italy),** **Hakan Göker (Hacettepe Üniversitesi, Ankara)** - Liquid Biopsy As a Tool For Assessing Prognosis and Monitoring of Aggressive Lymphoma: **Gianluca Gaidano (University of Eastern Piedmont, Italy)** - The Role of Bispecific Antibodies in B Cell Lymphoma: **Maria Gomes da Silva (Portuguese Institute of Oncology of Lisbon, Portuguese)** - Novel Therapeutic Strategies for Mantle Cell Lymphoma: **Marco Ladetto (University of Eastern Piedmont, Italy)**
15:00-15:15	**COFFEE BREAK**
15:15-15:55	**ROCHE SATTELITE SYMPOSIUM** **Redefining the Treatment Landscape in R/R DLBCL** **Scientific Chair: Muhit Özcan (Ankara Üniversitesi, Ankara)** - Future Directions in Lymphoma Treatment: The Role of Glofitamab: **Graham Collins (University of Oxford, United Kingdom**)
15:55-16:10	**COFFEE BREAK**
16:10-17:10	**HODGKIN LYMPHOMA** **Scientific Chairs: Paul Bröckelmann (University Hospital of Cologne, Germany),** **Muhit Özcan (Ankara Üniversitesi, Ankara)** - Contemporary First-Line Treatment of HL: **Paul Bröckelmann (University Hospital of Cologne, Germany)** - Current Approaches in Relapsed/Refractory HL: **Graham Collins (University of Oxford, United Kingdom)**
17:10-17:30	**COFFEE BREAK**
17:30-18:30	**PLASMA CELL DISORDERS** **Scientific Chairs: Thierry Facon (Lille University Hospital, France)** **Meral Beksaç (Liv Hospital, Ankara)** - Treatment Options in Elderly Non Frail: **Thierry Facon (Lille University Hospital, France)** - Treatment Options in Elderly Frail: **Monika Engelhardt (University Hospital Freiburg, Germany)**
18:30-18:45	**CLOSING REMARKS**

PROCEEDINGS

Genetics of B-cell Precursor ALL and its therapeutic implications in children and adults

Anthony Moorman

Leukaemia Research Cytogenomics Group, Centre of Cancer, Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, United Kingdom

Acute lymphoblastic leukaemia (ALL) is defined by a wide spectrum of chromosomal, genetic and genomic abnormalities which drive the initiation and progression of the disease. Numerous chromosomal abnormalities, gene fusions, copy number alterations (CNA) and point mutations have been described in ALL; many of which are pathognomonic of the disease, prognostic or predictive biomarkers. Recent and ongoing studies are revealing the full genomic landscape of the disease and a number of important themes are emerging which impact on how these abnormalities can be used to improve therapeutic decisions and therefore the outcome of patients. Firstly, the total number of genetic alterations per patient is in the "tens" rather than the "hundreds" - as observed in solid tumours. Secondly, an initiating or founder mutation/abnormality can be identified in the majority of cases. Thirdly, this founder mutation is accompanied by a distinctive spectrum of cooperating lesions. Finally, the frequency of founder and cooperating abnormalities is often low with the majority occurring in <10% cases. The frequency of these genetic and genomic abnormalities is strongly age-specific and those associated with a good outcome tend to be more prevalent among children whereas those associated with high risk disease are more frequent among adults.

Despite the vast array of somatic genetic/genomic abnormalities identified and linked with prognosis, only a handful are used currently to risk stratify patients to specific treatments or therapeutic pathways. Childhood and adults patients with *BCR-ABL1*, and increasingly ABL-class fusions, receive tyrosine kinase inhibitors in addition of standard chemotherapy.[1-4] While this targeted intervention improves, outcome additional risk factors (e.g. *IKZF1* deletions) are still relevant in these patients.[2,3,5] The majority of modern paediatric protocols will assign patients with the classic high-risk genetic abnormalities [*KMT2A* fusions, near haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes), *TCF3::HLF* or iAMP21] to the high-risk arm of the trial which will include more intensive chemotherapy and often a stem-cell transplant; or for the very high risk cases CAR-T cell therapy .[6] The prognostic impact of the genomic subtypes such as *CRLF2*-rearrangements, *PAX5* P80R, *IKZF1* N159Y, *PAX5*-altered, as well as *MEF2D*- and *ZNF384*-rearranged cases is less well established in paediatric although some study groups do assign selected patients (e.g. *CRLF2*, *EPOR* and *JAK2* rearrangements) to receive targeted therapy. *ETV6::RUNX*1 and high hyperdiploidy have been linked with an excellent outcome are increasingly being used to stratify patients to lower intensity treatment.[6] However, it should be noted that the definition of "low risk" high hyperdiploid is variable with some groups using the traditional chromosome number range of 51-67 chromosomes and others using the pattern of chromosome gain (e.g. triple trisomy, UK-HeH profile).[7,8]

There is more variability in the list of high-risk abnormalities in adult ALL, but the majority include *KMT2A::AFF1* fusion, low hypodiploidy, and complex karyotype; with some adding t(1;19)(q23;p13)/*TCF3::PBX1*. More recently, abnormalities leading to deregulated JAK-STAT signalling JAK-STAT abnormalities [*IGH::CRLF2*, *P2RY8::CRLF2* and *JAK2* fusions] have been linked with a very poor outcome.[9]

More recently, the prognostic effect of secondary genomic lesions – typically deletions and deletion/mutation profiles – have been recognised and incorporated into risk algorithms.[10,11] However, there is no standard approach and study groups have opted for different interventions for the same abnormality, e.g. *IKZF1* deletion.[12,13] Some study groups have opted to use deletion profiles to identify risk groups and alter therapy but again there are differences in definition and approach. The BFM-AEIOP group have opted to use CNA to

identify high risk patients via the IKZF1^{plus} profile[10] while the ALLTogether consortium is focussing on identifying low risk patients using the UKALL-CNA profile.[11] In adult ALL, the prognostic impact of IKZF1 deletions and other CNA seems is more controversial. Whilst a few protocols have reported a prognostic impact of *IKZF1* deletions and implemented a treatment change other studies have reported no adverse effect.[14-16]

MRD is widely recognised to be the single most powerful prognostic factor in paediatric and adult ALL.[17] However MRD alone is not sufficient to predict outcome. Recent studies have shown that the prognostic effect of MRD is modulated by the genetic make-up of the leukemic clone[18] and that the prognostic effect of some genetic abnormalities varies by MRD risk group.[10] As a result, risk algorithms integrating risk factors have emerged. For example, the current DCOG trial and AEIOP-BFM-ALL2017 combine genetics and MRD to stratify patients: medium risk MRD patients with *IKZF1* deletion and MRD positive patients with IKZF1^{plus}, respectively. Analysis of data from UKALL2003 demonstrated that patients with good risk cytogenetics and MRD one log higher than the standard threshold had an excellent outcome and did not benefit from augmented therapy.[18] Therefore, using a single timepoint and a single threshold to assign risk is an over-simplification which can lead to patients being either over- or under-treated. Statistical modelling of large well characterised patient cohorts has revealed that using subtype specific MRD thresholds can improved risk prediction. Moreover, fully integrating multiple risk factors into a single prognostic index can help to define risk groups which are more flexible than those generated by the sequential application of binary cut-points.[19,20]

In this talk, I will review the major genomic abnormalities that are currently being used tailor therapy in both paediatric and adult ALL. In addition, I will discuss the use of statistical modelling to truly integrate risk factors and create a new generation of risk stratification algorithms to assign patients to the most appropriate treatment pathway.

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Current Treatment Standards in AML and New Therapeutic Developments

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Curing acute myeloid leukemia (AML) by eradicating the last leukemic blast cells still requires intensive chemotherapy, in most cases including allogeneic stem cell transplantation.[1] Because AML is a disease of the elderly, with a median age of 69 years,[2] about half of all patients cannot tolerate intensive chemotherapy and are offered less intensive approaches.[3] The only exception is **acute promyelocytic leukemia (APL)**, which can be treated with a well-tolerated combination of arsenic trioxide (ATO) and all-trans-retinoic acid (ATRA), resulting in a cure in the vast majority of patients.[4,5]

For most patients with non-APL, a decision must be made as to whether the patient is eligible and/or willing to undergo intensive chemotherapy.

Intensive chemotherapy is based on a backbone of standard dose cytarabine plus daunorubicin or sometimes idarubicin as part of the "7+3" schedule.[1,6] A daily dose of 60 mg/m^2 of daunorubicin is sufficient, as 90 mg/m^2 adds potential toxicity and no additional efficacy. Patients with a good response or blast clearance after the first cycle can proceed to post-remission treatment without the need for double induction.[7] High-dose cytarabine-based regimens are generally used for patients with inadequate blast reduction.[8]

In certain genetic subgroups, "7+3" is supplemented with novel targeted agents. While comprehensive genetic testing may take a few days, waiting for the results does not affect the overall prognosis in a clinically stable patient without tumor lysis syndrome, disseminated intravascular coagulation, or leukostasis.[9] Subgroup-specific modifications are the addition of the conjugated CD33 antibody gemtuzumab ozogamicin (GO) in CBF AML or NPM1mut-FLT3wt AML, the use of the FLT3 inhibitors midostaurin or quizartinib in FLT3-mutated AML, or the replacement of "7+3" by its liposomal formulation CPX-351.[6]

Postremission treatment is based on the risk of relapse determined by genetics or MRD, on eligibility for allogeneic stem cell transplantation (allo SCT), and on availability of a suitable donor. While allo SCT is preferred in patients with unfavorable genetics and persistent MRD, it is only used in the event of relapse in patients with favorable genetics.[10] In intermediate-risk patients, deferring allo SCT in the first CR to relapse may be an appropriate choice in patients with a monitorable MRD marker, a difficult donor constellation, or borderline eligibility for allo SCT.[11] In patients without primary allo SCT, higher doses of cytarabine are generally used for 2-3 cycles as chemoconsolidation.[6] While sorafenib maintenance is indicated in FLT3-ITD mutated AML after allo SCT,[12] oral azacitidine may be used in poor risk patients without allo SCT option.[13] In intermediate-risk and FLT3mut AML, its value is less clear, and in favorable-risk patients, maintenance carries the risk of overtreatment.

In patients ineligible for intensive therapy, the combination of the bcl-2 inhibitor venetoclax plus the hypomethylating agents azacitidine or decitabine as continuous treatment in 28-day cycles is the standard of care,[14] while the combination of the IDH1 inhibitor ivosidenib with azacitidine is an alternative and less hematotoxic option for patients with IDH1 mutations.[15] As with intensive therapy, waiting for diagnostic results in a clinically stable patient does not affect the overall prognosis.[16]

In relapse, the chance of a long-term remission is significantly reduced. Cure is only possible in combination with allo SCT. Patients with FLT3 mutations should be bridged to transplantation with the oral FLT3 inhibitor giltertinib. All other patients generally receive a high-dose cytarabine based sal-

vage regimen for remission induction, possibly in combination with venetoclax (HAM-Ven or FLAG-Ida-Ven).[8] If allo-SCT can be achieved within 4-6 weeks after relapse, dose-intensive conditioning and immediate allo SCT without prior intensive salvage is a valuable alternative treatment option.[17] Early tapering of immunosuppression should reduce the risk of relapse, while regular donor lymphocyte infusions (DLI) and drug-based maintenance approaches are under clinical investigation.

For patients ineligible for allo SCT at relapse, gilteritinib can be used until disease progression in FLT3-mutant AML,[18] while venetoclax-based combinations with HMA or low-dose cytarabine (LDAC) can be used off-label in all other patients.[19,20] If reimbursed, the use of single-agent ivosidenib[21] or enasidenib[22] in IDH-mutated patients may be valuable. Recently, oral revumenib was approved as the first menin inhibitor for relapsed/refractory acute leukemia with KMT2A rearrangement.[23]

New treatment strategies currently being explored in clinical trials are the combination of novel agents with intensive chemotherapy backbones or with HMA (-venetoclax) in unfit AML patients. A second interesting question being addressed in trials is whether venetoclax is best used in combination with intensive chemotherapy in fit patients, or as an alternative to intensive chemotherapy in combination with HMAs. A third interesting future treatment area is immunotherapy, with promising expectations but rather sobering clinical results so far. The use of immunotherapy in situations with low AML burden and the exploration of novel immune constructs and novel targets will most likely pave the way for improved treatment, especially in subgroups with high medical need.

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Liquid Biopsy as a Tool for Assessing Prognosis and Monitoring of Aggressive Lymphoma

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Introduction. Lymphomas are a diverse group of hematologic cancers that originate from the clonal expansion of B cells, T cells, or natural killer (NK) cells at various stages of differentiation. These malignancies exhibit substantial variability in their biological behavior, clinical prognosis, and response to treatment. With the advent of precision medicine, hematologic oncology has seen significant progress, allowing for more individualized treatment approaches based on each patient's molecular tumor profile.

Accurate characterization of a lymphoma's genetic and molecular landscape is essential for diagnosis, prognosis, and therapeutic planning. Traditionally, this information has been obtained through tissue biopsy, which is still a central procedure in clinical practice. However, tissue biopsy present several limitations: they are invasive, challenging to repeat for serial monitoring, and often fail to capture the full spectrum of tumor heterogeneity, especially when disease is present at multiple sites.

In response to these challenges, liquid biopsy has gained momentum as a complementary method for molecular diagnostics in lymphoma. This non-invasive technique enables the detection of tumor-related biomarkers from readily accessible sources such as blood, saliva, urine, cerebrospinal fluid, or stool. Compared to conventional tissue biopsy, liquid biopsy offers numerous advantages since it can: *i*) sample multiple disease sites simultaneously, *ii*) facilitate real-time monitoring, and *iii*) support longitudinal assessments throughout the course of therapy.

Liquid biopsy technologies analyze various tumor-derived components circulating in body fluids, including circulating tumor cells (CTCs), cell-free RNA (cfRNA), extracellular vesicles (EVs), tumor-educated platelets (TEPs), and most notably, circulating tumor DNA (ctDNA). Among these, ctDNA has emerged as the most extensively studied biomarker in hematologic malignancies due to its utility in tumor genotyping and dynamic monitoring of treatment response.

cfDNA consists of fragmented DNA molecules released into the bloodstream during processes like apoptosis, necrosis, or active secretion from cells. Discovered in human plasma as early as 1948, cfDNA research gained new relevance with the identification of fetal cell fee DNA (cfDNA) in maternal blood in 1977. Cancer patients typically exhibit elevated levels of cfDNA, largely due to increased DNA release from tumor cells. Importantly, cfDNA fragmentation is not random. In healthy individuals, cfDNA fragments deriving mostly from apoptotic cells and are about 160–170 base pairs in length, reflecting DNA wrapping around nucleosomes. In contrast, ctDNA, which is derived specifically from malignant cells, tends to be shorter, with an average fragment size around 143 base pairs. The biological mechanisms driving this difference are not yet fully understood.

Unlike cfDNA, ctDNA carries tumor-specific genetic and epigenetic features, such as point mutations, structural rearrangements, and methylation patterns. ctDNA is highly dynamic, with a short half-life of 1 to 2 hours, allowing for a near real-time reflection of tumor status. Its levels in circulation vary between patients, depending on factors like cancer type, tumor burden, disease progression, and treatment response. These unique attributes make ctDNA a powerful tool in oncology. It can aid in early diagnosis, track treatment effectiveness, identify minimal residual disease (MRD), and guide the selection of personalized therapies.

Liquid biopsy in diffuse large B cell lymphoma. Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of

non-Hodgkin lymphoma (NHL), accounting for approximately 30–35% of all cases. It is a biologically heterogeneous disease, with significant variability both among patients and across different tumor sites within the same individual. Standard frontline therapy typically involves the R-CHOP regimen (rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone), which achieves durable complete remission in over 60% of patients. More recently, Pola-R-CHP, which incorporates polatuzumab vedotin in place of vincristine, has been introduced as a first-line option, particularly for patients with intermediate- to high-risk disease as determined by the International Prognostic Index (IPI).

Despite advances in treatment, the molecular complexity of DLBCL continues to pose challenges for accurately predicting prognosis and identifying patients at risk of relapse or resistance to therapy. Traditional diagnostic tools, such as tissue biopsy, often fail to fully capture the genomic heterogeneity of the disease, particularly in cases with spatially distributed tumor involvement. This has prompted growing interest in alternative, more dynamic diagnostic methods.

ctDNA has emerged as a promising tool for improving DLBCL management. Using advanced sequencing techniques such as CAPP-seq (Cancer Personalized Profiling by Deep Sequencing), ctDNA analysis enables the detection of key genetic alterations associated with DLBCL subtypes, including mutations in *MYD88*, *CD79B*, and *EZH2*, which may be missed in single-site biopsies. Studies have demonstrated a high degree of concordance between ctDNA and tissue-based genotyping, supporting its utility as a reliable surrogate for molecular profiling.

Molecular classification of DLBCL, initially based on tissue sequencing, has identified clinically meaningful subtypes with distinct genetic and clinical features. The LymphGen algorithm is a probabilistic model that assigns tumors to molecular clusters such as MCD, BN2, N1, A53, and EZB, each defined by specific mutational signatures and therapeutic implications. Recent evidence suggests that this classification can also be applied to ctDNA with high fidelity. In a prospective study involving 166 newly diagnosed patients, Moia *et al.* reported a 95.8% concordance between plasma ctDNA and tissue biopsy in molecular cluster assignment. Importantly, patients in the A53 and MCD clusters showed poorer outcomes, while those in BN2 and ST2 clusters had better prognoses, consistent with tissue-based findings.

Baseline ctDNA levels have also been established as powerful prognostic indicators. Elevated pretreatment ctDNA is associated with inferior progression-free survival (PFS), event-free survival (EFS), and overall survival (OS). In one large-scale study by Kurtz *et al.*, ctDNA concentration was a more accurate predictor of EFS than conventional prognostic markers, including cell-of-origin classification, IPI, and total metabolic tumor volume (TMTV). Moreover, combining ctDNA levels with molecular subtype information further refines risk stratification. Notably, even among patients with high ctDNA levels, those assigned to favorable molecular clusters like ST2 and BN2 tend to fare better.

Beyond baseline assessment, dynamic changes in ctDNA during treatment provide early and sensitive measures of response. Early molecular response defined as a 2-log reduction in ctDNA after one treatment cycle, and major molecular response defined as a 2.5-log reduction after two cycles, are both strongly associated with improved survival outcomes. These reductions remain independently predictive even when adjusted for traditional prognostic variables. Such molecular metrics may complement or even enhance conventional imaging techniques like PET/CT in treatment monitoring.

The utility of ctDNA extends to emerging therapies such as chimeric antigen receptor (CAR) T-cell therapy. Higher pre-infusion ctDNA levels and shorter fragment sizes (<170 bp) have been linked to poorer clinical outcomes post-infusion. Conversely, ctDNA clearance by days 14 and 28 after CAR-T administration predicts improved complete response rates and longer survival. Moreover, ctDNA profiling in relapsed/refractory (R/R) DLBCL has uncovered mechanisms of resistance involving alterations in genes related to B-cell identity (e.g., *PAX5*, *IRF8*), immune evasion (*CD274*), and microenvironmental regulation (*TMEM30A*). These insights may inform strategies to overcome resistance and personalize CAR-T therapy.

ctDNA is also gaining traction as a tool for MRD monitoring. Serial ctDNA testing after treatment can identify molecular relapse before radiographic progression is evident. In post-transplant patients, persistent ctDNA has been associated with a higher risk of disease recurrence even in radiologically negative individuals. This supports the use of ctDNA for early intervention and tailored follow-up strategies.

A key innovation in MRD detection is PhasED-Seq, a sequencing method that improves sensitivity by detecting multiple mutations on the same DNA fragment, thereby minimizing background noise. Preliminary data indicate that PhasED-Seq may outperform CAPP-seq in identifying residual disease, although further validation is ongoing.

In summary, ctDNA might offer a profound improvement in the management of DLBCL by offering a minimally invasive, highly sensitive platform for molecular classification, response monitoring, MRD detection, and treatment guidance. Its integration into clinical practice and trials is rapidly expanding, promising more personalized and effective care for patients with this complex lymphoma subtype.

Hodgkin lymphoma. A major obstacle in the genomic profiling of Hodgkin lymphoma (HL) is the extremely low abundance of malignant Hodgkin/Reed-Sternberg (HRS**)** cells in tissue biopsies—typically constituting only 0.1% to 3% of the total cell population. This scarcity limits the effectiveness of conventional, tissue-based genotyping in providing comprehensive molecular insights. To overcome these challenges, plasma ctDNA has emerged as a promising non-invasive alternative for genetic profiling in HL. Patients with HL exhibit cfDNA concentrations roughly twice as high as those seen in healthy individuals (~3,400 vs. ~1,700 hGE/mL of plasma), with median ctDNA levels around 200 hGE/mL. Remarkably, despite the lower tumor burden in HL compared to other aggressive lymphomas, ctDNA levels correlate closely with radiologic tumor volume—similar to patterns observed in DLBCL. This suggests that HRS cells may shed more DNA into circulation, likely due to their high apoptotic turnover.

In a pivotal study involving both newly diagnosed and refractory HL cases, ctDNA analysis successfully identified approximately 87.5% of the mutations detected in tissue biopsy specimens, reinforcing its role as a reliable molecular profiling tool. Furthermore, ctDNA demonstrated a higher median variant allele frequency (VAF) than corresponding tissue samples, likely reflecting the limited tumor cell content in HL biopsies. Importantly, mutations such as *XPO1*^{E571K}, *STAT6*, and *SOCS1,* detectable through ctDNA, can aid in differentiating HL from other lymphoma subtypes, including DLBCL, primary mediastinal B-cell lymphoma, anaplastic large cell lymphoma, and mucosa-associated lymphoid tissue lymphoma.

Baseline ctDNA levels prior to treatment have been linked to several adverse clinical features, including high total metabolic tumor volume (TMTV), elevated lactate dehydrogenase (LDH), advanced-stage disease, and higher Hasenclever prognostic scores (≥3). These associations suggest that pretreatment ctDNA may integrate traditional prognostic indicators into a single molecular readout. Additionally, specific ctDNA-detected mutations carry prognostic significance, for instance, detection of *XPO1*^{E571K} by droplet digital PCR (ddPCR) is associated with significantly shorter PFS (57.1% vs. 90.5%) at two years for mutation-positive vs. mutation-negative patients. Similarly, *TP53* mutations in ctDNA correlate with inferior PFS.

