HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Speech Abstracts

Abstract 001

POEMS SYNDROME: CLINICAL FEATURES, DIAGNOSIS, AND TREATMENT APPROACHES

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POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes) is a rare paraneoplastic syndrome with multisystem involvement [1]. It typically arises from monoclonal plasma cell proliferation and is considered an atypical variant of multiple myeloma [2]. In the pathogenesis of the disease, markedly elevated levels of vascular endothelial growth factor (VEGF) play a crucial role, and most of the symptoms are associated with this mechanism [3]. The clinical presentation of POEMS syndrome is quite heterogeneous. In most patients, the polyneuropathy is a subacute, distal, sensorimotor and progressive demyelinating neuropathy; motor involvement is often prominent and significantly impairs patients' quality of life [4]. Organomegaly particularly hepatomegaly, splenomegaly, and lymphadenopathy is commonly observed. Endocrinopathy may present with a wide spectrum of disorders, including diabetes mellitus, hypothyroidism, and hypogonadism. Monoclonal gammopathy frequently of the λ (lambda) light chain type is a critical diagnostic finding. Cutaneous manifestations may include hyperpigmentation, hemangiomas, excessive hair growth (hypertrichosis), and skin thickening. Additional features can include papilledema, edema, ascites, pulmonary hypertension, and thromboembolic events [5,6]. The diagnostic criteria were first defined by Dispenzieri and colleagues and are currently based on a system of 'major and minor criteria.' For diagnosis, in addition to the two mandatory major criteria (polyneuropathy and monoclonal plasma cell proliferation), at least one additional major criterion and one minor criterion must be present. Measurement of VEGF levels is an important biomarker both for diagnosis and for monitoring treatment response [5]. Treatment is aimed at eliminating the underlying clonal plasma cell population. In patients with localized bone lesions, radiotherapy may be effective particularly in cases of limited disease. For widespread disease, systemic therapies are preferred. Immunomodulatory agents such as lenalidomide and thalidomide, as well as bortezomib based regimens, have been found effective. Autologous hematopoietic stem cell transplantation (HSCT) can provide long-term remission in suitable patients. Monitoring treatment response via VEGF levels shows that reductions in VEGF parallel clinical improvement [7,8]. Prognosis has markedly improved with treatment. Contemporary approaches have increased the 5-year survival rate to approximately 60–70%. However, delayed diagnosis—due to frequent misattribution of symptoms to other neurological or endocrine disorders—is a significant issue at presentation. Therefore, multidisciplinary collaboration among hematologists, neurologists, and endocrinologists is critical for timely diagnosis and effective treatment [9]. In conclusion, POEMS syndrome is a rare but clinically highly complex disorder. Early diagnosis and appropriate treatment improve both survival and quality of life. Given the syndrome's clinical heterogeneity, increasing awareness especially within hematology practice is of great value [10].

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Abstract 002

UPDATES ON TARGETED THERAPIES IN ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is a malignant disease of bone marrow stem cells that can be fatal with current treatment methods. The median age of patients is 68, and a substantial proportion of cases are attributable to geriatric patients.