Beyond baseline risk stratification, ctDNA is also proving valuable in monitoring treatment response and predicting relapse. Persistently high ctDNA levels at key timepoints, such as C1D15, C3D1, and after four treatment cycles are associated with shortened PFS. When used alongside PET/CT imaging, longitudinal ctDNA monitoring improved detection of disease progression in 38% of patients. Notably, a dual-negative result (both ctDNA and PET/CT negative) had a 99% negative predictive value, underscoring the added diagnostic precision of ctDNA.

In advanced-stage HL patients treated with ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine), a 2-log reduction in ctDNA after two cycles was strongly predictive of complete response. This prognostic marker also extends to immunotherapy settings. In a study of previously untreated HL patients receiving pembrolizumab-based regimens, ctDNA clearance after two treatment cycles and at end-of-treatment was significantly associated with prolonged PFS.

In addition to its diagnostic and prognostic roles, ctDNA has advanced our understanding of tumor heterogeneity in HL. Recent integrative analyses that combined somatic copy number alterations with non-silent mutations have defined two robust molecular subtypes: Cluster H1 and Cluster H2. Cluster H1, which accounts for ~70% of cases, is characterized by mutations in key signaling pathways such as NFκB, JAK/STAT, and PI3K. Cluster H2, found in ~32% of patients, features a higher burden of chromosomal alterations and mutations in *TP53* and *KMT2D*, genes associated with genomic instability. Clinically, H2 tumors display a bimodal age distribution and elevated ctDNA levels, both indicators of higher tumor burden and more aggressive disease. Importantly, even after adjusting for ctDNA levels, H2 cluster membership remained independently associated with worse prognosis, confirming the value of molecular subtyping via liquid biopsy for refining risk stratification.

Conclusions and perspectives. Liquid biopsy is emerging as a complementary tool in the management of lymphoid malignancies, offering a minimally invasive approach to tumor characterization and monitoring. In **DLBCL**, it effectively mirrors the tumor molecular landscape and recapitulates the prognostic relevance of molecular clusters such as those defined by LymphGen, providing dynamic insights into tumor burden, treatment response, and relapse risk. In **HL**, where traditional biopsies are limited by low tumor cell content, liquid biopsy enables a comprehensive molecular characterization, improves prognostic stratification, and helps identify therapeutic targets. Though less explored in **indolent lymphoproliferative neoplasms**, early evidence suggests that liquid biopsy may also hold prognostic value in this setting. Beyond mutation detection, **cfDNA fragmentation patterns** offer emerging opportunities for prognostic assessment, disease monitoring, and even inferring transcriptional activity from plasma samples. Moving forward, integrating liquid biopsy with **PET imaging, clinical data, and histopathological markers** is essential for the design of next-generation clinical trials and the development of personalized treatment strategies, particularly for high-risk lymphoma patients.

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Current Approaches in Relapsed Classical Hodgkin Lymphoma

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A number of challenges exist when considering relapsed classical Hodgkin lymphoma (cHL). First, as an uncommon condition randomised trials are not easy to perform resulting in an evidence base which is far from ideal on which to base treatment recommendations. Secondly, first-line treatments are evolving rapidly and this may have an impact on what is suitable to use at relapse. Thirdly, different countries have different reimbursement mechanisms making availability of high-cost drugs variable around the world. This makes a 'one size fits all' approach impossible.

Prognosis at relapse appears to be dependent on a number of factors including time to relapse (with refractory disease associated with a worse outcome than later relapsed disease), extranodal involvement or stage IV disease, a poor performance status and if traditional chemotherapy is used, achievement of a complete metabolic response to 2nd line treatment[1]. As other agents (such as checkpoint inhibitors) are introduced, some traditional factors such as achieving a complete metabolic response prior to autologous stem cell transplantation (ASCT), appear to be less important[2]. The tumour microenvironment at relapse also appears to play a role in prognosis[3] and with the introduction of targeted agents, prognosis has been improving[4].

When a chemotherapy-only approach is used first-line and when chemotherapy only is available at relapse, the goal of 2nd line treatment is to attain a complete metabolic remission (CMR). This recommendation is based on data showing the outcome of autologous stem cell ASCT as superior for patients in a CMR compared to less deep responses[5]. Furthermore, subsequent data suggested that it did not matter if one or two relapse lines of treatment were required; if a CMR was achieved then outcomes from ASCT remained favourable[6]. An absence of randomised trials means the choice the 2nd line chemotherapy is essentially based on what an individual centre is used to using, whilst avoiding agents likely to impair the success of stem cell collection such as melphalan.

A number of studies have now shown that incorporating targeted agents into 2nd line treatment is associated with improved outcomes. The BRESELIBRET trial compared ESHAP with ESHAP combined with brentuximab vedotin (BV) the anti-CD30 antibody-drug conjugate. A significant improvement in CMR was observed[7]. Non-randomised studies incorporating a checkpoint inhibitor have shown very high response rates[8]. Interestingly, the outcomes of ASCT appear superior if a checkpoint inhibitor is used prior to ASCT suggesting that they may have the property of sensitising the tumour to the effects of high dose chemotherapy[9,10]. Where available then it would seem sensible to incorporate a targeted agent – preferably a checkpoint inhibitor – into second line therapy.

A major question in the field is whether the ASCT is needed for all patients. ASCT uses high doses of chemotherapy and is associated with an increase in late toxic effects such as 2nd cancers and heart disease[11]. The BRESELIBET study took patients in CMR after induction chemotherapy and treated them with consolidation BV rather than an ASCT. With a median follow up of 17.3 months, an estimated 24-month progression free survival (PFS) of 74% was observed albeit at the expense of a considerably incidence of higher-grade peripheral neuropathy[7]. Furthermore, Moskowitz and colleagues investigated pembrolizumab consolidation in place of an ASCT in patients achieving a CMR to pembrolizumab combined with GVD. With a median follow up of 30 months, a 24-month PFS of 60% was observed. Interestingly patient with stage IV disease at relapse seemed to do less well and a subsequent randomised trial excluding stage IV patients is planned[12].

Recently, two prospective studies in children (with one including adolescents and young adults) with low-risk relapsed cHL have been reported. The Checkmate 744 study treated all patients initially with BV combined with nivolumab[13]. If CMR was not achieved patients would switch to BV with bendamustine and all were planned to receive consolidation radiotherapy. After a median follow up of 32 months, a 3y PFS of 95% was observed. Furthermore, the EuroNet group have reported the outcomes of a prospective risk-adapted non-randomised study in patients up to 18 year of age with relapsed disease[14]. Reinduction chemotherapy with IEP alternating with ABVD was given and a PET scan performed. Those with low-risk disease (defined as late relapse after 2 cycles of first line chemo or any relapse achieving a CMR after IEP / ABVD and at least 50% volume reduction), had a 2nd cycle of IEP / ABVD and received consolidation radiotherapy to all site of relapse. For high-risk disease (all primary progression patients and those with inadequate response to one cycle of IEP / ABVD), received a 2nd cycle of IEP / ABVD and ASCT with or without radiotherapy. 59 patients were in the low-risk group and 41 followed the non-transplant strategy. A 5-year PFS of 89.7% in this group was observed (88.9% in the low-risk group who did receive ASCT). This data suggests there are indeed some patients who do not need high-dose chemotherapy with ASCT. However, both these prospective trials used radiotherapy as consolidation, well known to be associated with its own late effects issues.

To conclude with a set of general recommendations is challenging. However a number of broad principles emerge from the current data:

- The outcome of patients with relapsed cHL is generally good and has improved considerably with the advent of targeted agents.
- If available, the incorporation of targeted agents into 2nd line treatment is associated with favourable outcomes, with checkpoint inhibitors appearing most beneficial particularly for patients proceeding to ASCT.
- Emerging evidence suggests there are patients with low-risk relapse who can avoid ASCT although consolidation radiotherapy has been used in the largest published studies to date.

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Novel Therapeutic Strategies for Mantle Cell Lymphoma

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Mantle Cell Lymphoma (MCL) is a rare and aggressive B-cell lymphoma with a historically poor prognosis, as most patients eventually relapse or become refractory to treatment. Traditional therapy has typically involved chemotherapy regimens like R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone), followed by high-dose Ara-C and autologous stem cell transplantation (ASCT) for younger, fit patients, along with rituximab maintenance (Le Gouill et al., NJM 2017).

In recent years, the TRIANGLE trial demonstrated that first-line treatment with a combination of ibrutinib, rituximab, and standard chemotherapy, followed by maintenance therapy significantly improved survival in younger patients, leading to a new standard treatment in this context (Dreyling et al., Lancet 2024; Dreyling et al., ASH 2024). For elderly or frail patients, novel approaches including Bruton's tyrosine kinase inhibitors (BTKis) like acalabrutinib have shown promise, provided durable responses and delayed disease progression while minimized toxicity compared to traditional regimens (Dreyling et al. ASH 2024). These advances represent a shift toward more targeted treatments, improving outcomes and maintaining quality of life in this patient population.

BTKi has long been the cornerstone of treatment for relapsed/refractory (R/R) MCL (Wang et al., NJM 2013), and its expanding use in front-line therapy, alongside novel agents, has reshaped the treatment landscape. Future strategies will likely distinguish between BTKi-naïve and BTKi-exposed patients, allowing for more personalized approaches in the R/R MCL patients.

Additionally, immunotherapy has shown significant promise. Chimeric Antigen Receptor (CAR) T-cell therapy has provided deep, lasting remissions in heavily pretreated patients (Wang et al. JCO 2023), especially if BTKi-exposed and bispecific antibodies (bsAbs) are emerging as a powerful tool for eliciting anti-tumor responses, with encouraging early results offering potential breakthroughs for advanced disease patients (Phillips et al., JCO 2024).

As the treatment landscape continues to evolve, ongoing research is focused on refining therapeutic strategies, improving patient outcomes, and maintaining quality of life for MCL patients.

The Role of Bispecific Antibodies in B Cell Lymphoma

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Bispecific CD3 x CD20 antibodies (BsAbs) are T cell engaging agents that recently entered the field of B NHL therapy with very promising results in diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). Glofitamab, epcoritamab (both in 2023) and odronextamab (in 2024) are approved in Europe and other jurisdictions for the treatment of DLBCL, while mosunetuzumab (since 2022) and more recently epcoritamab and odronextamab (2024) received approval for FL.

Although varying in structure, dose, schedule, route of administration and treatment duration, these agents share a common mode of action, promoting synapse formation between lymphoma cells and T cells with MHC unrestricted T cell activation, expansion and cytotoxicity. Toxicity patterns, like in CAR T cell therapy, are a consequence of immune activation and inflammation and are dominated by cytokine releasing syndrome (usually low grade and restricted to the first cycles when step up dosing and prophylactic steroids are employed) and infections, that can be severe and constitute the most frequent cause of non-relapse mortality. Neurotoxicity, tumor lysis and tumor flare are rare. Toxicity is in general predictable and lower than what is seen after CAR T treatment.

Glofitamab (administered intravenously for a fixed duration period, 12 cycles), epcoritamab (administered subcutaneously until disease progression) and odronextamab (administered intravenously until disease progression) were approved for the treatment of LBCL in patients having received at least two prior lines of treatment. The approvals were based in three phase 2 trials of similar size, including 127 to 157, heavily pretreated patients with frequent high risk factors. High complete remission rates (32-40%) were obtained, that translated into prolonged disease control in approximately 60-65% of CR patients, with an acceptable toxicity at the current two to three year follow up.

Their efficacy, as well as non-overlapping toxicities, generated interest in examining BsAbs in diverse combinations (with chemoimmunotherapy, IMIDs, antibody drug conjugates like Polatuzumab and targeted agents) and in earlier lines of treatment. The recently published results of the phase 3 randomized controlled trial STARGLO, where Glofitamab in combination with Gemcitabine and Oxaliplatin was compared with Rituximab plus Gemcitabine and Oxaliplatin, highlight the potential of these combinations by showing a significant prolongation of overall survival as well as CR rates and PFS. These outcomes are also supported by the phase 2 results of the combination of Epcoritamab with the same regimen. Many other combinations, (for instance with ICE, DHAX, lenalidomide and polatuzumab) are currently under evaluation in different settings and show a promising apparent increase in CR rates compared to single BsAbs. These preliminary results led to the design and initiation of phase 3 comparative trials, leading to the expectation that, in the future, BsAbs-containing combinations may become the preferred option in specific disease and patient settings, particularly when CAR T cell therapy is not available or not considered adequate.

Additionally, trials for high risk patients at front line are currently comparing Glofitamab, Epcoritamab and Odronextamab combined with RCHOP or R Pola CHP with conventional chemoimmunotherapy. Their results, not yet available, may change the current treatment paradigms for diffuse large B cell lymphoma.

Unmet needs remain in the treatment of FL, an indolent but incurable disease with heterogeneous clinical course. Patients relapsing within the first two years of front-line treatment (POD24), as well as multiple relapsed patients, have compromised long term survival. Mosunetuzumab, Epcoritamab and Odronextamab were recently approved for FL patients with at least two prior lines of treatment. The approvals were based of relatively large phase 2 trials including heavily pretreated patients with high risk factors (including frequent refractory disease and 40-50% POD24+ cases). High overall (80%) and complete response rates (60% to 73%) were observed. Complete remissions were durable and lead to prolonged PFS and

OS with acceptable toxicity. With a median follow up now longer than 3 years Mosunetuzumab, the first of these agents to be approved for FL, showed a median duration of response of 35.9 months, while the duration of complete remission is still not reached and estimates for overall survival exceed 80%. Although follow up is still limited in the setting of this generally indolent disease, these results are extremely promising.

The earlier use of BsAbs (at second and even first line treatment lines for high risk patients) and the potential of synergistic combinations are also being explored in follicular lymphoma. Phase 2 and phase 3 monotherapy and combination trials (either with Lenalidomide, Rituximab plus Lenalidomide or chemoimmunotherapy) are ongoing at first line and relapse, with initial results showing very high complete remission rates and no additional safety signals.

Mantle cell lymphoma is a rare B NHL subtype with a heterogeneous clinical behaviour. Despite important progresses in front line and relapse treatment strategies, including the use of BTK inhibitors, relapse/refractory disease has poor outcomes. Approved third line treatments include CAR T cell products (brexucabtagene autoleucel and lisocabtagene maraleucel) and the non-covalent BTK inhibitor Pirtobrutinib, are not curative. Although data on the use of BsAbs in mantle cell lymphoma patients is still scarce, preliminary results from an expansion cohort of 60 relapsed refractory patients treated with Glofitamab showed a very promising overall and complete response rates (85% and 78% respectively) that were durable with a 19.7 month follow up. Promising ORR and CR rates were also observed with Mosunetuzumab combined with polatuzumab in a limited patient set. Ongoing trials are comparing Glofitamab with investigator choice of Rituximab Bendamustine or Rituximab lenalidomide in the setting of relapse/refractory disease and the association of Glofitamab with Pirtobrutinib.

Future perspectives in the field include a better understanding of resistance mechanisms and the identification of patients who are more or less likely to benefit. Host immune (in) competence, genetic tumor characteristics and unfavorable tumor microenvironment, as well as loss of target (CD20) antigen under treatment, are contributing factors for treatment resistance. Clinically, patients with refractory disease, high tumor burden, elevated LDH and relapsing shortly (< 3 months) after CAR T cell therapy may benefit less from BsAbs, at least as monotherapy.

Additional future avenues to explore include a myriade of new agents, from trispecific/multispecific antibodies to other immune cell engagers, compounds targeting additional B cell molecules (CD19, CD22, CD79b) and new combinations (eg with immune stimulators). The role of minimal residual disease analyses for treatment adaptation is not yet established, but results of ctDNA studies as a marker of disease burden and disease response look promising.

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Treatment Options in Elderly Frail Newly Diagnosed Multiple Myeloma (NDMM) Patients (pts)

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Introduction: Treatment options for NDMM, including immunotherapies (IO) in clinical trials (i.e. Cartitude 5+6), have largely increased and evolved from melphalan/prednisone (MP) to MPT, VMP, leading to Daratumumab (Dara)-VMP (Alcyone), Rd (First), VRd and Dara-Rd (Maia study) advances. Recently, also quadruplets (Isatuximab (Isa)-VRd and Dara-VRd in Imroz and Cepheus studies, respectively) have been approved.[1,2] The challenge today is to choose wisely between doublets, triplets and quadruplets in NDMM, the more, if pts are elderly and/or frail.[1–5]

Methods: The presentation will focus on the new EHA/EMN 2025 guidelines for transplant-eligible (TE) and –ineligible (TI) NDMM pts,[6] briefly illustrate challenges of treatment options today and the current treatment reality via two representative elderly NDMM cases from our university of Freiburg medical center.

The talk will also illustrate the above clinical study results for TI, elderly and frail NDMM pts and will propose how treatment may be performed individually to gain efficacy, safety and long treatment endurance for TI NDMM pts.

Results: Whilst quadruplets due to both Imroz (Isa-VRd -> Isa-Rd vs. VRd -> Rd in TI NDMM) and Cepheus (Dara-VRd -> Dara-Rd vs. VRd -> Rd) have been approved,[1,2] pts in these registration studies had to be fit and ≤80-years of age. Imroz also aimed to determine non-frailty (0/1) via simplified frailty score vs. frail pts (≥2), which included 70% vs. 30% pts, respectively,[7] whilst Cepheus did not include frail pts. Expectedly in Imroz, treatment duration, PFS and OS in frail vs. non-frail pts was shorter.[7] Moreover, safety and grade 5 events remain of concern with quadruplets and less fit NDMM pts[1,2,6], suggesting precautions, comedication, frequent outpt visits, appropriate dose reductions (including weekly rather than twice weekly bortezomib schedules to avoid PNP) as important, and alternative schedules, such as Dara-Rd or Dara-R in Maia and IFM2017-03 for frail or very frail pts, respectively, to remain standard of care.[6] In addition, frailty assessment at diagnosis and sequentially over time remain beneficial to guide treatment.[8–11] Frailty studies comparing different comorbidity scores have demonstrated that various frailty scores can be used to assess frailty in MM, but via retrospective data that some are more suitable than others.[10] On top, physical training and even WHO-defined exercising (150 minutes/week) have been proven as safe, feasible and effective in MM pts to increase treatment tolerance, avoid treatment complications and improve pts' quality of life (QoL).[12,13]

Conclusions: CD38 antibody (ab)-VRd followed by CD38ab-Rd is a new standard of care in TI NDMM pts.[6] The benefit of CD38ab-VRd in younger and older pts, in fit and "frailer" pts have been proposed,[2] but these quadruplets need to be used with knowledge that a) lenalidomide can (and must often) be reduced, b) bortezomib should be used weekly, and c) alternatives - i.e. in case of recurrent infections - are: CD38-Rd (Maia) or CD38-Vd (Alcyone without melphalan) or CD38-R (IFM2017-03) alone.[6] QoL should be monitored over time to ensure that this remains stable or improves. The safety profile of CD38ab-VRd must be well known by MM physicians, pts and relatives and SAEs grade 5 must be avoided. Precautions, such as dose reductions, antiinfective prophylaxis (cotrim/acyclovir), vaccinations (Covid, influenza, RSV, pneumococcus, etc.) and IVIG 10g q4 must be provided as substantial co-medication for quadruplets. Additionally, quadruplet CD38ab-VRd, followed by continuous CD38ab-Rd needs constant reassurance of pts/relatives that treatment stop leads to inferior PFS and OS, thus treatment cessations should be avoided. Onkopedia, NCCN, EHA/EMN guidelines 2024/2025[6] add to treatment recommendations in TI NDMM and have included therein that frailty studies remain important to guide TI MM pts, all aiming to improve the MM prognosis further.[14,15]

Conflicts of interest: ME+RW received honoraria from Amgen, J&J, GSK, Sanofi, Takeda, Stemline, Oncopeptides, all unrelated to this abstract and ICLLM presentation

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Contemporary First-Line Treatment of Classic Hodgkin Lymphoma

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Recent developments in the treatment of advanced-stage classic Hodgkin lymphoma (cHL) have led to substantial improvements in patient outcomes, particularly with the integration of novel therapeutic combinations and response-adapted strategies. Two major phase III trials - evaluating PET-guided therapy and immunotherapy-based regimens - have successfully introduced targeted agents into the first-line setting. First, the GHSG HD21 trial hast demonstrated that excellent outcomes can be achieved with PET-guided treatment with the Brentuximab vedotin (BV) containing novel BrECADD regimen, which is substantially better tolerable and more effective than BEACOPPesc. compromising efficacy. Second, six cycles of the combination of nivolumab with AVD (N-AVD) was better tolerable and resulted in superior short-term outcomes than BV-AVD. These approaches have contributed to higher progression-free survival rates and reduced toxicity in the patient population with advanced-stage disease.

Despite this progress, significant unmet clinical needs remain:

- **Early-stage cHL**: While cure rates with 2-4 cycles of usually A(B)VD based chemotherapy and consolidative radiotherapy are high, there is an ongoing need to reduce long-term toxicity from radiation and chemotherapy, particularly in younger patients, without increasing relapse risk. New approaches that allow for de-escalation of treatment while maintaining efficacy are still being refined.
- **Older adults with cHL**: Patients over 60 continue to have inferior outcomes due to comorbidities and poor tolerance of standard regimens. There is a need for less toxic yet effective treatment options tailored to this age group.
- **Refractory or relapsed disease**: Durable remissions remain challenging to achieve for patients whose disease is resistant to initial therapy or who relapse after standard treatment. Novel immunotherapeutics and cell-based therapies are promising but require further optimization and long-term follow-up.
- **Biomarker development and risk stratification**: Tools like circulating tumor DNA (ctDNA) sequencing, serum TARC kinetics, and spatially resolved tumor microenvironment profiling are in development. These aim to improve early response assessment and further personalize therapy, but they are not yet widely implemented in clinical practice.
- **Health disparities and access**: Global inequities in access to PET-guided treatment, BV and immunotherapies, and supportive care remain a barrier to uniform outcomes, particularly in low- and middle-income settings.

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ABSTRACTS

■ Acute Myeloid Leukemia

P-01 **Abstract Referance : 23**

FROM CYTOGENETICS TO MOLECULAR BIOLOGY IN THE MANAGEMENT OF ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is a hematological malignancy characterized by rapid progression and genetic heterogeneity. Accurate diagnosis and prognosis are essential for appropriate management. At Hassan II University Hospital in Fes-Morocco, the use of classical and molecular cytogenetic techniques, along with molecular biology, plays a central role in AML diagnosis and therapeutic decision-making. This study aims to evaluate the diagnostic and prognostic approach to AML at the hospital, focusing on the application of these advanced techniques.

A retrospective study was conducted on patients diagnosed with AML. Classical cytogenetics, including karyotyping, was performed to identify chromosomal abnormalities. In parallel, molecular cytogenetic techniques such as fluorescence in situ hybridization (FISH) were used to detect specific chromosomal translocations. Molecular biology techniques, including polymerase chain reaction (PCR) and next-generation sequencing (NGS), were applied to identify gene mutations commonly associated with AML, such as FLT3, NPM1, and CEBPA. Clinical data on treatment protocols and outcomes were collected and analyzed.

The findings demonstrate the value of combining classical and molecular cytogenetic techniques with molecular biology in the management of AML. Classical cytogenetics remains essential for detecting large chromosomal abnormalities (such as t(8;21), t(15;17), inv16, del(5q-)…), while molecular techniques provide critical insights into genetic mutations that influence disease behavior and response to therapy. The use of these complementary approaches allows for more accurate diagnosis, better prognostic evaluation, and tailored treatment plans.

The management of AML at Hassan II University Hospital has been significantly improved by the integration of classical and molecular cytogenetics along with molecular biology. This comprehensive approach has enhanced the accuracy of diagnosis, informed better prognostic assessments, and enabled more personalized treatment strategies. The use of these combined techniques is essential for optimizing patient care and improving clinical outcomes. Continued advancements in molecular diagnostics will be key to further refining treatment approaches and enhancing survival rates in AML patients.

Keywords: acute myeloid leukemia, cytogenetics, gene mutations.

■ Acute Lymphoblastic Leukemia

P-02 **Abstract Referance: 24**

DYNAMICS OF TREATMENT RESPONSE HAS A PROGNOSTIC VALUE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA

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Introduction: T-cell acute lymphoblastic leukaemia (T-ALL) is an aggressive and genetically heterogeneous cancer. The outcome of patients with T-ALL has improved; however, it is still inferior compared to B-cell ALL patients, and relapsed/refractory patients have a poor prognosis. Although prognostic models based on genetics have been proposed, only minimal/measurable residual disease (MRD) at the end of induction (EOI) is widely used to stratify patients. Our previous study of UKALL T-ALL data confirmed that treatment response was the key prognostic factor in T-ALL and that sex, age, white blood cell count and cytogenetics did not contribute significantly to predicting outcome in this subtype. Specifically, we showed that the percentage of blasts at day 8 (D8blasts) was a significant predictor of outcome and added prognostic impact to EOI MRD especially among patients who were MRD positive but not refractory [*Hemasphere* (2024);8(S1):36-37]. The aim of this study was to develop and validate dynamic prognostic models with multiple time points.

Methods: Data from 707 T-ALL patients aged 1-24 years old recruited to UKALL2003 or UKALL2011 between 2003 and 2018 were used in this study. We focussed on D8blasts measured by morphology and MRD at the EOI assessed by standardised Ig/TCR PCR. Dynamic prognostic models were developed using Nonlinear Mixed-Effects (NLME) and Area Under the Curve (AUC) methods, complex and simple approaches respectively, and validated using Kaplan-Meier method. Event-free survival (EFS), relapse rate (RR) and overall survival (OS) were performed, and all rates are quoted at 5 years.

Results: The OS rates for the two cohorts were: UKALL2003 (n=386) 86% (95% CI: 82-89) and UKALL2011 (n=321) 85% (80-88). The dynamic models (NLME and AUC models) were developed using the UKALL2003 cohort and validated using the UKALL2011 cohort. Both models produced very similar results; therefore, for clarity, we have presented data only from the AUC model. The AUC model generated personalised-risk scores, which assessed as a continuous variable in a Cox model, produced statistically significant hazard ratios for the risk of relapse: UKALL2003 1.01 (1.00-1.02), p=0.02; UKALL2011 1.02 (1.01-1.02), p<0.001. Threshold analysis revealed optimal cut-points defining standard-risk (SR) and high-risk (HR) groups: UKALL2003 190 (80%) / 47 (20%) and UKALL2011 126 (73%) / 47 (27%), respectively. Patients in the HR group had a significantly higher risk of relapse in both trials (Figure 1 A-B). Similar results were observed for EFS and OS. Unsurprisingly, there was a strong correlation between EOI MRD and the risk groups defined by the dynamic model with the majority of MRD low risk (UKALL2003 <0.01% and UKALL2011 <0.005%) cases assigned to the SR group (88 (46%) in UKALL2003 and 47 (37%) in UKALL2011) and the majority of refractory (MRD ≥5%) cases assigned to the HR group (15 (32%) in both trials). Among the remaining cases (UKALL2003 ≥0.01% & <5%; UKALL2011 ≥0.005% & <5%), the HR group had 25 (53%) and 29 (62%) patients in UKALL2003 and UKALL2011, respectively. These patients had a significantly higher relapse rate compared to patients with similar EOI MRD levels but in the SR group: UKALL2003 30% v 4% (p=0.001) and UKALL2011 38% v 15% (p=0.009) (Figure 1 C-D).

Conclusion: This study confirms the utility of treatment response for predicting outcome in childhood and adolescent patients with T-ALL. We have demonstrated for the first time that statistical modelling of multiple treatment response timepoints is feasible and can identify distinct prognostic subgroups which could be clinically relevant. Crucially, we have demonstrated that dynamic models had a significant advantage over EOI MRD

stratification. Future risk stratification strategies should take into account treatment response over multiple timepoints in order to predict outcome with greater accuracy.

Keywords: T-ALL, dynamic model, prognosis

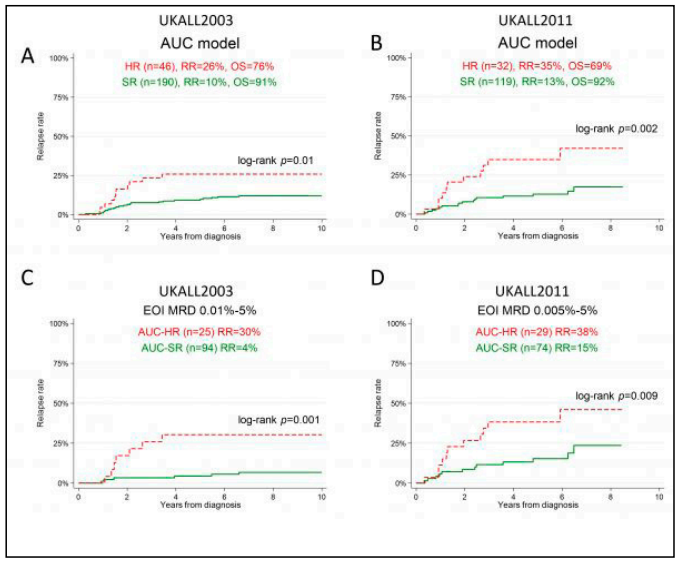

Figure 1. Clinical outcomes of the risk groups defined by the AUC model (A, B) and interaction between AUC risk groups and EOI MRD (C, D). Patients without complete remission or with unknown relapse status was excluded in this graph (AUC, Area Under the Curve; EOI MRD, minimal/measurable residual disease at the end of induction; SR, standard-risk; HR, high-risk; RR, relapse rate; OS, overall survival).

Non-Hodgkin's Lymphoma

P-04 Abstract Referance: 40

KERATINIZATION AND EXTRACELLULAR MATRIX ALTERATIONS IN DYSREGULATED GENES OF NON-HODGKIN LYMPHOMA

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Background: The most prevalent hematological disease in the world, non-Hodgkin's lymphoma (NHL), is responsible for around 3% of cancer diagnoses and fatalities. The various subtypes of NHL are divided into: Diffuse Large Cell B lymphoma (DLCBL), Follicular Lymphoma (FL), Marginal Zone Lymphoma (MALT), Chronic Lymphocytic leukemia, Nodal Marginal Zone Lymphoma (NMZL) and Mantle Cell Lymphoma (MCL). Each subtype of NHL is linked to distinct risk factors, making it a heterogeneous illness.

Methodology: GSE32018 was selected from GEO2R database, which comprised 114 B NHL patients with various subtypes and 7 controls of freshly frozen lymph nodes and reactive tonsils, that were put into analysis for dysregulated genes. DAVID was used to analyze the functional enrichment of upregulated and downregulated genes. Significantly enriched terms were identified based on p value <0.05 and Benjamini-Hochberg correction.

Results: Functional Annotation of 50 dysregulated (upregulated and downregulated) genes was categorized into enrichment of biological processes, cellular components and molecular processes that showed the significant enrichment in keratinization process, involvement of structural and extracellular matrix-related processes, which may contribute to the disease's cellular alterations with enrichment of protease inhibitors and cytokines revealing the immune relating processes in NHL respectively.

Conclusion: Our study highlighted the importance of keratinization in NHL and how matrix-related proteins could be altered in dysregulated genes of Non-Hodgkin Lymphoma and its various types, alongside the impact of immune-related molecules during multiple types of this disease.

Keywords: Non-Hodgkin Lymphoma, Gene dysregulation, Bioinformatic Analysis

Chronic Myeloid Leukemia

P-05 Abstract Referance: 45

PROGNOSTIC SIGNIFICANCE OF MICRORNA-532 -3P AND MICRORNA-582-5P GENE EXPRESSION IN A COHORT OF EGYPTIAN AML PATIENTS

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Background: Acute myeloid leukemia (AML) is a hematologic malignancy characterized by genetic and epigenetic aberration that affect the prognosis and therapeutic outcomes of the patients. MicroRNAs (miRs) have emerged as pivotal regulator of gene expression, influencing cancer pathogenesis, progression, and response to therapy.

Aim: To evaluate the prognostic significance of miR-532-3p and mir-582-5p gene expression in a cohort of Egyptian AML patients.

Patients and Methods: Gene expression of the circulating plasma miR-532-3p, and miR-582-5p in a cohort of 71 denovo newly diagnosed AML patients, as well as, 20 age and gender-matched healthy controls were evaluated using real-time quantitative PCR.

Results: MiR-532 -3p expression level was significantly lower in AML patients than controls (P-value <0.001). Though miR-582-5p expression level was lower in AML patients than controls, yet the difference was statistically insignificant (P-value =0.45). There was a statistically significant difference between the high and low miR-532-3p expressers regarding the gender and platelets count (P-value 0.03, and 0.04, respectively). Meanwhile, no statistically significant difference was encountered between high and low miR-532-3p or miR-582-5p expressers as regards age, clinical characteristics, laboratory data, and clinical outcomes, including overall survival (OS) and disease-free survival (DFS) (P-value > 0.05). However, there was a statistically significant positive correlation between miR-582-5p expression level and DFS with a p-value of 0.04. A highly statistically significant positive correlation between miR-532-3p, and miR-582-5p expression levels (p-value 0.001) was demonstrated, in which the increase in miR-582-5p will be associated with the increase in both miR-532-3p and DFS.

Conclusion: The down regulation of miRNA-582-5p and miRNA-532-3p in AML patients compared to controls, suggesting their antioncogenic role in AML. Furthermore, their plasma gene expression could serve as potential novel non-invasive molecular biomarkers for predicting DFS for further larger multicentric studies.

Keywords: AML, miR-532-3p-, miR-582-5p, oncogene, biomarker

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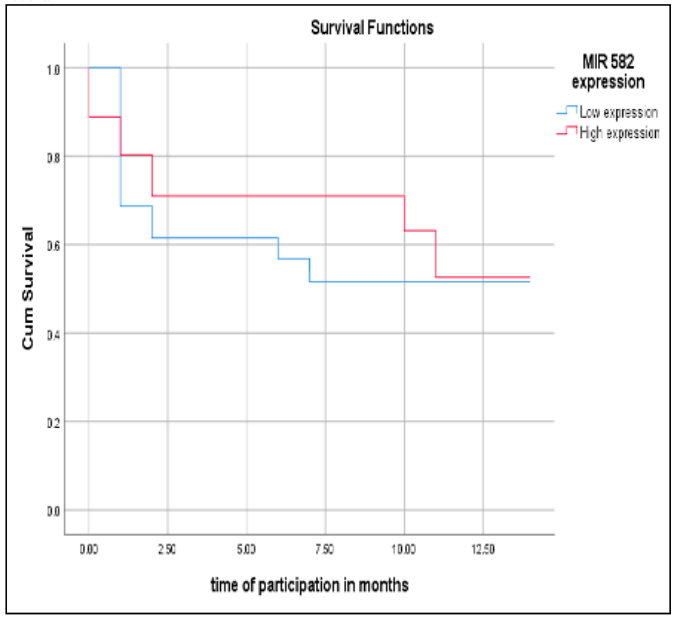
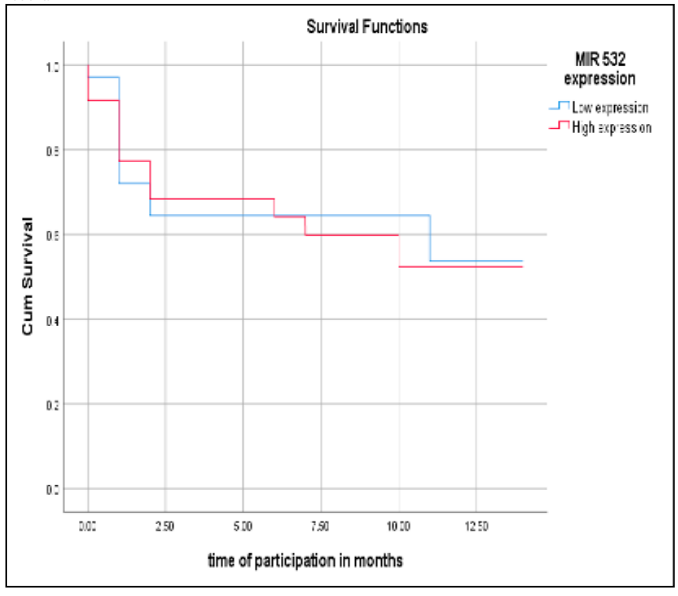
Kaplan Meier for Overall Survival Stratified According to Low and High MiR-582- 5P Gene Expression among AML Patients



Kaplan Meier for Overall Survival Stratified According to Low and High MiR-532- 3p Gene Expression among AML Patients



■ Non-Hodgkin's Lymphoma

P-06 **Abstract Referance: 11**

DIFFUSE LARGE B-CELL LYMPHOMA WITH SECOND RELAPSE IN LEUKEMIC PHASE

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Introduction: The leukemic phase of DLBCL is a rare condition and may be difficult to distinguish from acute leukemia or other types of non-Hodgkin lymphoma (1-2). The leukemic phase usually occurs as a progressive phase or in stage IV disease and is rare at the time of diagnosis in DLBCL (3-4). We presented our patient who came in the leukemic phase of DLBCL in its second relapse.

Case Report: A 68-year-old woman presented with complaints of neck swelling, weight loss, and night sweats. Complete blood count was normal. Superficial ultrasonography revealed multiple lymph nodes in bilateral cervical, inguinal, and axillary regions, the largest of which measured 20 mm in short axis, some with a reticular appearance, some with a compressed hilum, and thick cortex. An excisional biopsy was performed from the cervical region. The biopsy revealed tumor cells positive for immunohistochemical markers CD20, BCL-2, CD79A, and 50% positive for C-MYC, 1-2% positive for MUM-1, and negative for CD3, CD5, CD10, BCL-6, CD23, CD30, and Cyclin D1. The Ki-67 index was 80-90% (Figure 1). Diagnosis of non-germinal center type Diffuse Large B Cell Lymphoma (DLBCL) was made. Bone marrow biopsy was also found to be consistent with DLBCL involvement. The patient with stage 4, high IPI score was given Rituximab-Gemcitabine-Cyclophosphamide-Vincristine- Prednizon (R-GCVP) because of low ejection fraction. Prophylactic intrathecal methotrexate was administered because of the high probability of central nervous system recurrence of lymphoma. After 3 cycles of R-GCVP, a partial metabolic response to treatment was observed with PET-CT. Continuation of R-GCVP treatment was planned but the patient developed strabismus during follow-up. Contrast brain MRI was performed to investigate central nervous system involvement. A mass was detected on contrasted pituitary MRI, which, when evaluated radiologically and clinically together, was considered as lymphoma infiltration. The patient was planned to start MATRix chemotherapy protocol. After 3 cycles of MATRix chemotherapy, a follow-up contrasted pituitary MRI showed significant regression. Thereupon, the patient was planned for autologous hematopoietic stem cell transplantation (AHSCT). When he was admitted for AHSCT one month later, he had complaints of fatigue and abdominal pain. Complete blood count revealed a white blood cell count of 16.760/mm^3, hemoglobin 8.6 g/dL, and platelet count of 169.000/mm^3. Peripheral smear showed leukocytosis and 34% medium- to large-sized atypical lymphoid cells with condensed nuclear chromatin and inconspicuous nucleoli (Figure 2). In the flow cytometry performed on peripheral blood, a lymphoid cell population of approximately 45% was observed, showing positive expression of CD19, CD20, CD22, CD45, CD79a and negative expression of CD3, CD5, CD7, CD23, CD34, CD56, Tdt. During this period, the patient's leukocyte count increased rapidly and reached 50.000/mm^3, and was accepted as being in the leukemic phase of DLBCL. Since he was unfit and refractory to standard chemotherapy, Rituximab-Ibrutinib-Lenalidomide treatment was started. There was no response to this treatment. He died due to renal failure and sepsis within a short period of 1 month after the leukemic phase diagnosis.

Discussion: Lymphomas are diagnosed primarily based on histologic findings, although dissemination of these lymphoma cells into the circulation (leukemic phase) can be diagnosed based on cellular immunophenotypic analysis by flow cytometry (2). Immunophenotypically, these cells show strong membrane positivity for B cell lineage markers such as CD19, CD20 and follicular center markers such as CD10 (40%) and BCL6 (60%). Non-germinal center type DLBCL will show positivity for CD38 and MUM1 (4-5).

Keywords: Diffuse Large B-Cell Lymphoma, Leukemic Phase, Prognosis

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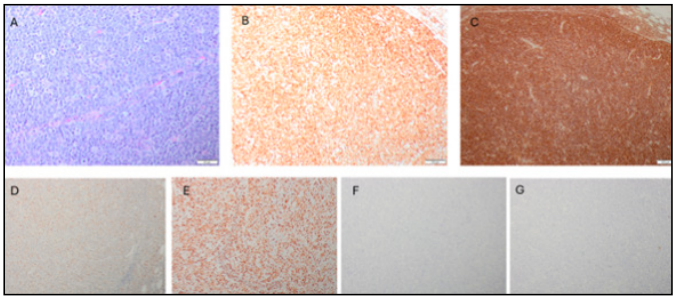

Figure 1. A: Hematoxylin-Eosin (50 µm), B: Bcl2 positive (scale bar:100 µm), C: CD20 positive (scale bar: 200 µm), D: C-myc %50 positive (scale bar: 100 µm), E: Kİ-67 %80-90 (scale bar: 100 µm) F: Bcl6: negative (scale bar: 100 µm) G: CD10 negative (scale bar:100 µm)

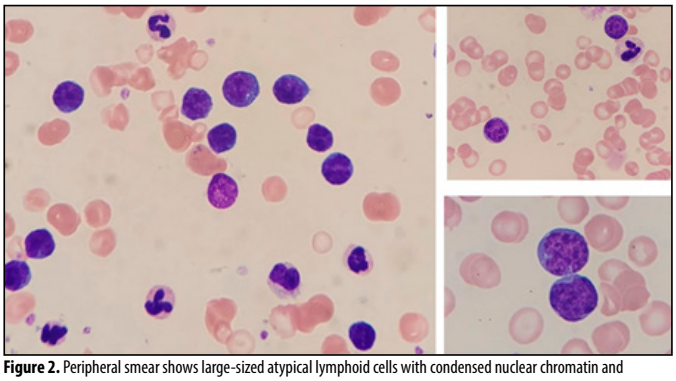

Figure 2. Peripheral smear shows large-sized atypical lymphoid cells with condensed nuclear chromatin and inconspicuous nucleoli

Stem Cell Transplantation

P-07 **Abstract Referance: 47**

LATE EXTRAMEDULLARY RELAPSES IN AML AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Myeloid sarcoma, an extramedullary tumor of myeloid origin, can occur in various sites and may precede or accompany Acute myeloid leukemia (AML) relapse. We present a unique case of a patient with AML who experienced multiple extramedullary relapses—including testicular, intraocular, and periorbital involvement—despite achieving long-term remission following allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Case: A 60-year-old male patient, diagnosed with AML-M5, presented to the Ophthalmology Department with a one-month history of pain and swelling in the left eye. Orbital MRI revealed a newly developed soft tissue lesion suggestive of leukemic infiltration, involving the superior-lateral rectus muscles, lacrimal gland, and left optic nerve, extending to the orbital apex. He was referred to our hematology clinic for further evaluation. The patient's AML history began with a diagnosis 17 years ago, achieving complete remission after mitoxantrone and cytarabine (ARA-C) induction therapy, followed by three cycles of high-dose cytarabine consolidation. Subsequently, he underwent allo-HSCT from HLA-matched sibling donor using a myeloablative regimen. At the six-month follow-up, bone marrow relapse was confirmed, prompting an additional cycle of high-dose cytarabine followed by donor lymphocyte infusion (DLI). Remission was maintained for four years. In the 4.5th year post-transplant, relapse occurred with a left testicular mass, and biopsy confirmed granulocytic sarcoma. No bone marrow or CNS involvement was detected. Orchiectomy was performed, followed by radiotherapy (RT, 2400 cGy). Intrathecal methotrexate and subcutaneous cytarabine (ARA-C, 50 mg/day for five days monthly, SC) were administered for three months as CNS prophylaxis, despite no CNS involvement, achieving remission. In the 10th year post-transplant, the patient reported vision loss in the left eye. Vitrectomy pathology suggested AML infiltration. He declined intensive systemic chemotherapy but consented to maintenance therapy with ARA-C. Follow-up MRI later revealed diffuse choroidal thickening with contrast enhancement in the left eye, prompting enucleation. Pathology confirmed myeloid sarcoma. Six cycles of ARA-C were administered, and remission was maintained. In the 16th year post-transplant, left eyelid swelling prompted repeat orbital MRI, revealing a new soft tissue lesion consistent with leukemic infiltration, involving the superior-lateral rectus muscles, lacrimal gland, and optic nerve, extending to the orbital apex. Systemic evaluation (complete blood count, peripheral smear, bone marrow, and lumbar puncture) showed no involvement. Periorbital biopsy confirmed myeloid sarcoma, and RT was initiated.

Conclusion: Late extramedullary relapses in AML after allo-HSCT are uncommon but significant events. These relapses occur outside the bone marrow, in sites like the skin, soft tissues, testicles, or eyes, and can happen years after the transplant, even after prolonged remission. There are no established guidelines for the treatment of EM relapse after allo-SCT. The common practice is a combination of local and systemic treatment including intensive chemotherapy, local radiotherapy, DLI, and/or retransplantation. Some patients, like those with isolated relapses and prolonged survival, can respond well, but outcomes are generally poor, with overall survival rates often below 15% at two years post-relapse. The best treatment of isolated EM relapse after allo-SCT is unknown. Treatment options for patients with EM relapse should be considered individually. Further research is needed to optimize therapeutic strategies for late extramedullary relapses and improve long-term outcomes in AML.

Keywords: Acute Myeloid Leukemia; Relapse; Transplantation, Myeloid Sarcoma

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■ Acute Lymphoblastic Leukemia

P-08 **Abstract Referance: 48**

INHIBITION OF SKP2 AND FBXO5 KNOCKDOWN INDUCE APOPTOSIS AND ENHANCE DOXORUBICIN SENSITIVITY IN BCP-ALL CELLS

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Background: The F-box proteins are important components of SCF ubiquitin ligases (Skp1, cullin, and F-box). These proteins play a critical role in the progression of the cell cycle and several pathways involved in the metabolism and activity of cells. FBXO5 and Skp2 are two F-box proteins that are upregulated in malignancies. Less well appreciated is the effect of FBXO5 and Skp2 inhibition on the potentiation of chemotherapeutic-induced cell death in B cell precursor acute lymphoblastic leukemia (BCP-ALL). In this study, Skp2 inhibition and downregulation of FBXO5 are evaluated in BCP-ALL derived cells, NALM-6 and SUP-B15.

Materials and methods: In the present study, FBXO5 was knocked down in NALM-6 and SUP-B15 cells using the shRNA mechanism. Skp2 was inhibited by SZL P1-41 in both the presence and absence of doxorubicin. Induction of apoptosis was evaluated using an Annexin-V/PI staining kit. mRNA and protein expression levels were assessed by qRT-PCR and western blot analysis, respectively.

Results: In both cells, inhibition of Skp2 or knockdown of FBXO5 induces caspase-mediated apoptosis. Furthermore, doxorubicin potentiates the apoptosis of NALM-6 and SUP-B15 cells. The knockdown of FBXO5 leads to the elevation of cells with more than four nuclei, while the inhibition of Skp2 results in the arrest of cells in the G1 phase of the cell cycle. Both doxorubicin-treated and doxorubicin-untreated cells showed increased expression of DNA damage genes. In addition, SKP2 inhibition and FBXO5 knockdown reduced FBXO5 and SKP2 in NALM-6 cells. In SUP-B15 cells, FBXO5 knockdown led to an increase in SKP2 expression.

Conclusion: FBXO5 and Skp2 may play a critical role in cell proliferation in NALM-6 and SUP-B15 cells. These factors may be considered important targets for treatment of BCP-ALL in presence of doxorubicin.

Keywords: Acute lymphoblastic leukemia, Apoptosis, Cellcycle, FBXO5, Lentivirus, SKP2

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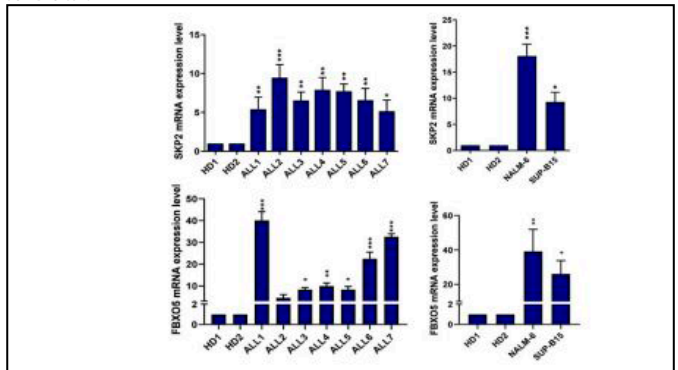
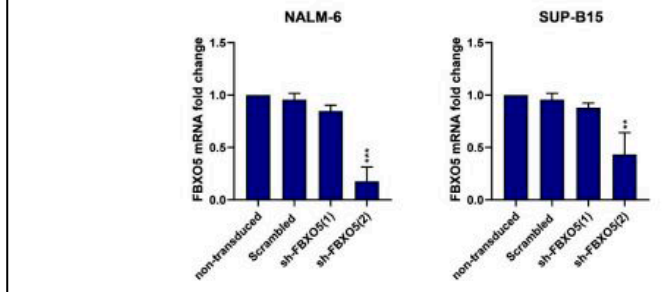
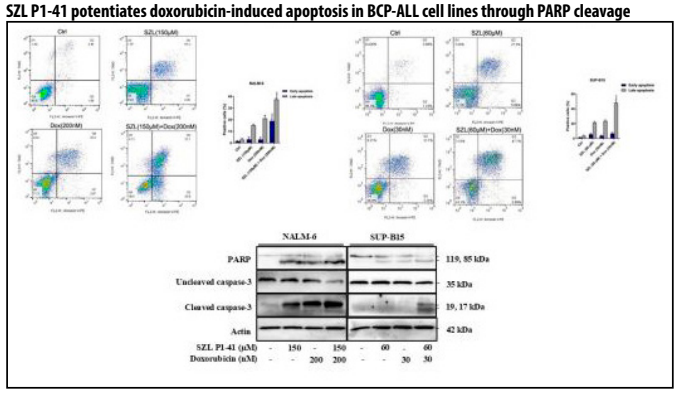
Expression of FBXO5 (Emi1) and SKP2 in patients with B-cell Acute lymphoblastic leukemia, NALM-6 and SUP-B15 cells



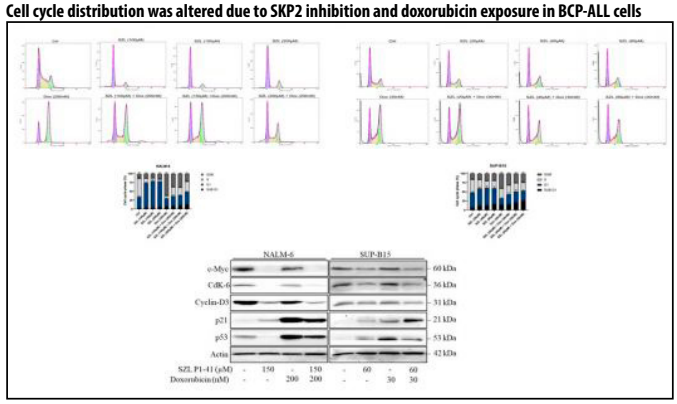
Expression of FBXO5 after transduction of cells with lentiviruses



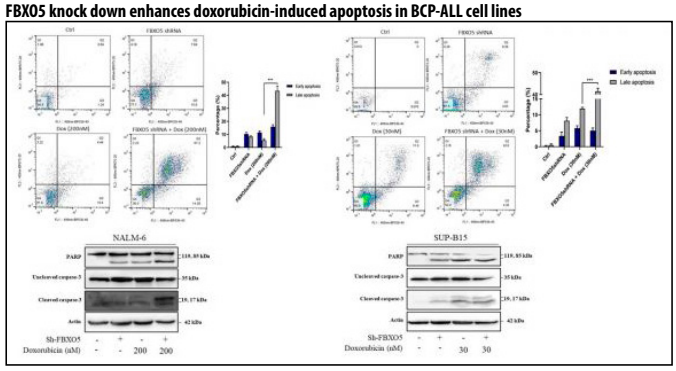
SZL P1-41 potentiates doxorubicin-induced apoptosis in BCP-ALL cell lines through PARP cleavage



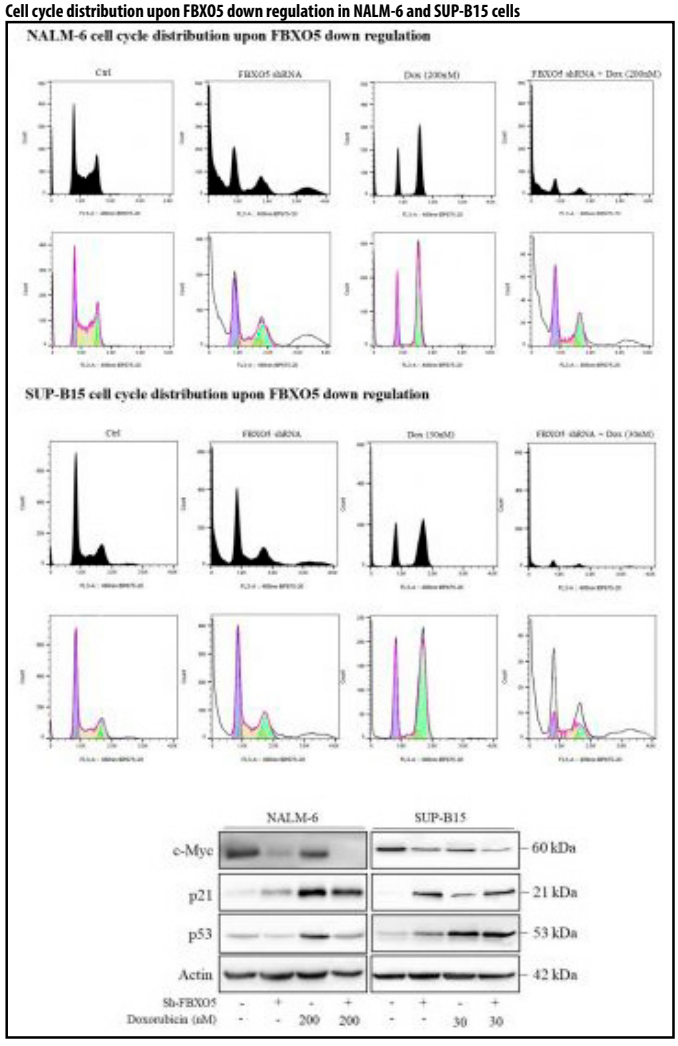
Cell cycle distribution was altered due to SKP2 inhibition and doxorubicin exposure in BCP-ALL cells



FBXO5 knock down enhances doxorubicin-induced apoptosis in BCP-ALL cell lines



Cell cycle distribution upon FBXO5 down regulation in NALM-6 and SUP-B15 cells



■ Other

P-09 **Abstract Referance: 33**

THE INTEREST AND THE EFFICACY OF THE REVISED INTERNATIONAL THROMBOSIS SCORE IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

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Introduction: Essential thrombocythemia (ET) is one of the myeloproliferative syndromes. It is characterized by hyperplasia of the meg karyocytic lineage. Given the morbidity and mortality associated with this pathology, the risk of thrombotic events in such population has been addressed by several prognostic scores including the revised international prognostic score for thrombosis (R-IPSET) which was developed to identify patients at higher risk of thrombotic events.

Aims: The aim of this work is to evaluate the interest of the R-IPSET score for assessing thrombotic risk in patients with ET.

Patients and Methods: Our retrospective study analyzed data from the files of patients followed, in our Hematology Department of Monastir, Tunisia, at Fattouma Bourguiba University Hospital, for ET from 2008 to 2024.

Results: We collected 88 patients diagnosed with ET. The median age at diagnosis was 62 years while noting a slight female predominance and a sex ratio of 0.92. The main thrombotic factors analyzed in our study included age over 60 years (55.7%), history of thrombosis (34.1%), cardiovascular risk factors (67%), and positivity of the JAK2V617F mutation (56.8%). The revised thrombosis stratification (R-IPSET) including the four factors mentioned above allowed patients to be classified into 4 categories: Patients at very low risk (no risk factors) (N=13 or 15%), at low risk (presence of the JAK2V617F mutation) (N=12 or 14%), at intermediate risk (age >60 years) (N=11 or 13%) and at high risk (history of thrombosis or age >60 years with positive JAK2V617F) (N=50 or 58%) (Table 1). All our patients were devised into different risk groups according to the ELN and the IPSET prognostic scores (Tables 2 and 3). The tables below describe the percentage of patients who had thrombotic complications (events) during follow-up according to different prognostic score used.

The last table (4) shows that in our study only 5.6% of patients who received initial cytoreductive treatment experienced thrombotic complications during the follow-up of the disease. This rateis much higher for patients who received delayed cytoreductive treatment. This demonstrates the effectiveness of hydroxyurea in management and the prevention of thromboembolic complications during ET.

Conclusion: In conclusion, the R-IPSET model did not demonstrate, in our study, a superiority in the assessment of the risk of thrombotic events, therefore allowing us to conclude that whatever the prognostic score used, an optimal stratification of each patient is necessary to guarantee better management of ET and its possible complications.

Keywords:TE-R-IPSET SCORE

Table 1. Classification of patients according to the R-IPSET score

R-IPSET	*Percentage*	*Initial cytoreductive treatment*	*Delayed cytoreductive treatment*	*Without treatmen t*	*Thrombotic events*
Very low risk	15%	53,8%	30,7%	15,5%	7,7%
Low risk	14%	50%	8,4%	41,6%	8,3%
Intermediate risk	13%	90%	0%	10%	9%
High risk	58%	94%	6%	0%	8%

Table 2. Classification of patients according to the ELN risk score

ELN risk prognostic	*Percentage*	*Initial cytoreductiv e treatment*	*Delayed cytoreductiv e treatment*	*Without treatment*	*Thrombotic events*
Low risk	30%	52%	20%	28%	8%
High risk	70%	93,44%	4,91%	1,63%	8%

Table 3. Classification of patients according to the R-IPSET score

IPSET score	*Percentage*	*Initial cytoreductive treatment*	*Delayed cytoreductive treatment*	*Without treatment*	*Thrombotic events*
Thrombotic events	15%	53.8%	30.8%	15.4%	8%
Intermediate risk	25.7%	72.7%	4.54%	22.72%	9%
High risk	59.3%	92%	5.88%	1.96%	8%

Table 4. Therapeutic characteristics of the study population

Patients with initial cytoreductive treatment	*82%*	*5.6%*
Patients with delayed cytoreductive treatment	9%	37.5% (Of which 25% had the complication before treatment)
Patients without treatment	9%	0%

Acute Lymphoblastic Leukemia

P-10 Abstract Referance: 43

PROFILE OF FEBRILE NEUTROPENIA EPISODES IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA : A MONOCENTRIC STUDY

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Introduction: Febrile neutropenia (FN) is a potentially life-threatening complication in children with acute lymphoblastic leukemia (ALL) undergoing chemotherapy. The induction phase of the treatment is particularly critical, as it is associated with severe immunosuppression. This study aims to investigate the profile of FN episodes during the induction phase, focusing on biological factors, microbiological findings, and clinical outcomes.

Methodology: We conducted a retrospective observational study including children diagnosed with ALL and during the induction phase of chemotherapy at our Hematology department between 2020 and 2025. Data collected included demographic characteristics (age, gender), fever characteristics, complete blood counts, C-reactive protein (CRP) levels and microbiological cultures.

Results: A total of 29 children were included in the study, among them 23 patients (79,3%) experienced at least one episode of FN during the induction phase hence 41 episodes of FN were recorded. The median age of our study population was 7 years (2-17 years) with a male predominance (sex-ratio at 2). The median duration of neutropenia was 15 days, 56,4 % of the FN episodes were associated with severe neutropenia (<100 cell/mm3). The median CRP level was 35, notably 480 was the highest level. FN episodes were distributed as follows: Fever of unknown origin (22%), fever clinically documented (34%) and fever microbiologically documented (44%).

As for microbiologically documented fevers, Gram positive bacteria (coagulase-negative Staphylococci) were the most frequently isolated (75 % of the positive blood cultures).

Furthermore, empirical intravenous antibiotic therapy was initiated in 27 cases, and the required modifications based on culture results were carried out. While guided intravenous antibiotics were prescribed in 14 cases.

Our antibiotic therapy was considered appropriate according to the international guidelines. The evolution was favorable for all cases of FN without any adverse outcomes.

Conclusion: Overall, FN is a very important complication during the induction phase of chemotherapy in children with ALL, particularly due to its frequent association with profound neutropenia and bacterial infections, necessitating early diagnosis and appropriate treatment which is why close monitoring and early intervention are crucial to improve outcomes. Further studies are recommended to evaluate preventive strategies and optimize management protocols for FN in this vulnerable population.

Keywords: febrile neutropenia,bacteremia,acute lymphoblastic leukemia

Non-Hodgkin's Lymphoma

P-11 Abstract Referance: 52

CASE REPORT: REFRACTORY HIGH-GRADE B-CELL LYMPHOMA TREATED WITH VIPOR REGIMEN AND STEM CELL TRANSPLANTATION

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A 31-year-old male patient was diagnosed with high-grade B-cell lymphoma in July 2023. Following six cycles of R-CHOP, the disease progressed. After two cycles of salvage R-DHAP, the disease remained refractory, and after two cycles of R-ICE, residual disease was observed. Despite one cycle of R-GDP, the disease continued to progress, leading to hematopoietic stem cell mobilization. An autologous stem cell transplant was planned. The pathology report, revised at our center, confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL), ABC subtype. Due to disease progression under R-GDP, the VIPOR regimen was initiated. If a response was achieved, an autologous stem cell transplant was scheduled.

The patient had no known comorbidities other than hepatitis B carrier status. On October 31, 2024, he was admitted to the hematology department for stem cell mobilization. The R-GEMOX protocol was initiated on November 6, 2024. On November 16, 2024, a peripheral blood count revealed 392,480/µL leukocytes and 105,280/µL neutrophils, while the complete blood count showed 36,230/µL leukocytes and 27,560/µL neutrophils. Autologous peripheral blood stem cell collection was performed without complications, yielding 8.7×10^6 $CD34^+$ cells/kg.

On November 18, 2024, the patient was clinically stable with normal vital signs. A contrast-enhanced CT scan of the neck, thorax, and abdomen was performed for response evaluation. The neck CT showed no mass lesion or pathological lymphadenopathy. The thoracoabdominopelvic CT revealed a soft tissue density mass extending from the apical segment of the right upper lung lobe to the anterior aspect of the pulmonary trunk. Additionally, a small nodule in the right middle lung lobe, bilateral nephrolithiasis, and a sequelae cortical defect in the lower pole of the right kidney were noted.

On November 26, 2024, the VIPOR regimen (obinutuzumab, lenalidomide, ibrutinib, prednisolone, and venetoclax) was initiated. By December 19,

2024, the venetoclax dose was escalated from 50 mg to 100 mg, increasing by 100 mg daily until reaching a maximum dose of 400 mg/day.

On January 3, 2025, a PET scan was performed. In the superior mediastinum, a 4.5 × 4.3 × 5.7 cm mass was detected in the midline and left side, exhibiting pathological 18F-FDG uptake (SUVmax: **20.82)**. A significant reduction in the mediastinal mass size was observed, but a **residual lesion remained**, necessitating **consultation with radiation oncology**, and **25 doses of radiotherapy were scheduled**.

On March 7, 2025, after five cycles of chemotherapy, a contrast-enhanced CT scan of the neck, thorax, and abdomen was performed for response assessment. The patient was discharged with scheduled follow-ups and planned allogeneic stem cell transplantation.

On March 11, 2025, a contrast-enhanced thoracoabdominal CT scan was reviewed alongside the January 2025 PET scan. A lobulated-contoured mass in the left side of the anterior superior mediastinum was observed. The mass contained areas of contrast enhancement and measured approximately 38 × 45 mm at its widest point. Compared to the previous scan, no significant change in size was detected. No additional mass lesions or pathological lymph nodes were observed in the mediastinum or hilar regions.

Keywords: Refractory high-grade B-cell lymphoma, VIPOR, Stem cell transplantation

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Acute Lymphoblastic Leukemia

P-12 Abstract Referance: 54

DARATUMUMAB, VENETOCLAX, AZACITIDINE, AND DEXAMETHASONE TREATMENT IN HEAVILY PRETREATED CHEMOREFRACTORY ETP-ALL/L.

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Introduction: Early T-precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) is a rare and aggressive subtype of T-ALL, characterized by genomic instability, poor prognosis, and resistance to standard chemotherapy. The clinical course is often challenging to manage, as patients tend to relapse early and show limited response to conventional treatment protocols. We report a case of relapsed/refractory (R/R) ETP-ALL/LBL that relapsed shortly after first-line combination chemotherapy and was unresponsive to second- and third-line regimens, but achieved complete remission (CR) with a combination of daratumumab, venetoclax, azacitidine, and dexamethasone.

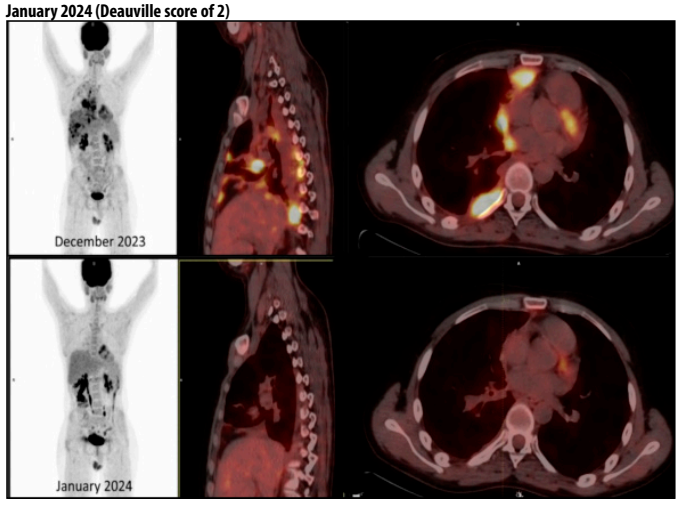
Case: A 21-year-old male presented in August 2020 with cervical lymphadenopathy. PET-CT revealed widespread lymphadenopathy (SUV max 3.8–11). A biopsy confirmed ETP-ALL/LBL, with immunohistochemistry showing positivity for CD3, CD7, CD34, CD117, HLA-DR, CD13, CD33, CD65, and a high Ki-67 index (90%). Bone marrow analysis revealed no blasts, and karyotype was normal with no CNS involvement. The patient was treated with the HOELZER protocol, a first-line regimen for T-ALL, which includes combination chemotherapy and intrathecal therapy for CNS prophylaxis. Following induction, the patient achieved complete remission (CR), with PET-CT confirming resolution of lymphadenopathy and no bone marrow involvement. Maintenance therapy was completed in April 2023, with regular follow-ups. Three months after completing maintenance therapy, the patient developed shortness of breath and fatigue. PET-CT showed relapse, including pleural effusion and multiple lesions (SUV max 7.5–9.4), confirmed by biopsy. Given the aggressive nature of his disease and prior responses to treatment, a more intensive approach was considered. The patient was started on second-line therapy with the FLEND protocol, which includes nelarabine, fludarabine, etoposide, and PEG-asparaginase, along with intrathecal CNS prophylaxis. Unfortunately, after one cycle, PET-CT showed disease progression.Third-line therapy using the BFM 2000 protocol was initiated, but after the first induction phase, the patient developed catheter thrombosis and pulmonary thromboembolism, requiring anticoagulant therapy. Despite supportive measures, PET-CT showed continued disease progression. At this point, a regimen of daratumumab, venetoclax, azacitidine, and dexamethasone was considered as a bridge to allogenic hemopoietic stem cell transplant(allo-HSCT). After one cycle of salvage therapy, PET-CT confirmed complete remission. Due to insurance delays preventing timely donor screening for allo-HSCT, a second cycle of salvage therapy was given to maintain remission. Unfortunately, the patient developed grade 4 neutropenia, leading to invasive pulmonary aspergillosis, Haemophilus influenzae type B infection, and gram-negative sepsis. Despite intensive care efforts, he passed away from acute respiratory distress syndrome (ARDS).

Discussion: This case demonstrates the potential of daratumumab, venetoclax, azacitidine, and dexamethasone to induce complete remission in a heavily pre-treated patient with relapsed/refractory ETP-ALL/LBL. The observed response suggests a possible synergistic effect of this novel combination and supports its further evaluation as a therapeutic option in this challenging setting. To our knowledge, this is the first report of such a regimen in R/R ETP-ALL/LBL. The lack of long-term follow-up and limited safety data highlight the need for additional studies and larger case series to confirm its efficacy and tolerability.

Conclusion: This patient's response to the combination therapy highlights its potential as an effective treatment for refractory ETP-ALL/LBL. Further research is necessary to confirm its efficacy and safety in broader clinical settings.

Keywords: Early T-ALL, Daratumumab, Venetoclax,Azacitidine, Dexamethasone, allo-HSCT

In December 2023, nodular pleural lesions in the right hemithorax exhibited increased FDG uptake with an SUV of 11.5. The size and metabolic activity of these pleural mass lesions decreased significantly in January 2024 (Deauville score of 2)



■ Acute Lymphoblastic Leukemia

P-13 **Abstract Referance: 56**

SYNERGISTIC ANTI-CANCER EFFECTS OF CARFILZOMIB WITH DOXORUBICIN/DEXAMETHASONE VIA P53-MEDIATED APOPTOSIS IN B-ALL CELLS

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Background: The ubiquitin -proteasome system (UPS) plays a crucial role in regulating the levels and functions of a large number of proteins in the cell, which are important for cancer cell growth and survival. The proteasome is highly activated in B-cell precursor acute lymphoblastic leukemia (BCP-ALL), which is the most common malignancy in children. The attempt to inhibit proteasome as a therapeutic strategy has been successful for some malignancies.

Materials and Methods: In this experimental study, human BCP-ALL cell lines NALM-6 and SUP-B15 were treated with carfilzomib with and without the chemotherapeutic agents. The XTT assay evaluated the viability of the cells. Cell cycle analysis and apoptosis assay were assessed by flow cytometry. RQ-PCR and western blotting evaluated the expression of pro-/anti-apoptotic signals. A drug combination study for synergistic or additive effects of carfilzomib with doxorubicin or dexamethasone was performed.

Results: We observed that carfilzomib alone induced G2/M cell cycle arrest and caspase-dependent apoptosis in the human BCP-ALL cells (NALM-6 and SUP-B15). Gene and protein expression analysis indicated the upregulation of pro -apoptotic as well as downregulation of the cell survival and proliferative signals (P-value<0.05). The synergy of carfilzomib with doxorubicin or dexamethasone was revealed in BCP-ALL cells.

Conclusion: Our results indicated that proteasome inhibition induces p53-mediated apoptosis in BCP-ALL cells. Since carfilzomib has a synergistic effect with anti-leukemic agents doxorubicin and dexamethasone in BCP-ALL cells, this combined-modality approach might be befitting for patients who do not respond well to conventional chemotherapy.

Keywords: Acute lymphoblastic leukemia, Carfilzomib, Dexamethasone, Doxorubicin

■ Acute Lymphoblastic Leukemia

P-14 **Abstract Referance: 57**

FROM DIAGNOSIS TO RELAPSE: A JOURNEY VIA EXPRESSION OF FERROPTOSIS-RELATED GENES, GPX4 AND LINC00618, IN BCP-ALL

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Background: Acute lymphoblastic leukemia remains a significant challenge in pediatric malignancies, particularly in relapse and treatment resistance. This study investigated the expression patterns of ferroptosis-related genes GPX4 and LINC00618 in different phases of pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL) patients to understand their potential roles in disease progression and treatment response.

Materials and Methods: This case-control study analyzed 82 samples (67 bone marrow, 15 peripheral blood) from BCP-ALL patients (14 new cases, 29 complete remission, 17 relapsed) alongside 22 healthy controls. The expression levels of GPX4 and LINC00618 were evaluated using quantitative real-time PCR, and their association with clinical parameters was assessed. Statistical analyses included parametric and nonparametric tests.

Results: GPX4 was significantly overexpressed in ALL patients compared to controls (Fold change: 2.08, p <0.01), with increased levels in new cases (Fold change: 2.45, p <0.01) and relapsed patients (Fold change: 2.03, p <0.05). Similarly, LINC00618 exhibited significant upregulation in patients (Fold change: 3.43, p <0.05), particularly new cases (Fold change: 4.67, p <0.01) and relapsed patients (Fold change: 4.87, p <0.05). Both genes were downregulated during the remission phase. A significant correlation was observed between LINC00618 expression at relapse and WBC count, platelet count, and hemoglobin level.

Conclusion: The parallel expression patterns of GPX4 and LINC00618 suggest their potential roles in disease progression and resistance. Their increased expression in proliferative phases and decline during remission may indicate involvement in leukemic cells survival and therapeutic responses. Further research is needed to clarify their molecular mechanisms and clinical significance.

Keywords: Acute lymphoblastic leukemia, GPX4, LINC00618, Ferroptosis

■ Chronic Myeloid Leukemia

P-15 **Abstract Referance: 58**

DIFFERENTIAL GENE EXPRESSION PATTERNS OF MIR-411 AND SPRY4: INDICATORS OF DISEASE PROGRESSION AND TREATMENT IN CML

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Background: Chronic myeloid leukemia (CML) is a clonal neoplasm originating from hematopoietic stem cells which is characterized by t(9;22)(q34;q11.2) fusion gene leading to forming an oncoprotein. miR-411 and SPRY4 may influence CML leukemogenesis by regulating proliferation, differentiation, and various signaling pathways induced by the oncoprotein.

Materials and Methods: In this cross-sectional study, a total of 90 blood samples were collected from individuals diagnosed with CML, covering three distinct clinical phases: 38 samples at the diagnosis, 38 samples one year after treatment, and 14 samples during the blastic phase. The expression levels of miR-411 and SPRY4 genes were measured using real-time PCR. Statistical analysis was conducted using nonparametric tests.

Results: miR-411 expression was significantly upregulated post-treatment compared to the time of diagnosis, and downregulated in the blastic phase compared to the post-treatment phase. In contrast, SPRY4 expression was significantly downregulated post-treatment compared to the time of diagnosis, and upregulated in the blastic phase compared to the post-treatment phase.

Conclusions: This study suggests that SPRY4 could play an oncogenic role and miR-411 could be a tumor suppressor in CML, although further studies are needed to clarify the role of these two genes in hematological malignancies such as CML.

Keywords: Chronic Myelogenous Leukemia, miR-411, SPRY4, Hematologic malignancies

■ Stem Cell Transplantation

P-16 **Abstract Referance: 61**

BRENTUXIMAB VEDOTIN AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA IN BULGARIA

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Brentuximab vedotin (BV) is the first approved novel agent for maintenance treatment of relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after autologous stem cell transplantation (ASCT). We aimed to determine the impact and safety of BV as maintenance/consolidation or treatment of relapse after ASCT in real - world setting. Retrospective analysis of individual patients data from four hematological centers in Bulgaria were collected. Our data demonstrated that the use of BV as consolidation in cHL and in patients relapsing after ASCT resulted improvement in both clinical response and overall survival. We investigated the outcome of 83 cHL patients receiving treatment with BV : (A group - patients with consolidation after ASCT= 68; B group - relapsed after ASCT=11; C group - patients with first line treatment continuing with ASCT=4;). Median follow - up was 73 months. Patients presented with an average of 3.5 lines of therapy before BV. At the time of analysis, 38 (44.5%) patients completed 16 courses of BV, and BV was discontinued in 30 (36%) patients. Sixty one (73.5%) patients had an ongoing CR and 15 (17.8%) had progressed. Ten (12%) died in the follow-up, eight with progressive disease and two while in CR. The 3 year PFS and OS rates were 78 % and 79% respectively. The most common adverse affect (AE) was peripheral neuropathy, with grade 3-4 only in 4 patients. Consolidation with BV after ASCT can result in remarcable PFS with an acceptable toxicity.

Keywords: Brentuximab vedotin, autologous stem cell transplantation

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■ Acute Myeloid Leukemia

P-17 **Abstract Referance: 62**

CDC27 GENE EXPRESSION PATTERNS AS A POTENTIAL BIOMARKER IN ACUTE LEUKEMIA

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Background: Treating Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) is difficult due to high relapse rates and drug resistance. Tumorigenesis is largely dependent on disruption of the cell cycle progression. While the role of Cell Division Cycle 27 (CDC27) in the anaphase-promoting complex/cyclosome is well-known, its significance in the pathophysiology of acute leukemia and its potential as a biomarker are less well understood.

Methods and results: This case-control study used samples from 100 leukemia patients (50 with ALL and 50 with AML) at Shariati Hospital in Tehran, Iran, along with 50 healthy individuals. The expression of CDC27 was analyzed using quantitative real-time PCR (RQ-PCR). Statistical analysis was done using the nonparametric Mann-Whitney U test. The results showed that AML and ALL patients had significantly higher levels of CDC27 expression compared to the control group. Although a weak correlation between CDC27 expression and hematological parameters was found, there was no significant correlation with sample type, demographics, clinical variables or prognosis.

Conclusions: This study highlights the potential of CDC27 as an oncogene, as well as a possible prognostic and diagnostic marker in acute leukemias. It suggests that CDC27 could be a valuable biomarker or therapeutic target in the treatment of AML and ALL.

Keywords: APC/C; Acute lymphoblastic leukemia; Acute myeloid leukemia; CDC27

■ Chronic Myeloid Leukemia

P-18 **Abstract Referance: 63**

DESIGN AND FABRICATION OF NOVEL MICROFLUIDIC-BASED DROPLETS FOR DRUG SCREENING ON A CHRONIC MYELOID LEUKEMIA CELL LINE

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Background: The challenges associated with traditional drug screening, such as high costs and long screening times, have led to an increase in the use of single-cell isolation technologies. Small sample volumes are required for high-throughput, cell-based assays to reduce assay costs and enable rapid sample processing. Using microfluidic chips, single-cell analysis can be conducted more effectively, requiring fewer reagents and maintaining biocompatibility. Due to the chip's ability to manipulate small volumes of fluid, high-throughput screening assays can be developed that are both miniaturized and automated. In the present study, we employ microfluidic chips for drug screening in chronic myeloid leukemia. This study aimed to establish a robust methodology integrating diverse assays, providing a holistic understanding of drug response.

Material and methods: Herein, we have used a chronic myeloid leukemia derived cell line (K562) for drug screening with an innovative microfluidic-based drug screening approach to investigate the efficacy of imatinib

in K562 cells. Cell viability was assessed using MTT assay. Apoptosis was measured using Annexin/PI staining by flow cytometry.

Results: Significant increased apoptosis was seen in K562 cells treated with imatinib in the microfluidic device compared to cells treated with imatinib in 24- and 96-well plates. Moreover, in the microfluidic chip, drug screening time was reduced from 48 hours to 24 hours.

Conclusion: Compared to traditional approaches, microfluidic-based drug screening efficiently evaluates the efficacy of imatinib in K562 cells. This approach is promising for drug discovery and treatment optimization, as it increases sensitivity and streamlines the screening process.

Keywords: Microfluidic-based droplets, Drug screening, Chronic myeloid leukemia

Acute Lymphoblastic Leukemia

P-19 **Abstract Referance: 64**

MICROFLUIDIC-BASED OPTIMIZATION OF TRANSDUCTION EFFICIENCY OF HIV-1-DERIVED LENTIVIRAL VECTORS IN BCP-ALL CELLS

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Background: HIV-1-derived lentiviral vectors (LVs) are capable of transducing human cells by integrating the transgene into the host genome. In order to do that, LVs should have enough time and space to interact with the surface of the target cells. Herein, we used a microfluidic system to facilitate the transduction of BCP-ALL cells.

Methods and results: We used a SU-8 mold to fabricate a PDMS microfluidic chip containing three channels with a 50 µm height and a surface matching 96-well plates. In order to produce LVs, we used HEK293T cells to package the second generation of LVs. First, we evaluated the cell recovery from the microfluidic chip. Cell recovery assessment showcased that 3 h and 6 h of incubation in microfluidic channels containing 100,000 NALM-6 (BCP-ALL) cells with 2µL of culture media yielded 87±7.2% and 80.6 ± 10% of cell recovery, respectively. Afterward, the effects of LV-induced toxicity were evaluated using 10-30% LV concentrations in time frames ranging from 3 h to 24 h. In 96-well plates, it took 12-24 h for the viruses with 20% and 30% concentrations to affect the cell survival significantly. These effects were intensified in the microfluidic system implying that microfluidic is capable of enhancing LV transduction. Based on the evidence of cell recovery and cell survival we chose 6 h of incubation with 20% LV.

Conclusion: The results from EGFP expression showcased that a microfluidic system could increase the LV transduction in BCP-ALL cells by almost 9-folds. All in all, the microfluidic system seems to be a great armamentarium in optimizing LV-based transduction.

Keywords: BCP-ALL, Lentiviral vector, microfluidic systems, Transduction efficiency

Non-Hodgkin's Lymphoma

P-20 **Abstract Referance: 65**

RARE DISEASE: DATA ON ADULT LYMPHOBLASTIC LYMPHOMA PATIENTS IN TURKEY

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Introduction: Lymphoblastic lymphoma (LBL) is a highly malignant tumor composed of immature lymphocytes derived from B or T cells. LBL is usually distinguished from ALL by the presence of less than 25% of bone marrow-invading blasts. Our study examined the data of LBL patients diagnosed and treated at centers within our country.

Material method: Thirty-eight patients from seven distinct tertiary adult hematology clinics were chosen for this investigation. Individuals aged 18 and older with a pathologically confirmed diagnosis of LBL, who had radiological assessments for clinical staging and received a minimum of one chemotherapy regimen, were included in the study.

Results: Overall survival (OS) for all patients was 23 months, 21 months for patients with T-LBL, and 56 months for individuals with B-LBL. Despite a significant difference in overall survival (OS) between patients diagnosed with T-LBL and those diagnosed with B-LBL, no significant difference in OS was found between the two groups (p>0.05). The median progression-free survival (PFS) of the patients was determined as 6 months.

Discussion: The data from our study indicate that elevated LDH levels, central nervous system involvement, involvement in three or more regions, cervical lymph node involvement, achieving remission after the initial treatment, and male gender (with no significant difference observed in the T-LBL subgroup) adversely affect prognosis.

Keywords: Lymphoblastic Lymphoma, prognosis, Survival

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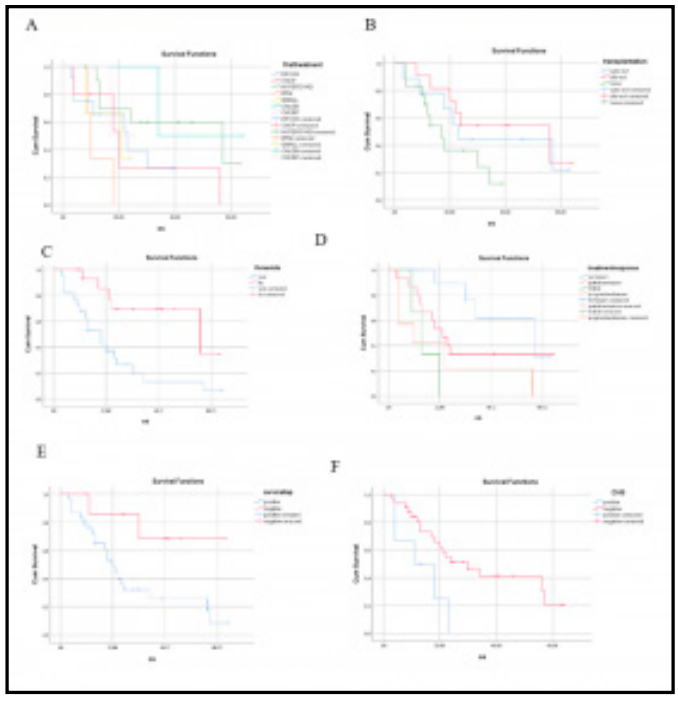

Figure 2. Prognostic factors related to the study (A) treatment protocols and relationship to OS. (B) Transplantation and relationship to OS. (C) Involvement of three or more sites and relationship to OS. (D) Response to first-line therapy and relationship to OS. (E) Cervical lymph node involvement and relationship to OS. (F) CNS involvement and effect on OS. OS: overall survival

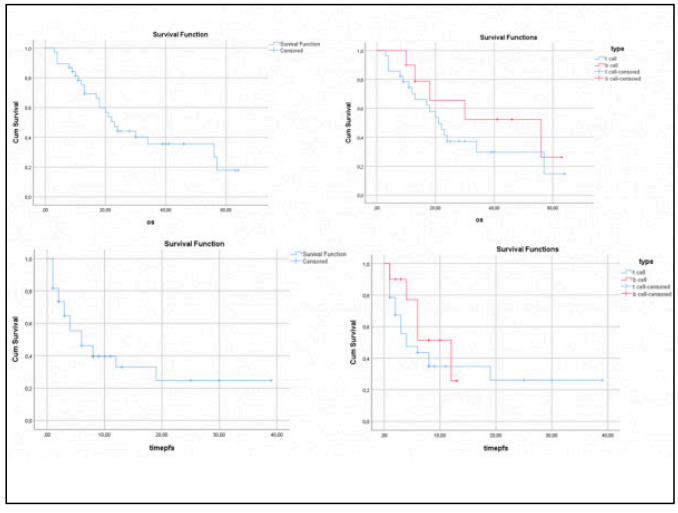

Figure 1. Kaplan–Meier curves for progression-free and overall survival. (A) Overall survival of the whole study population. (B) Progression-free survival of the whole study population. LBL : Lymphoblastic lymphoma ,T-LBL : T-cell lymphoblastic lymphoma, B-LBL : B-cell T-cell lymphoblastic lymphoma.

Tablo 1. Impact of Findings on Overall Survival in Study Participants

Situation	*-*	*OS (month)*	*T-LBL OS (month)*	*B-LBL OS (month)*	*P score*
Extraorgan involvement	yes	18	-	-	>0.05
Extraorgan involvement	no	-	-	-	>0.05
Transplantation	Auto-SCT	23	21	-	>0.05
Transplantation	Allo-SCT	56	24	56	>0.05
Transplantation	None	17	17	32	>0.05
Involvement of three or more regions	yes	18	18	18	<0.05
Involvement of three or more regions	no	56	-	56	<0.05
Bone marrow involvement	yes	22	22	13	>0.05
Bone marrow involvement	no	30	21	56	>0.05
CNS involvement	yes	11	-	3	<0.05
CNS involvement	no	30	-	-	<0.05
Presence of cervical LAP	yes	20	21	18	<0.05
Presence of cervical LAP	no	-	-	-	<0.05

Multiple Myeloma

P-21 **Abstract Referance: 66**

COULD HYPERAMYLASEMIA BE A SIGN FOR RELAPSING OF MULTIPLE MYELOMA?

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Introduction: Hyperamylasemia is mostly associated with pancreatic diseases, but also with salivary gland and other gastrointestinal diseases. It has been shown that it may related to some tumours (ovary, prostate, lung, breast) and multiple myeloma as a paraneoplastic syndrome. In this case, we presented a multiple myeloma patient who relapsed with hyperamylasaemia.

Case Report: A 67-year-old man who was diagnosed with multiple myeloma (IgG-kappa) seven years ago was followed with maintenance therapy with bortezomib after second autologous bone marrow transplantation in April 2024. He had amylase elevation between 100-140U/L after the second transplantation. However, in the fourth month of bortezomib maintenance therapy, it was incidentally found that he had hyperamylasemia over 3000 U/L. He had no symptoms such as abdominal pain, nausea or vomiting.

In the imaging studies, there was no sign of pancreatic or salivary gland diseases but bilateral pleural effusion with no specific symptoms- along with elevated amylase- was observed. Macroamylasemia was also excluded by laboratory examination. As we continued into the sixth month of bortezomib maintenance therapy, he developed pancytopenia and had an elevated amylase level over 9000 U/L. Suspecting relapse of multiple myeloma, bone marrow aspiration was performed and revealed that 88 % plasma cells. Laboratory findings were also consistent with relapsing multiple myeloma (Kappa/lambda ratio= 5590/4.2 and monoclonal gammopathy). Monitoring with PET-CT and MRI has shown some soft tissue mass compatible with plasmacytoma. It was decided to start DARA-POM-DEX therapy, and a dramatic decrease in amylase was observed from the first day(Figure 1).

Discussion: Multiple myeloma is known as a disease prone to relapse, and early recognition affects patient survival. There have been reports of

cases with unexplained elevated amylase related with activation of multiple myeloma like new diagnosis or relapse(1,2). Studies have shown that hyperamylasemia is associated with extramedullary diseases and is considered a poor prognosis factor in multiple myeloma(3). We suggest that hyperamylasemia could potentially serve as a marker for relapse in patients with multiple myeloma.

Keywords: Multiple myeloma, hyperamylasemia

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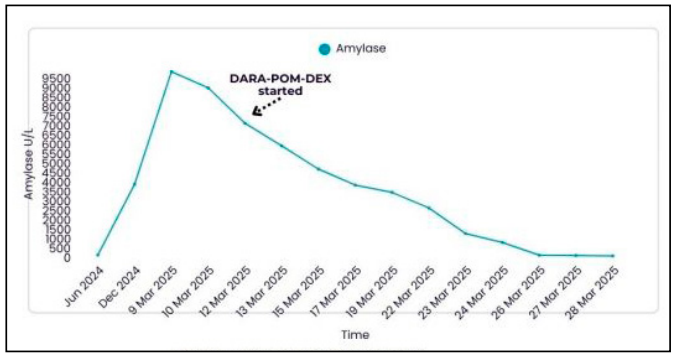

Figure 1. Amylase levels of the patient

■ Other

P-22 Abstract Referance: 14

A SPECTROPHOTOMETRIC METHOD HAS BEEN DEVELOPED FOR THE MEASUREMENT OF TRACE AMOUNTS OF CHLORAMPHENICOL.

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A spectrophotometric method has been developed for the measurement of trace amounts of chloramphenicol. This technique is based on the reduction of a nitro group to an amino group and oxidante coupling between drug and reagent, followed by a reaction in the presence of trifluoperazine hydrochloride and potassium iodate, resulting in the formation of a pigment. This pigment exhibits maximum absorption at a wavelength of 525 nm, demonstrating high sensitivity, with a molar absorptivity coefficient of 9.7585 × 103 L·mol-1·cm-1 and a Sandell sensitivity index of 3.311 × 10-2 µg/cm-2. The method adheres to Beer's law within a concentration range of 2 to 30 ppm, with a relative error ranging from -3.6% to +0.69%, and a standard deviation that varies from ±0.628% to ±0.113% depending on the concentration level. This method has been effectively utilized for the determination of chloramphenicol in pharmaceutical formulations, including ophthalmic solutions.

Keywords: chloramphenicol (CAP) ; spectrophotometric ; uv-visible

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■ Other

P-23 Abstract Referance: 68

RELAPSED/REFRACTORY IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE WITH TAFRO SYNDROME: A CASE REPORT

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Introduction: Castleman disease (CD) is a lymphoproliferative disorder characterized by histopathology of the lymph nodes. Multicentric Castleman disease (MCD), which shows lesions involving multiple sites in the absence of HHV-8, is classified as idiopathic (iMCD). The symptoms of iMCD are quite variable; patients have mild constitutional symptoms, while others develop life-threatening cytokine storm, organ failure, and death. Some patients have thrombocytopenia (T), anasarca edema (A), fever (F), reticulin fibrosis of the bone marrow (R), and organomegaly (O). The TAFRO subtype generally has more severe clinical manifestations and worse outcomes. They have been treated with a variety of agents, including corticosteroids, rituximab, and chemotherapy. Monoclonal antibodies that target IL-6 directly (siltuximab) or the IL-6 receptor (tocilizumab) are approved for the treatment of iMCD.

Case Report: A 49-year-old man who had complaints of back pain, abdominal swelling, and lower extremity edema. In 4 months, the patient was detected with hepatosplenomegaly, widespread ascites, and massive pleural effusion. Bilateral axillary lymphadenopathy pathology: Lymph node had a thin fibrous capsule and follicle structures with depleted germinal centers were observed in the cortex and paracortex. Hyaline vascular type Castleman disease, HHV-8 was negative. Bone marrow biopsy was performed due to thrombocytopenia and anemia. It was interpreted as 80% hypercellular, grade 2-3 reticulin fiber increase may be due to increased consumption.

R-CHOP were administered. 4 months later, the patient was admitted with the same symptoms and thrombocytopenia. When he had persistent fever, weekly Rituximab and steroid were administered. 8mg/kg Tocilizumab was continued every 14 days completed to 4 cycles. He remained in remission with cyclosporine 175mg/day for 1 year, but thrombocytopenia did not improve at all. The symptoms relapsed again and 1mg/kg methylprednisolone and CSA 200mg/day was administered. More than 50% reduction in cervical lymph nodes was observed compared to the previous CT. Steroids was tapered and stopped in 1 month. He applied again with a relapse 6 months later, had no fever but presented with ascites, anasarca. It was evaluated as iMCD TAFRO.

Blood analysis showed white blood cell count of 6700/µL with 84% neutrophils, hemoglobin of 8.7 g/dL and platelet count of 40000/µL. Biochemical test results were aspartate transaminase, 28 U/L; alanine transaminase, 11 U/L; alkaline phosphatase, 144 U/L; total protein, 4.9 g/dL; albumin, 2.9 g/dL; creatinine, 1.68 mg/dL; serum C-reactive protein, 108 mg/L. The spot urine protein/creatinine ratio was 132 mg/day. Viral serological markers of HBsAg, anti-HBs, anti-HCV, anti-HIV, EBV, CMV were negative. Serum protein electrophoresis showed polyclonal gammopathy and hypergammaglobulinemia. The IgG level was 9600 mg/dL.

Discussion: Nishimura Y et al. reviewed 54 cases either with iMCD-TAFRO, possible iMCD with TAFRO syndrome without lymph node biopsy and other identified co-morbidities. (1) The characteristic features of iMCD-TAFRO are thrombocytopenia, anasarca, fever and hyperinflammation, renal insufficiency, and organomegaly. All of them had fluid accumulation, anasarca remain one of the required clinical criteria which are common first definition of iMCD-TAFRO. The data suggested that 75% of iMCD-TAFRO cases had mild to moderate renal impairment; a number of patients required hemodialysis. (1) Various chronic inflammations may show MCD-like clinical features, such as a fever, anemia, thrombocytosis, and polyclonal hypergammopathy associated with hypercytokinemia. (2) In Mayo Clinic, the 5-year OS of patients were 65%. Treatments with tocilizumab and siltuximab improved the quality of life and survival of patients. (3)

Conclusion: In this case, we tried to emphasis the effectiveness of rituksimab-based treatments on an iMCD TAFRO patient with relapses and correct management with early diagnosis.

Keywords: Castleman Disease, anasarca, renal insufficiency, thrombocytopenia

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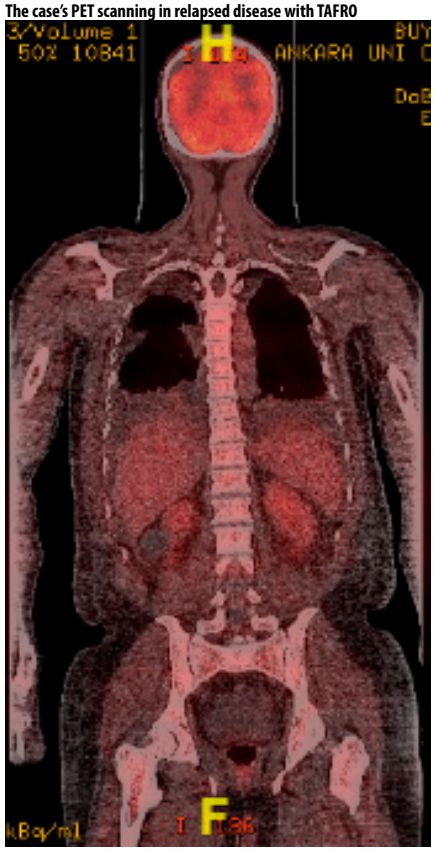
The case's PET scanning in relapsed disease with TAFRO



■ Non-Hodgkin's Lymphoma

P-24 **Abstract Referance: 69**

CLINICAL CHALLENGES IN MANAGING RELAPSED PLASMOBLATIC LYMPHOMA : A CASE REPORT

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Introduction: Plasmoblastic lymphoma (PBL) is a rare and aggressive form of non-Hodgkin's lymphoma characterized by differentiation of B cells into plasmoblasts, frequently affecting the mucous membranes, especially the oral and digestive systems. This lymphoma is commonly affecting immunocompromised patients, particularly those with HIV/AIDS, which presents a real challenge in addition to the absence of standardized treatment.

Observation: We report on the case of a 45-year-old patient with a history of Crohn's disease diagnosed in 1998, initially managed with sulfasalazine and complicated by an abscess which required drainage in 2011. The patient discontinued treatment voluntarily in 2012. In 2023, his disease further progressed resulting in an abscess with an enterocutaneous fistula between the sigmoid and the abdominal wall, necessitating surgical intervention.

Pathological examination of the resection specimen revealed colonic, rectal and cutaneous localization of a PBL, and immunophenotyping showed CD 138 (+) and MUM 1 (+) expression, with a Ki67 proliferation index estimated at 90% and CD20 negative. Serum protein electrophoresis (SPE) showed a monoclonal peak in the gamma zone of the IgA kappa type of 46.5 g/l. The patient was seronegative for the HIV infection and the bone marrow biopsy showed a medullary infiltration of the PBL.

The therapeutic approach involved administrating 4 courses of EPOCH (Etoposide, Prednisolone, Vincristine, Cyclophosphamide and Adriamycin) chemotherapy with a post-treatment evaluation via a CT scan revealing an uncertain complete remission (80%) based on CHEASON criteria. Additional findings included the absence of medullary infiltration in the bone marrow and the resolution of the monoclonal peak in the SPE. Subsequently, the patient underwent 4 more courses of EPOCH chemotherapy, with a post-treatment evaluation by entero-MRI confirming the complete remission.

Two months later, the patient experienced a relapse of his disease with a left gingivomaxillary mass that rapidly increased in size to 7 cm. The CT scan showed underlying lysis with damage to the sinus floor and destruction of the vestibular bone table. Anatomopathological examination of the mass revealed a gingival relapse of his PBL. A debulking chemotherapy course was initiated rapidly. Unfortunately, the patient's condition deteriorated further, leading to acute renal failure that necessitated hemodialysis. The complexity of the disease and associated complications resulted in the patient's passing, just one week after.

Conclusion: The treatment of PBL is intensive chemotherapy, but the results to date and the prognosis remains poor. This presents a real challenge and prompts us to look for new therapeutic approaches and to plan standardized protocols.

Keywords: relapsed plasmoblastic lymphoma

■ Multiple Myeloma

P-25 **Abstract Referance: 70**

ACQUIRED VON WILLEBRAND DISEASE REVEALING A SMOLDERING MULTIPLE MYELOMA: A CASE STUDY

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Introduction: Von Willebrand disease (VWD) is primarily a hereditary disorder secondary to a qualitative or quantitative deficiency of the VW factor involved in primary hemostasis, causing hemorrhagic syndromes. In rare instances, the disease can be acquired, typically secondary to other underlying conditions such as monoclonal gammopathies.

Case presentation: We report here the case of a 58-year-old patient, with a history of a controlled hypertension under treatment, who consulted the out-patient department of hematology for recurrent epistaxis with occasional gingivorrhagia that had been evolving for a year.

On clinical examination, the patient's general state of health was preserved, he presented only moderate epistaxis. The ENT examination eliminated a local cause and there were no other associated hemorrhagic syndromes or other abnormalities.

Biological findings showed a normal white blood count of 9 G/L, microcytic anemia of 8 g/dl and thrombocythemia of 561 G/L. Ferritin level was of 7. Hemostasis tests PT: 91% APT: slightly prolonged of 37/32, platelet occlusion time very allonged and a normal platelet aggregation test with ADP, collagen and epinephrine. vWF antigene at 58%, vWF Ristocitine Cofactor at 12%. These findings collectively support the diagnosis of type 2 VWD, especially 2A or 2M.

The etiological work-up for this case identified negative immunological tests. Serum protein electrophoresis showed monoclonal gamma peak of IgG lambda type of 13.5 g/l. Creatinine was normal (92 µmol/l), beta2 microglobulin of 2.58 mg/l and calcemia level was normal (2.40 mmol/l).

Multiple myeloma (MM) was suspected and bone marrow aspiration showed 21% of plasmocytic proliferation which is consistent with the diagnosis of MM. The patient was prescribed on oral corticosteroids for one month, with martial therapy for his iron deficiency anemia. The initial evolution was marked by a decrease in the frequency and abundance of epistaxis with normalization of the level of Hb within 2 months.

Further investigations showed a normal ratio of variable light chains and radiological examination with MRI showed no signs in favor of MM which confirms the diagnosis of smoldering MM.

Conclusion: In this case, diagnosing VWD early through appropriate testing would ensure optimal management and prevention of serious complications. It also highlights the need for increased awareness among healthcare s to consider VWD in the differential disease for unexplained bleeding syndromes.

Keywords: Acquired Von Willebrand Disease Multiple Myeloma

■ Multiple Myeloma

P-26 **Abstract Referance: 71**

DARATUMUMAB DILEMMAS: ACHIEVING CLARITY IN COMPATIBILITY TESTING OF BLOOD FOR MULTIPLE MYELOMA PATIENT

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Background: Daratumumab (DARA) is a novel CD38 monoclonal antibody, approved by the Food and Drug Administration (FDA) for the targeted immunotherapy of relapsed or refractory multiple myeloma (MM). With this background, we aimed to primarily understand if DARA was the key culprit causing incompatible cross matches in our case. Additionally, we propose strategies to effectively resolve similar issues in future cross-matching scenarios.

Materials and Methods: We conducted comprehensive immunohematology (IH) workups, including ABO and Rh (D) typing, Coombs tests, and autologous control assessments. Antibody detection utilized a poly-specific column agglutination test (CAT) for anti-IgG and anti-C3d.

Case Report: We present the case of a 60-year-old Indian male with refractory MM, who required frequent transfusions due to anemia. A pan-reactive antibody was identified, lacking specificity for any blood group antigens. Notably, DARA's significant presence in the patient's history coincided with easily obtainable blood typing results. Our observations revealed multiple incompatible cross matches during the anti-human globulin phase, while immediate spin cross matches showed compatibility.

Discussion: Literature indicates that DARA can cross-react with erythrocytes, sensitizing them and leading to serological challenges that complicate the identification of compatible packed red blood cell (PRBC) units for transfusion. To mitigate unnecessary delays in patient care, prompt resolution is crucial. Effective communication between the blood centre physician and bedside clinicians is essential to navigate and resolve these complexities.

Keywords: CD38, Daratumumab, Multiple Myeloma, Dithiothreitol, Allogenic crossmatches

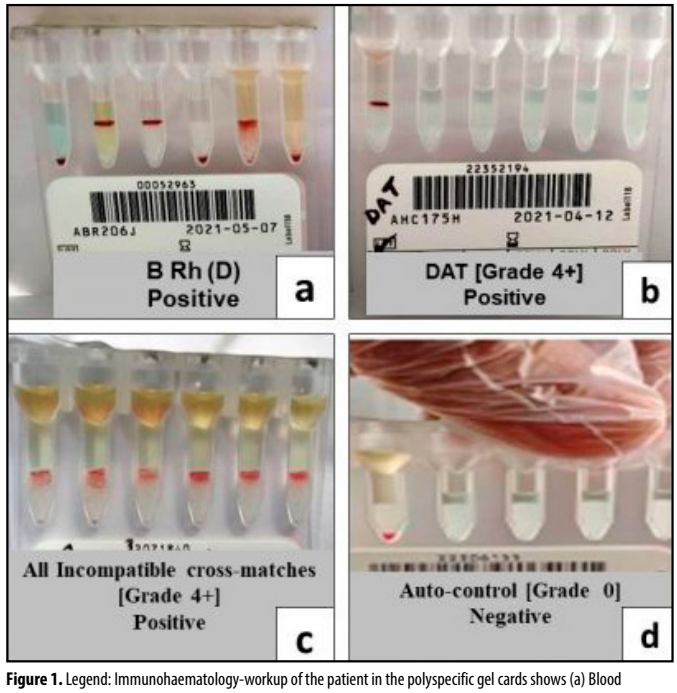

Figure 1. Legend: Immunohaematology-workup of the patient in the polyspecific gel cards shows (a) Blood grouping as B Rh (D) positive (b) A positive DAT (c) Multiple incompatible crossmatches at AHG phase (d) A negative autologous control

■ Chronic Myeloid Leukemia

P-27 Abstract Referance: 37

THE OUTCOMES OF PATIENTS WITH BLAST CRISIS CML WITH AND WITHOUT ALLOGENEIC HEMOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Even in the era of tyrosine kinase inhibitors (TKIs) the outcomes of patients with blast crisis (BC) chronic myeloid leukemia (CML) continue to be poor. Median overall survival (OS) according to the literature does not exceed 12 months. At the same time the issue of the role and timing of transplantation remains relevant.

Objective: This study was meant to compare outcomes in BC CML cohorts based on whether these patients received allogeneic hemopoietic stem cell transplantation (alloHSCT).

Patients and methods: From 2001 to 2024 170 patients with BC CML were included in this study. The diagnosis of BC CML was verifed according to the World Health Organization 2022 criteria. Among all patients alloHSCT was realized in 79 patients (46%) and was not performed in 91 patients (54%). The groups with and without alloHSCT were comparable in crucial biological charachteristics (additional chromosomal abnormalities (ACAs) (p=0.4); complex karyotype / 3q26 (p=0.3); *BCR:ABL1* mutations (p=0.5); extramedullary disease (EM) (p=0.4)). Median time from BC to alloHSCT was 10 months (0.5-72). AlloHSCT was performed from matched-related donor (n=18, 22%), haploidentical donors (n=11, 14%), matched unrelated donors (n=30, 39%), mismatched unrelated donors (n=20, 25%). The main reasons for not performing alloHSCT were lack of response to therapy (62%), disease progression (26%) and donor unavailability (12%). Overall survival (OS) was defned as the time from the start of treatment to death or last visit.

Results: With a median follow-up of 63.3 months (57.1 – 69.5) 5-year OS in the total patient cohort was 26.5% (95% CI: 19.5-33.8). The median OS of patients with alloHSCT by landmark analysis performed 6 months from the date of BC was 60 months (16.3 - NA), compared to 21.4 months (7.7 - NA) in the group without alloHSCT (p=0.044) (Figure 1A). Performing alloHSCT within the first 10 months of BC verification by landmark analysis does not demonstrate an impact on improvement in OS (p=0.3) (Figure 1B). ACAs (HR 3.1, 95% CI: 1.7-5.8, p<0.001), including complex karyotype / 3q.26 (HR 2.8, 95% CI: 1.5-5.1, p=0.001) had a negative impact on OS regardless of alloHSCT performance according to single-factor analysis. Age, time of BC development (BC de novo vs BC after CP/AP), immunologic variant of BC, mutations in *BCR::ABL1* gene, EM and variant of BC therapy had no effect on OS. According to multivariate analysis the crucial predictor improving the OS was alloHSCT (HR 0.3, 95% CI: 0.2-0.4, p<0.001). While any ACAs statistically significantly worsened the prognosis (HR 1.9, 95% CI: 1.3-2.8, p=0.002).

Conclusions: In spite of the widespread use of 2nd and 3rd generation TKIs the prognosis of patients with BC CML is still dismal. AlloHSCT demonstrates its advantage in patients with BC in the era of new-generation TKIs. At the same time performing alloHSCT in the first 6 months demonstrates the best results. In order to improve the results in this cohort these patients should be directed to transplant center as soon as the second chronic phase is achieved.

Keywords: Chronic myeloid leukemia, blast crisis

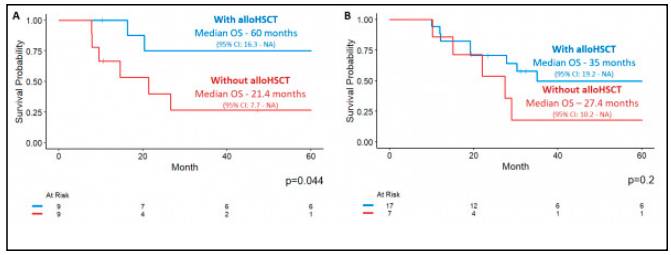

Figure 1. Overall survival of patients with BC CML depending on alloHSCT performed: A - landmark analysis at 6 months, B - landmark analysis at 10 months

■ Stem Cell Transplantation

P-28 Abstract Referance: 72

PRETRANSPLANT ABSOLUTE LYMPHOCYTE COUNT PREDICTS OVERALL SURVIVAL IN ATG-BASED UNRELATED DONOR STEM CELL TRANSPLANTATION

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Introduction: Antithymocyte globulin (ATG) is commonly used as prophylaxis against graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplantation. Traditionally, ATG dosing is based on the recipient's body weight; however, emerging evidence suggests that dosing strategies targeting recipient T lymphocyte levels may improve outcomes. Several studies have demonstrated that absolute lymphocyte count (ALC) at the time of preconditioning or prior to ATG administration may influence the risk of GVHD and survival. This study aimed to evaluate the impact of pretransplant ALC on transplantation outcomes.

Methods: We retrospectively analyzed data from 56 adult patients (≥18 years) diagnosed with acute leukemia or myelodysplastic syndrome who underwent unrelated donor (MUD) allogeneic peripheral stem cell transplantation with ATG (Grafalon, 10 mg/kg/day on days -3, -2, and -1; total dose 30 mg/kg) between August 2018 and December 2024 at our center. Data collected included conditioning regimens, ALC on the first day of conditioning and first day of ATG, engraftment times, pretransplant disease status, incidence of acute and chronic GVHD, CMV reactivation, relapse, progression-free survival, and overall survival (OS). Preconditioning ALC was analyzed using cut-off values of ≥0.5 $\times 10^9$/L, ≥0.75 $\times 10^9$/L, and ≥1 $\times 10^9$/L. Statistical analysis was performed using SPSS Version 27.

Results: The median age was 47.5 years (range 18–73), with 38 patients (67.9%) being male. The median follow-up time was 580 days (range 12–2242). Fifty-one patients (91.1%) had acute leukemia, and five (8.9%) had MDS. Twenty donors (35.7%) were 9/10 matched, and 36 (64.3%) were 10/10 matched. Reduced-intensity conditioning (RIC) was used in 17 patients (30.4%), while 39 (69.6%) received myeloablative conditioning (MAC). Median preconditioning ALC was 1.05 $\times 10^9$/L (range 0–4), and median pre-ATG ALC was 0.07 $\times 10^9$/L (range 0–1.54). Thirty-five patients (62.5%) developed aGVHD (any grade), and 11 (19.7%) developed cGVHD (any grade). No significant difference in OS was observed between patients with and without GVHD. GVHD rates did not differ significantly across ALC cut-offs of 0.5, 0.75, and 1 $\times 10^9$/L. At the final follow-up, 27 patients (48.2%) were alive, and 29 (51.8%) had died. Relapse occurred in 22 patients (39.3%), and 11 patients (19.6%) experienced non-relapse mortality (NRM). Relapse was significantly more common in patients transplanted in non-complete remission (non-CR) status. When relapse and NRM were analyzed according to ALC cut-offs, no significant differences were found. Median OS was not reached in patients with ALC ≥0.75 $\times 10^9$/L, whereas it was 280 days in those with ALC ≤0.75 $\times 10^9$/L (p = 0.008). No significant difference in OS was observed for cut-offs at 0.5 and 1 $\times 10^9$/L (p = 0.079 and p = 0.16, respectively). Among patients, 46 (82.1%) were in complete remission (CR) before

transplant, and 10 (17.9%) had active disease (non-CR). Median OS was not reached in CR patients but was 331 days in non-CR patients (p = 0.016).

Conclusion: Pretransplant ALC, particularly at a threshold of ≥0.75 $\times 10^9$/L, appears to be associated with improved overall survival in patients undergoing unrelated donor allogeneic stem cell transplantation with ATG-based GVHD prophylaxis. However, no significant correlation was observed between ALC and the incidence of acute or chronic GVHD, relapse, or non-relapse mortality. These findings suggest that ALC may serve as a useful biomarker for risk stratification and guiding individualized ATG dosing strategies. Further prospective studies are warranted to validate these results and optimize ATG administration based on immune profiling.

Keywords: allogeneic stem cell transplantation, lymphocyte, anti thymocyte globulin

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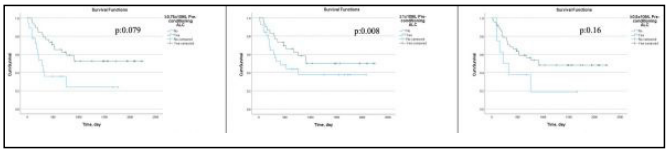

Figure 1. Survival curves according to preconditioning ALC values

Table 1. Patients characteristics

Variables	All Patients (n:56)
Age, yr, median (min-max)	47,5 (18-73)
Recipient sex, man, n (%)	38 (67,9)
Diagnosis, n (%)	
AML	34 (60,7)
ALL	16 (28,9)
MDS	5 (8,9)
Mix-lineage leukemia	1 (1,8)
Follow-up Time, day, median (min-max)	580 (12-2242)
CD34, x10^6/kg, median,	6 (2,2-8)
HLA matching, n (%)	
9/10	20 (35,7)
10/10	36 (64,3)
Pretransplant disease status, n, %	
CR1	38 (67,9)
CR2	8 (14,3)
Non-CR	10 (17,9)
Conditionin regimen intensity, n, %	
RIC	17 (30,4)
MAC	39 (69,6)
Pre-conditioning ALC, x10^9/L, median (min-max)	1,05 (0-4)
Pre-ATG ALC, x10^9/L, median, (min-max)	0,07 (0-1,54)
Pre-conditioning ALC, n, %	
≥0.5 x10^9/L	48 (85,7)
≥0.75 x10^9/L	38 (67,8)
≥1 x10^9/L	30 (53,5)
aGVHD, n (%)	
All	35 (62,5)
Grade 1-2	22 (39,3)
Grade 3-4	13 (23,2)
cGVHD, n (%)	
All	11 (19,7)
Limited	8 (14,3)
Extensive	3 (5,4)
Survival, alive, n (%)	27 (48,2)
Relaps, n (%)	22 (39,3)
Non-relaps mortality, n (%)	11 (19,6)

■ Stem Cell Transplantation

P-29 **Abstract Referance: 74**

DISSEMINATED NOCARDIOSIS IN AN IMMUNOCOMPROMISED POST-TRANSPLANTED PATIENT; A CASE REPORT

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Introduction: Nocardia species are gram-positive rods normally found in soil and water. They commonly cause infections in immunocompromised patients particularly those with deficient cell-mediated immunity. Nocardiosis can be localized to a single organ, such as the skin or lung, or disseminated [1]. We describe the case of a post-transplanted patient with disseminated nocardiosis diagnosed and monitored by FDG-PET/CT scan.

Case Report: A 61-year-old man with AML received allogeneic peripheral stem cell transplantation in September 2023 and haploidentical stem cell transplantation from his son in July 2024 due to relapse. He was on immunsupressive therapy with tacrolimus. He was admitted to the transplantation outpatient clinic with neck and right upper quadrant abdominal pain, fever, malaise and elevated AFR. Emprical therapy with amoxicillin clavulanic acid and valacyclovir was started due to his pain throughout the dermatome. No clinical benefit was observed, the patient was hospitalized for further investigation and iv antibiotics. Blood cultures were taken and carbapenem treatment was started.

Ultrasound imaging of the patient revealed an abscess in the neck. Nocardia farcinica was grown in the abscess aspiration and no mass lesion or abscess was detected on abdominal imaging. Central nervous system imaging showed no appearance compatible with nocardia. No infective endocarditis was detected on transthoracic echocardiography. FDG PET/CT was planned to evaluate this metastatic infection in the patient whose other imaging studies showed no abscess/mass formation.

PET/CT showed diffuse FDG uptake which may be compatible with disseminated nocardia. Amikacin was added to the treatment of the patient whose neck abscesses progressed under meropenem/imipenem treatment. Immunosuppressive treatment was reduced and discontinued in a controlled manner. The patient, who received carbapenem for 45 days and amikacin for 30 days in total, was discharged with oral trimethoprim/sulfamethoxazole treatment with regression of the findings in control PET and resolution of pain and fever complaints. (2,3)

Conclusion and Discussion: Nocardiosis in the immunocompromised host is a challenging medical entity. TMP-SMX prophylaxis may be helpful in preventing primary Nocardia infection or relapse after treatment, although infections can occur despite prophylaxis. In the case of metastatic infection, nocardia should also be considered. FDG-PET/CT is valuable in the diagnosis and management of individuals with nocardiosis.

Keywords: nocardiosis, immunocompromised host, nocardia, nocardia farcinica

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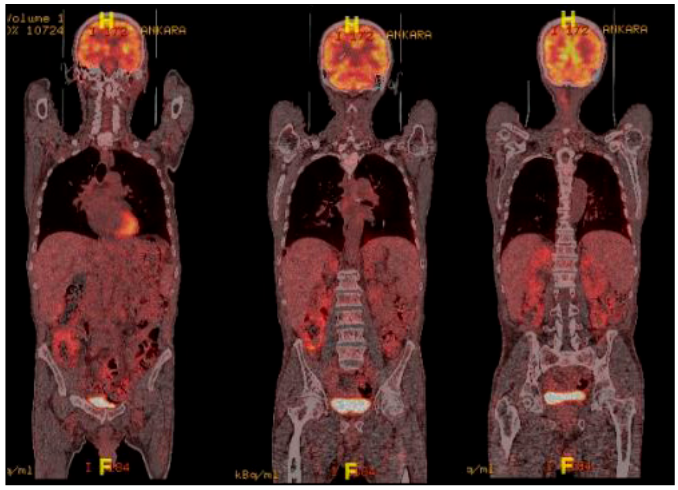

Figure 2. Antibiyoterapi sonrası FDG-PET/CT kontrol görüntülemesi

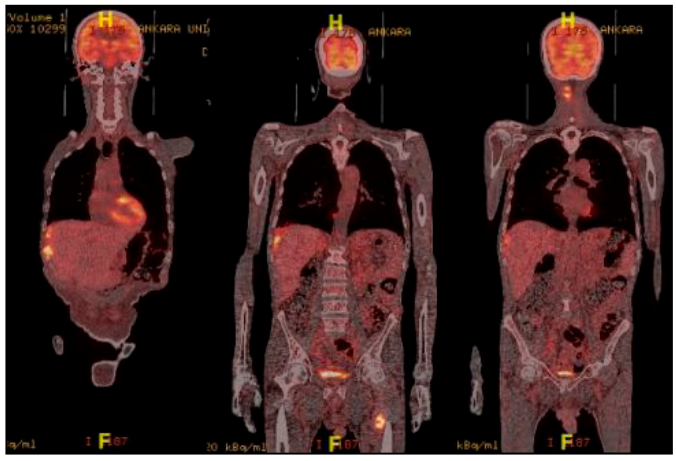

Figure 1. Antibiyoterapi öncesi FDG-PET/BT

Acute Lymphoblastic Leukemia

P-30 Abstract Referance: 75

A CHILDHOOD T CELL ACUTE LYMPHOBLASTIC LEUKEMIA HARBORING BCR-JAK 2 FUSION: A CASE REPORT

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Introduction: T cell acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy that occurs in 15% of all pediatric ALL. Its Prognosis depends on several factors: age, white blood cell count at diagnosis, genetics and response to initial therapy. Certain cytogenetic and molecular abnormalities serve as key prognostic markers, offering a window into the potential course of the disease and its response to treatment.

The BCR-JAK2 fusion is a rare genetic mutation described in some hematologic malignancies, including ALL, acute myeloid leukemia and myeloproliferative neoplasms. This fusion leads to constitutive activation of the JAK-STAT signaling pathway, promoting uncontrolled cell proliferation and survival.

Case presentation: We present here a 13-year-old child with T cell ALL. He presented initially with a history of 2 weeks of progressive asthenia and dyspnea. The clinical examination showed multiple lymphadenopathy and hepatosplenomegaly. Thoracic X-ray showed mediastinal widening. Thoraco-abdominal Computed Tomography (CT) scan revealing an anterior mediastinal mass associated with supradiaphragmatic and infradiaphragmatic lymphadenopathy, along with homogeneous hepatosplenomegaly and the echocardiography confirmed a moderate pericardial effusion without signs of compression.

Laboratory findings revealed hyperleukocytosis of 191 G/L, hemoglobine level of 12.6 g/dl and slight thrombopenia of 98 G/L. Peripheral blood smear showed the presence of 30% of lymphoblastic cells. The Bone marrow examination with immunophenotyping confirmed the diagnosis of T cell ALL with infiltration of 75% of lymphoblasts. Cytogenetic examination showed a structural abnormality on chromosome 9 in one clone, along with monosomy 22: 45, XY, der(9) t(9;22)(p24;q11), -22 (4) → Abnormal clone with a derivative chromosome 9 resulting from a translocation between chromosomes 9 and 22, monosomy of chromosome 22 and molecular examination did not isolate the known BCR-ABL fusion but showed a rare mutation fusion (BCR-JAK2).

The patient was classified as very high risk according to the Children's EORTC protocol because of the aggressivity of his cytogenetic abnormalities. Induction chemotherapy was initiated, and the patient was prescribed Dexamethasone, Vincristine, Daunorubicin, high dose Methotrexate, Cyclophosphamide and L'Asparaginase. He achieved complete cytologic remission after the induction chemotherapy and currently the patient is undergoing the intermediate phase of the EORTC protocol, and he keeps the complete remission. He is scheduled for an Haplo-identical allogeneic bone marrow transplantation.

Conclusion: The BCR-JAK2 fusion is knowingly associated with unfavorable prognosis as it is not only affiliated with multiple complications during therapy but also responsible for early relapse.

Keywords: Acute Lymphoblastic leukemia BCR JAK2 fusion cytogenetics

Stem Cell Transplantation

P-31 Abstract Referance: 76

SUBSTITUTING CLADRIBINE FOR FLUDARABINE IN A REDUCED-INTENSITY CONDITIONING REGIMEN

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Introduction: Fludarabine and cladribine are purine nucleoside analogs used in the treatment of various lymphoid and myeloid hematological malignancies. Unlike fludarabine, cladribine is effective on both dividing and non-dividing cells, possesses direct antileukemic and hypomethylation activities, and exhibits a more pronounced and longer-lasting immunosuppressive effect on CD4+ lymphocytes. These advantages of cladribine over fludarabine make it a promising alternative, especially considering the positive results from limited studies on its use in conditioning regimens. This prospective cohort study aims to compare the safety and efficacy of using cladribine in place of fludarabine in a low-intensity conditioning (RIC) regimen, which includes fludarabine, low-dose melphalan, and low-dose total body irradiation (TBI), during a fludarabine shortage.

Methods: Sequential high-risk hematological malignancy patients scheduled for allogeneic stem cell transplantation between November 2019 and December 2022 were included in the study. Due to a drug shortage, cladribine was used substituted for fludarabine. All patients were deemed eligible for RIC. The RIC protocol included intravenous melphalan (75 mg/m^2/day) on day -2, 200 cGy TBI on day -1, and either subcutaneous cladribine (10 mg/m^2/day) or intravenous fludarabine (40 mg/m^2/day) from days -5 to -2. Graft versus host disease (GvHD) prophylaxis involved a combination of calcineurin inhibitor (CNI) with mycophenolate mofetil (MMF) for HLA-matched family donors and a combination of post-transplant cyclophosphamide

with CNI and MMF for HLA-mismatched family and unrelated donors and haploidentical donor transplants. The primary objective was to compare the safety of cladribine and fludarabine. The secondary objective was to identify any survival advantages. Patient characteristics, toxicities, complications, and survival outcomes were recorded. A type 1 error of 5% (two-tailed) was considered statistically significant in analyses.

Results: A total of 70 sequential patients (27 in the cladribine cohort and 43 in the fludarabine cohort) were included in the study. The median age was 59 years, and 64.3% of the patients were male. The median follow-up after transplantation was 16.8 months. Acute GvHD incidence was higher in the fludarabine cohort. No grade 3-4 toxicities were observed. Overall survival (OS), progression-free survival (PFS), and transplant-related mortality (TRM) were similar in both cohorts.

Conclusion: The prolonged immunosuppressive effect of cladribine on T cells may be responsible for the lower incidence of acute GvHD. Cladribine appears to be a safe and effective alternative to fludarabine in this RIC regimen for allogeneic stem cell transplantation. The choice between cladribine and fludarabine should be made considering patient-specific factors (disease characteristics, GvHD risk, and comorbidities).

Keywords: fludarabine, cladribine, reduced intensity conditioning

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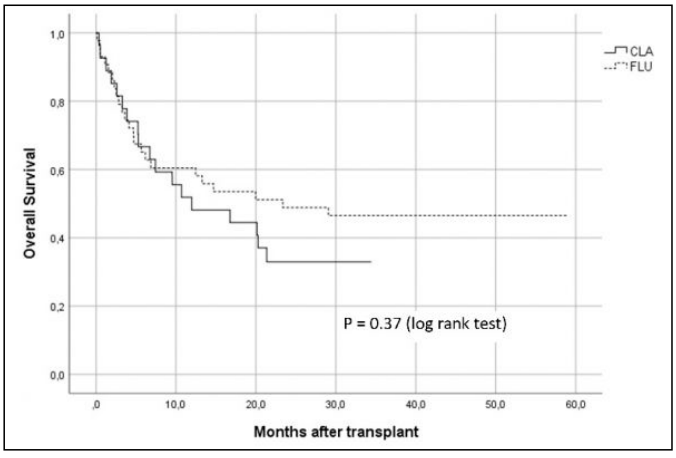

Figure 1. Overall survival according to study cohorts

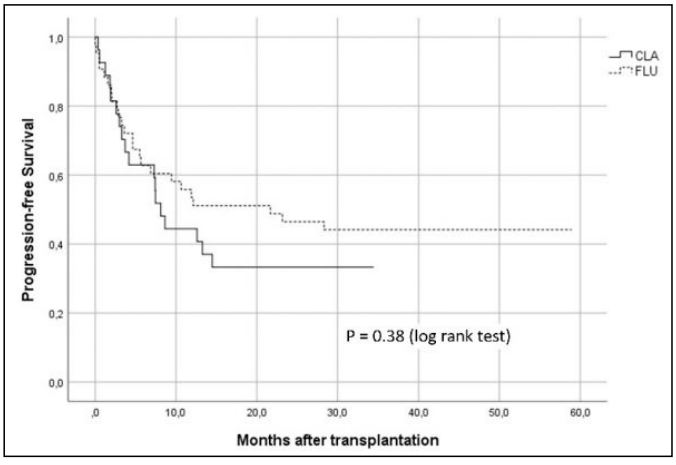

Figure 2. Progression-free survival according to study cohorts

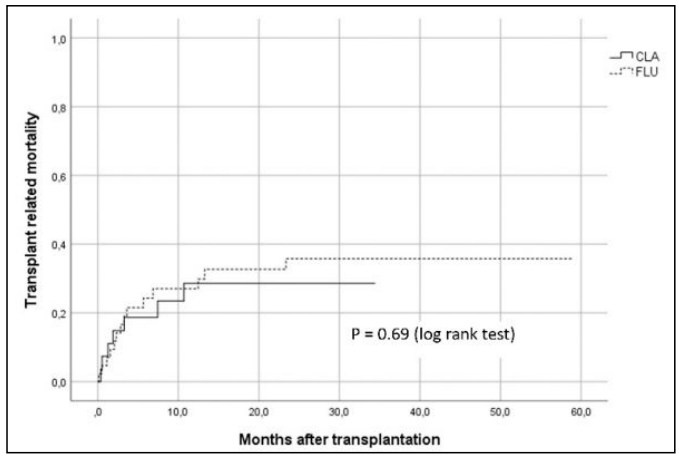

Figure 3. Transplant related mortality according to study cohorts

Stem Cell Transplantation

P-32 **Abstract Referance: 77**

DARATUMUMAB-BASED INDUCTION AND CONSOLIDATION COMBINED WITH AUTOLOGOUS STEM CELL TRANSPLANTATION IN PRIMARY AMYLOIDOSIS

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Introduction: While autologous stem cell transplantation (ASCT) is an important treatment modality in primary amyloidosis, the optimal consolidation strategy remains unclear, particularly due to the reported high transplant-related mortality (TRM) in patients with cardiac involvement and the successful outcomes with first-line targeted therapies such as daratumumab.

Methods: All patients who underwent ASCT with a diagnosis of primary amyloidosis at our center between September 2013 and December 2024 were retrospectively evaluated. Comparisons between groups for demographic features, disease risk, and daratumumab use were performed using non-parametric tests, and post-transplant survival analyses were conducted using the Kaplan-Meier method. All statistical analyses were performed using SPSS version 25, with a statistical significance of P<0.05.

Results: A total of 14 patients were included in the study. The median age at diagnosis was 61 years (range 44-73), and 57.1% (n=8) of the patients were female. The estimated median follow-up was 131 months (95% CI: 98-164 months), and the median time from amyloidosis diagnosis to ASCT was 8.6 months (range 4.3-72.9). Half of the patients received daratumumab-based induction therapy, and 64.3% received daratumumab-based maintenance therapy. At diagnosis, 42.9% of patients had Mayo stage 3-4 disease, with cardiac and renal involvement present in 28.6% and 78.6% of cases, respectively. Hematological response was observed in all patients following induction therapy. Reduced-intensity conditioning (Mel140) was used in 42.9% of the patients. No TRM was observed. Overall survival (OS) at 12 and 24 months were 85.0% (95% CI: 65.4-100.0) and 66.0% (95% CI: 30.7-100.0), respectively; progression-free survival (PFS) at 12 and 24 months were both 77.0% (95% CI: 53.5-100.0). No significant association was observed between Mayo stage and OS (p=0.21, log-rank). However, the OS was worse in the Mayo stage 1-2 group (n=8) compared to the stage 3-4 group (p=0.02, log-rank). Demographic features, frequency of cardiac involvement, and daratumumab use were similar between these patient groups. No relationship was observed between cardiac involvement and OS or PFS (p=0.36 and p=0.98, log-rank, respectively). Daratumumab-based induction showed no

significant association with OS or PFS (p=0.96 and p=0.87, log-rank, respectively). Similarly, daratumumab-based maintenance showed no significant association with OS or PFS (p=0.61 and p=0.58, log-rank, respectively).

Conclusion: ASCT is associated with promising survival outcomes in the treatment of selected patients primary amyloidosis. The use of daratumumab in induction and maintenance therapies may enhance the effectiveness of the treatment. These findings need to be further validated through randomized controlled trials.

Keywords: primary amyloidosis, autologous stem cell transplantation

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Table 1. General characteristics of patients

Age at diagnosis, median (min-max)		61 (44-73)
Sex, n (%)	Male	6 (42,9)
	Female	8 (57,1)
Accompanying other plasma cell disorders (multiple myeloma and Waldenstrom's macroglobulinemia), n (%)		12 (85,7)
Interval between plasma cell disorder and amyloidosis, months, median (min-max)		0 (0 – 67,0)
Interval between autologous stem cell transplantation and amyloidosis, months, median (min-max)		8,6 (4,3 – 72,9)
Daratumumab based induction, n (%)		7 (50,0)
Mayo 2012 stage, n (%)	Stage 1-2	8 (57,1)
	Stage 3-4	6 (42,9)
Cardiac involvement, n (%)		4 (28,6)
Renal involvement, n (%)		11 (78,6)
Bone marrow involvement, n (%)		2 (14,3)
Proteinuria at diagnosis, mg/day, median (min-max)		2.992 (128 – 23.500)
Pretransplant hematological response, n (%)	Complete	8 (57,1)
	Partial	2 (14,3)
	Very good partial	4 (28,6)
Pretransplant renal response, n (%)	Complete	2 (18,2)
	Partial	7 (63,6)
	No response	2 (18,2)
Pre-transplant cardiac response, n (%)	Partial	1 (25,0)
	No response	3 (75,8)
Conditioning, n (%)	Mel140	6 (42,9)
	Mel200	8 (57,1)
Post-transplant +2nd month hematological response, n (%)	Complete	11 (78,6)
	Partial	1 (7,1)
	Very good partial	2 (14,3)
Post-transplant +2nd month renal response, n (%)	Complete	2 (18,2)
	Very good partial	1 (9,1)
	Partial	4 (36,4)
	Stable disease	3 (27,2)
	Progression	1 (9,1)
Post-transplant +2nd month cardiac response, n (%)	Very good partial	1 (25,0)
	Partial	1 (25,0)
	No response	2 (50,0)
Daratumumab-based maintenance, n (%)		9 (64,3)

■ Other

P-33 **Abstract Referance: 78**

A CASE REPORT OF HAIRY CELL LEUKEMIA IN A PATIENT DIAGNOSED WITH ASTROCYTOMA

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Introduction: Hairy cell leukemia (HCL) is an indolent mature B cell malignancy that involves the bone marrow and spleen. Pilocytic astrocytoma is a generally benign and slow-growing brain tumor that mostly affects children and young adults. Here, we will present a case of a patient who was followed up with pilocytic astrocytoma for 15 years and diagnosed with hairy cell leukemia while being evaluated for leukopenia.

Case report: A 40-year-old male patient was admitted to our clinic with leukopenia and neutropenia. The patient, who underwent surgery in May 2010 for a right temporal mass that caused seizures, was diagnosed with pilocytic astrocytoma (WHO grade 2). After total excision, the patient has been following up with observation without radiotherapy or chemotherapy. In the physical examination, he had no hepatosplenomegaly or lymphadenopathy. Since 2011, the leukocyte and the neutrophil count had been ranging between 2.69 -3.3 x 10^9 L (4.5-11 X10^9 L), 1 - 1.3 X10^9 L (1.8-7.7 x 10^9 L), respectively. He had no thrombocytopenia or anemia. B12, foic acid levels, iron parameters, and lactate dehydrogenase levels were normal. No viral, bacterial, parasitic, or fungal infection was detected. There was no history of autoimmune disease, vasculitis or use of medications that could cause neutropenia. Biochemical tests, hormone levels, tumor markers, and antibody testing for autoimmune disorders were normal. A computed tomography (CT) scan of the neck, thorax, and abdomen was performed on the patient to detect low-grade malignancy. No pathologically sized lymph nodes were observed, but minimal hepatomegaly (16.5 cm) and minimal splenomegaly (13 cm) were detected. Positron emission tomography (PET-CT) examination did not reveal pathological 18F-FDG uptake in any area of the body. The patient underwent bone marrow biopsy. In the bone marrow biopsy, there was granulocyte series dominance, an increased ratio in the erythroid series, and mild dysmorphism in megakaryocytes, with 40% small atypical lymphoid infiltration of interstitial and intrasinusoidal cells. Morphological and immunophenotypic findings supporting low-grade B-cell lymphoma infiltration were observed. In the flow cytometry examination, 23% of the nucleated cells in the bone marrow aspiration sample were lymphoid , 2% were monocytic, 59% were granulocytes, 14% were erythroid series cells, 1.7% were myeloid progenitor cells, and 0.27% were plasma cells. 73% of the lymphocytes were T cells, 20% were B cells, and 7% were NK cells. In 80% of non-hematogenous "B" cells, CD45 p+, HLA DR +, CD19 p+, CD5-, CD10 z+, CD38 - , CD23 +, FMC7 p+, CD11c p+, CD22 p+, CD79b +, CD25 p+, CD20 p+, ckappa, clambda +, CD43 -, CD200 p+, CD27 - , CD103 p+ , CD123 + were observed. Findings were evaluated as data compatible with hairy cell leukemia (HCL). In immune histochemical examination, infiltrative cells were observed to be diffusely strong positive with CD103, BRAF (VE1). It was observed that some cells among the infiltrative cells were faintly positive with cyclin D1. Bcl-6, CD10, LMO2, SOX11, CD23, and CD5 were negative in infiltrating lymphoid cells. The patient who was identified with HCL after a bone marrow biopsy examination is being monitored with observation without treatment because there are no treatment indications.

Discussion: Hairy cell leukemia (HCL) is diagnosed by immunophenotypic bright CD20, CD25, CD103, CD200, Annexin A1, BCL1, and BRAF V600E expression (1). BRAF mutations, especially BRAF V600E mutation, are frequently detected in HCL (1, 2). BRAF gene mutations can also be frequently seen in pilocytic astrocytomas. (BRAFV600E mutation and KIAA1549-BRAF fusions) (3). The diagnosis of hairy cell leukemia in our patient, who has been followed up for pilocytic astrocytoma for 15 years, is interesting in terms of similar genetic mutations seen in both diseases. According to our research, this is the first case in the literature in which both diseases coexist.

Keywords: Hairy cell leukemia, Pilocytic Astrocytoma, BRAF mutations

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Acute Myeloid Leukemia

P-34 Abstract Referance: 79

A CASE OF ALL-TRANS RETINOIC ACID-INDUCED DIFFERENTIATION SYNDROME PRESENTING WITH NEPHROTIC SYNDROME

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Introduction: Differentiation syndrome (DS) is a frequent and potentially life-threatening complication of acute promyelocytic leukemia (APL) treatment, particularly with all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO). Its clinical spectrum commonly includes fever, dyspnea with pulmonary infiltrates, pericardial and pleural effusion, hypotension, acute renal failure, and weight gain exceeding 5 kg. The incidence of DS varies widely, ranging between 2% and 37%. Although rare, atypical findings such as nephrotic-range proteinuria, Sweet-like rash, bradycardia, and intestinal necrosis may also occur.

Case Presentation: A 28-year-old woman was diagnosed with low-risk acute promyelocytic leukemia and started on the PETHEMA induction protocol with idarubicin and ATRA. During treatment, the patient developed complications including febrile neutropenia, candida esophagitis and Mallory-Weiss syndrome. On the 25th day of induction therapy, she developed a fever occurring 4-5 times a day without general deterioration, together with a widespread maculopapular rash on the skin. She was started on antihistamines and topical treatments in view of a drug eruption. On day +28, the physical examination was supplemented by bilateral +3 pitting oedema and facial swelling without associated dyspnea (Figure 1). Laboratory results showed an albumin level of 2.1 g/dL and proteinuria of 5.5 g/day. Chest imaging showed no pulmonary infiltrates; however, an effusion of approximately 15 mm in the right hemithorax and 13 mm in the left hemithorax was observed. The patient was considered to have moderate DS due to the presence of fever, pulmonary effusion and oedema. ATRA was discontinued and dexamethasone 10 mg twice daily was started. Within 48 hours of treatment, the oedema resolved almost completely and proteinuria decreased (Figure 2). Dexamethasone was gradually tapered and discontinued, and ATRA was restarted. In this case, induction therapy was completed without recurrence of DS. The patient remains in complete remission and is being followed up in the hematology outpatient clinic.

Discussion: Differentiation syndrome represents a rare yet severe complication of APL management with ATRA and ATO, necessitating early diagnosis and immediate therapeutic intervention. Corticosteroids play a pivotal role in mitigating DS-associated organ damage, and their timely administration can prevent progression to critical states requiring inotropic support or mechanical ventilation.This case emphasizes the importance of recognizing atypical manifestations of DS, including nephrotic syndrome, in clinical practice. Prompt initiation of steroid therapy and suspension of ATRA/ATO therapy are paramount in cases of moderate to severe presentations.

Keywords: acute promyelocytic leukemia, nephrotic, proteinuria

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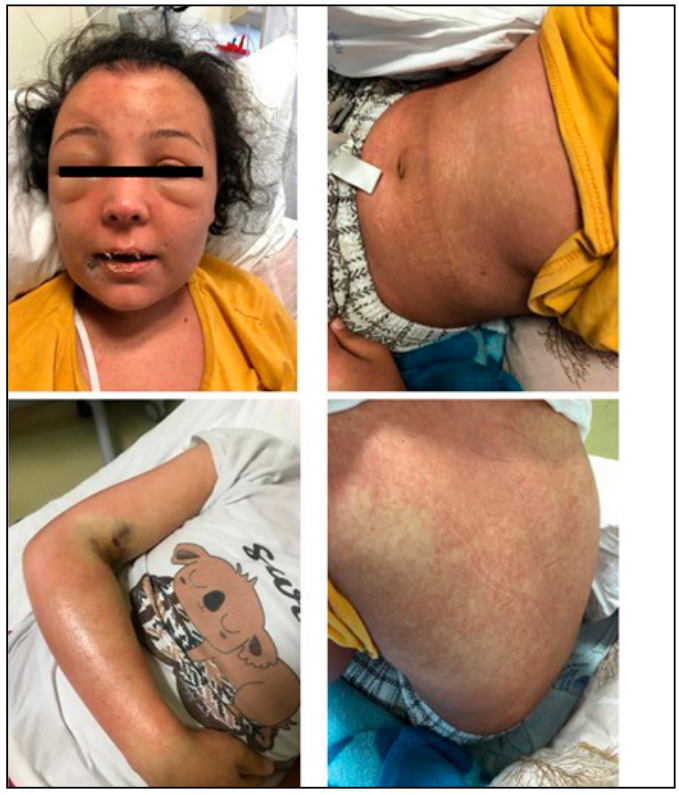

Figure 1. Skin rashes and facial swelling before differentiation therapy

Figure 2. Resolved oedema at 48th hour of treatment

■ Acute Lymphoblastic Leukemia

P-35 **Abstract Referance: 80**

FLOW CYTOMETRIC CHARACTERISATION OF ACUTE LEUKAEMIA IN ADOLESCENT AND ADULT ETHIOPIANS

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Background: Flow cytometric characterisation of acute leukemia is a key diagnostic approach for clinical management of patients, but is minimally practised in resource-constrained settings like Ethiopia.

Objective: This study aimed to determine the immunophenotypes of acute leukemia by flow cytometry at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia.

Methods: A cross-sectional study was conducted on adolescent and adult inpatients consecutively admitted from April 2019 to June 2021. Peripheral blood samples were stained for surface and cytoplasmic markers, and analysed by four-colour flow cytometry.

Results: Of 140 cases aged 13 years to 76 years, 74 (53%) were men and 66 (47%) were women, 68 (49%) had acute lymphocytic leukemia (ALL), 65 (46 %) had acute myelogenous leukemia (AML), and 7 (5.0%) had acute leukemia non-otherwise specified. Acute lymphocytic leukemia was more common among adolescent and male cases; AML was more common among adult and female cases. Among ALL subtypes, B-cell acute lymphocytic leukemia cases (73.5%) were more common than T-cell acute lymphocytic leukemia (26.5%). A subset of acute leukemia, CD19+/CD56+ AML was identified in 3 cases (6% of AML). Of the B-cell ALL cases, 21 (42%) were CD34+/CD10+/CD66c+, 10% were CD34+/CD10+/CD66c–, 32% were CD34-/CD10+, and 6% were CD34+/CD10–. An unexpectedly high number of T-cell ALL cases that lacked surface CD3 were observed to have significantly higher levels of aberrantly expressed myeloid markers.

Conclusion: We observed multiple phenotypes identifying subtypes of acute leukemia cases, extending our previous studies in Ethiopia.

Keywords: flow cytometry , acute leukaemia, Ethiopia

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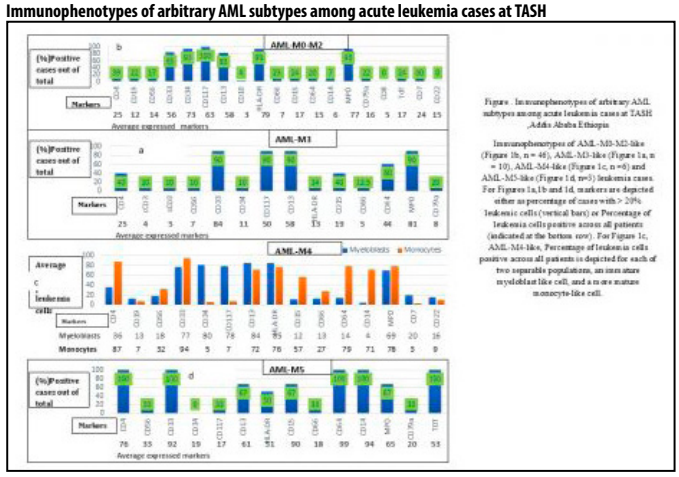
Immunophenotypes of arbitrary AML subtypes among acute leukemia cases at TASH



■ Myeloprofilerative Disorders

P-36 **Abstract Referance: 39**

THE BENEFIT OF ALLOGENEIC HSCT ON SURVIVAL OF CMML PATIENTS IN THE MOLECULAR STRATIFICATION ERA: A MULTICENTER STUDY

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative intervention for chronic myelomonocytic leukemia (CMML), yet treatment-related mortality (TRM; 20-40%) continues to limit its application. While current consensus prioritizes HSCT for higher-risk patients based on CPSS stratification and pre-2014 evidence, recent advances in molecular profiling (CPSS-mol, Mayo models), optimized supportive care, haploidentical donor protocols, and improved geriatric safety may have reshaped risk-benefit considerations. This multicenter study evaluates survival outcomes in Chinese CMML patients and redefines allo-HSCT's therapeutic role in the molecular era.

Methods: We conducted a retrospective analysis of 393 CMML patients (2015-2023) from 14 Chinese centers. Risk stratification utilized CPSS, MDAPS, CPSS-mol, and MMM models. Landmark analysis (148-day threshold) addressed time-dependent bias, with multivariate regression validating findings.

Results: The cohort had a median age of 58 years (range 4-85), with 72.8% CMML-1 and 35.6% myelodysplastic subtype. Risk distribution across models showed: CPSS (51.1% low, 26.5% intermediate-1 [int-1], 16.0% int-2, 6.4% high), MDAPS (38.2% low, 33.3% int-1, 20.6% int-2, 7.4% high), CPSS-mol (n=213: 7.5% low, 20.7% int-1, 51.2% int-2, 20.7% high), and MMM (6.6%

low, 26.2% int-1, 28.2% int-2, 39.0% high). Treatment patterns included hypomethylating agents/chemotherapy in 70.7% and HSCT in 37.9% (haploidentical 68.5%, matched sibling 26.2%, unrelated 5.4%).

Overall survival rates were 82.9% (1-year), 56.1% (3-year), and 46.7% (5-year). HSCT recipients exhibited superior 3-year OS versus non-recipients (64.9% vs 47.5%, p<0.001). In patients <70 years, CPSS-stratified analysis showed survival benefits for int-1 (63.4% vs 34.0%, p=0.038) and int-2 groups (61.1% vs 19.3%, p=0.049). MDAPS analysis revealed significant HSCT advantage in int-1 (p=0.004), int-2 (p=0.023), and high-risk groups (p=0.011). CPSS-mol stratification demonstrated benefit in int-2 group (p=0.046), while MMM showed advantage in high-risk group (p<0.001). Landmark analysis confirmed sustained HSCT superiority in CPSS int-1 (p=0.006)/int-2 (p=0.022), MDAPS int-1 (p=0.003)/int-2 (p=0.023)/high-risk (p=0.042), CPSS-mol int-2 (p=0.030), and MMM high-risk groups (p<0.001). The above results were further confirmed by regression analysis.

Conclusions: This study demonstrates allo-HSCT confers survival benefits across broader risk categories than previously recognized, including CPSS int-1/int-2, MDAPS int-1/int-2/high-risk, CPSS-mol int-2, and MMM high-risk patients. These findings advocate expanding transplant eligibility through integration of molecular stratification and modern HSCT platforms, while emphasizing dynamic risk-benefit reevaluation with emerging therapies.

Keywords: CMML; ALLO-HSCT; LANDMARK ANALYSIS; SURVIVAL BENEFIT

MDAPS

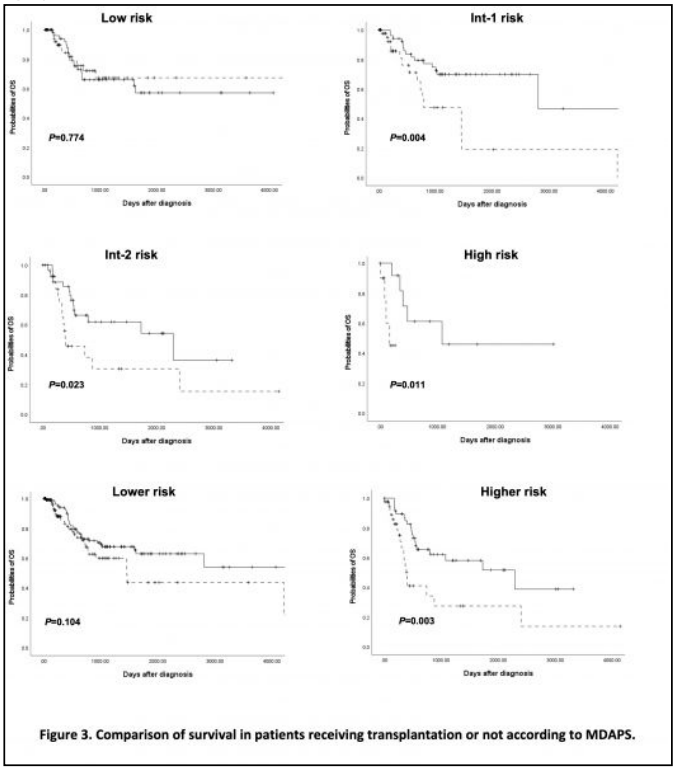

Figure 3. Comparison of survival in patients receiving transplantation or not according to MDAPS.

CPSS-MOL

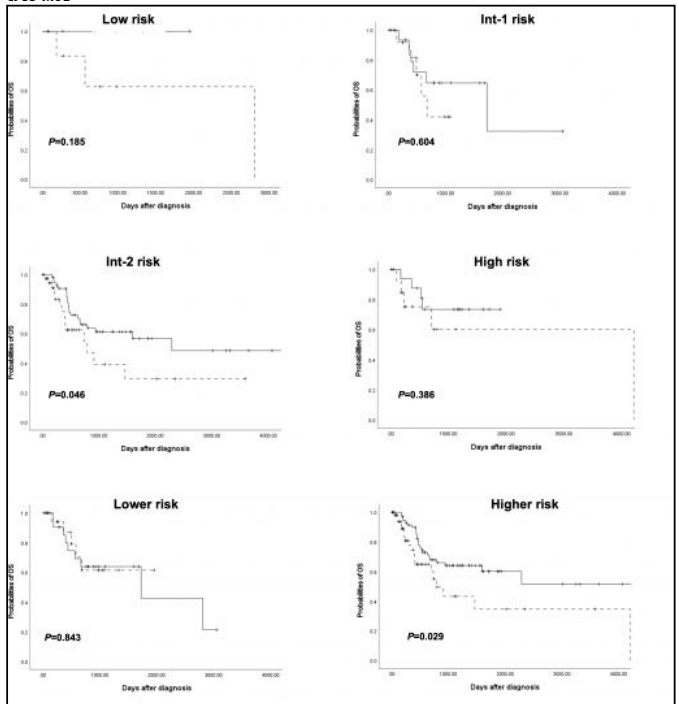

Figure 4. Comparison of survival in patients receiving transplantation or not according to CPSS-mol.

MMM

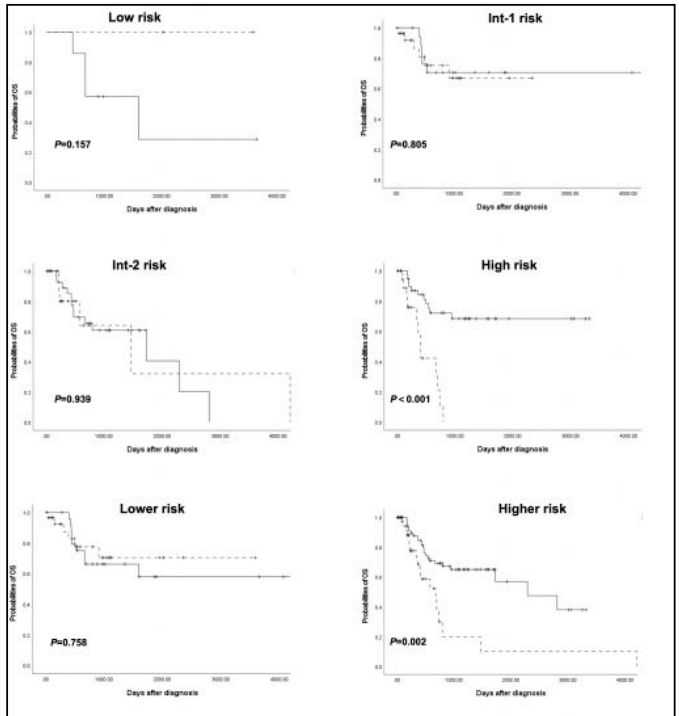

Figure 5. Comparison of survival in patients receiving transplantation or not according to MMM.

WHOLE COHORT

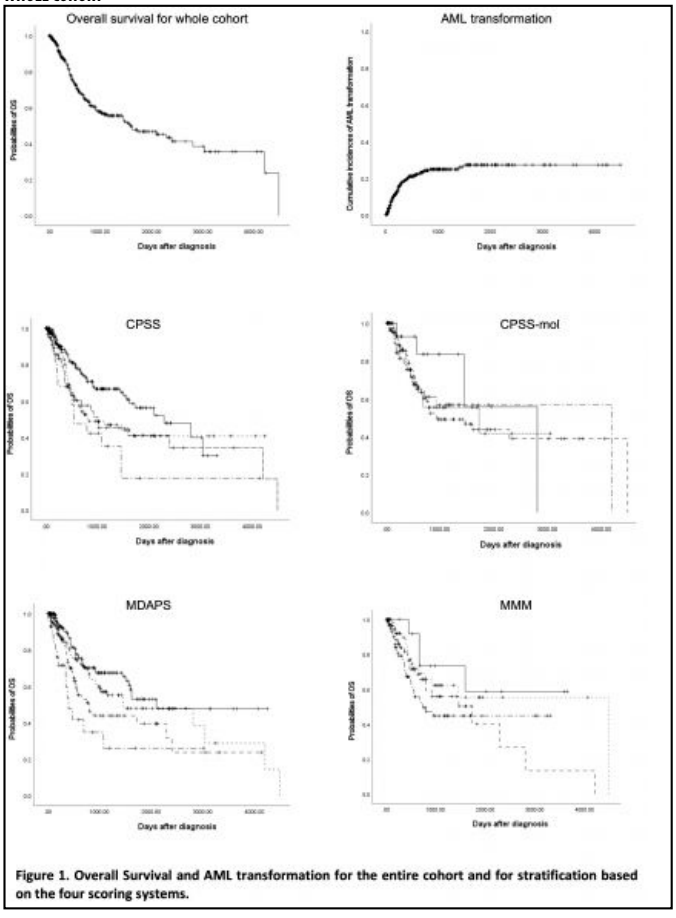

Figure 1. Overall Survival and AML transformation for the entire cohort and for stratification based on the four scoring systems.

CPSS

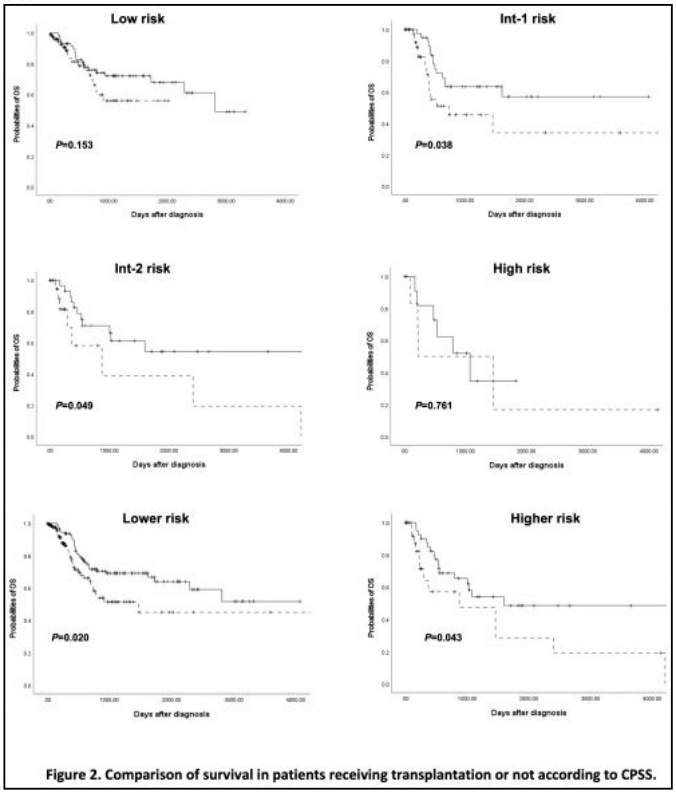

Figure 2. Comparison of survival in patients receiving transplantation or not according to CPSS.