Following the administration of induction chemotherapy, complete remission (CR) is observed in approximately 73% - 45% of patients in the ELN-2022 favorable-adverse risk groups, respectively. However, overall survival (OS) and progression-free survival (PFS) are not satisfactory despite current treatments. The five-year PFS was estimated at 52% - 16%, and the five-year OS was 55% - 15%, respectively. As the pathogenesis of AML becomes clearer, clinical trials on current targeted therapies are increasing, and being developed to accompany or replace standard AML treatments that have been similar for nearly 50 years. It is now evident that epigenetic-based treatments can lead to significant changes in the fundamental model that underpins therapeutic interventions. The combination of BCL2 inhibitor venetoclax with hypomethylating agents has significantly improved survival, particularly in elderly and unfit patients. Studies are ongoing to combine intensive therapies with induction and consolidation therapy. Three FLT3 inhibitors (midostaurin, gilteritinib, and quizartinib) have shown promising results in induction and consolidation therapies, salvage therapies, and follow-up therapies after allogeneic transplantation. A phase Ib-II trial of crenolinib, a potent type I second-generation FLT3 inhibitor, demonstrates that its use with intensive therapy in newly diagnosed AML patients under 60 years of age improves survival and results in higher rates of MRD negativity. In addition, ongoing trials are also evaluating the 7 + 3 + midostaurin versus 7 + 3 with gilteritinib (NCT04027309). Other targeted studies are ongoing with IDH inhibitors (ivosidenib and olutasidenib targeting IDH1 mutations; enasidenib targeting IDH2 mutations). Olutasidenib has been shown to provide better response rates and survival compared to ivosidenib in elderly, unfit patients, and combination with azacitidine also increases OS. Other promising studies for AML appear to be focused on menin inhibitors. The phase 1 trial of Revumenib (AUGMENT-101 trial) and Ziftomenib (KOMET-001 trial) (both studies in patients with KMT2A rearranged and NPM1m R/R AML) have yielded positive results, and phase 2 trials are eagerly awaited. A phase 1 trial evaluating a third oral Menin inhibitor, JNJ-75276617, results rates were similar to the other 2 inhibitors. Clinical trials are now ongoing these drugs in combination with additional low dose and high dose chemotherapy regimens (NCT05735184, NCT05886049). Another area is immunotherapy in AML. The success of allogeneic stem cell transplantation has demonstrated the potential for immunotherapy. Talacotuzumab and Pivekimab, targeted to CD123, appear to be particularly effective in relapsed-refractory (R/R) patients, and combination studies with FLAG-IDA are ongoing. Additionally, Tagraxofusp, a drug containing IL-3 ligand conjugated to the first 388 amino acids of diphtheria toxin, has been studied combination with Azacitidine/Venetoclax in newly diagnosed AML patients. MRD negativity was found in 71% of patients. Magrolimab, which acts on CD47, has promising results in patients with R/R AML. The potential of ongoing targeted therapies to provide new insights into the treatment of AML.

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Abstract 003

OLD TRADITIONS IN A NEW VILLAGE*... WHY ARE FACTORS STILL NECESSARY? CONTEMPORARY PARADİGMS İN HEMOPHILIA MANAGEMENT AND THE IRREPLACEABLE ROLE OF FACTOR REPLACEMENT

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Hemophilia is an X-linked recessive hereditary coagulation disorder characterized by a deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Beginning in childhood, it constitutes a lifelong global health problem, associated with substantial morbidity, mortality, and treatment costs. While novel approaches—including gene therapies and non-factor-based biologic agents—are reshaping therapeutic strategies, factor replacement therapies remain the indispensable cornerstone of hemophilia management due to persistent clinical, biological, and economic limitations. **Gene Therapy:** Gene transfer techniques utilizing adeno-associated virus (AAV) vectors (e.g., valoctocogene roxaparvovec, etranacogene dezaparvovec) have shown promise in maintaining sustained factor levels in adults. However, in pediatric populations, hepatocyte proliferation inevitably leads to loss of transgene expression. In addition, immune responses, hepatotoxicity, and the inability to administer repeat dosing represent major barriers to safety and efficacy in children. Ethical concerns further complicate implementation. For these reasons, gene therapy does not appear to be a feasible treatment option for pediatric hemophilia in the near future. **Non–Factor-Based Agents:** Emicizumab, a bispecific antibody that mimics the bridging function of factor VIII, has significantly reduced bleeding frequency and revolutionized care, particularly in hemophilia A patients with inhibitors. Its subcutaneous administration enhances treatment adherence. Nevertheless, its inability to rapidly increase factor levels in emergencies such as major surgery or trauma is a critical limitation. Likewise, RNA interference (RNAi) therapies such as fitusiran and tissue factor pathway inhibitor (TFPI) inhibitors (concizumab, marstacimab) have shown encouraging results in clinical trials. However, thrombotic risks and uncertainties surrounding long-term safety restrict their use in pediatric populations. **Factor Replacement Therapy:** Standard and extended half-life (EHL) FVIII/FIX concentrates, supported by more than four decades of safety data, continue to form the foundation of prophylaxis in childhood. EHL products have reduced treatment burden with once- or twice-weekly dosing, while playing a vital role in maintaining joint health and preventing trauma-related bleeding episodes. Factor replacement therapy remains the gold standard for the management of acute bleeding. **Global Access and Health Economics:** Gene therapies and biologic agents are accessible almost exclusively in high-income countries due to their prohibitive costs (USD 2–3 million per treatment; emicizumab approximately USD 400,000 annually). In contrast, in low- and middle-

income countries, factor replacement remains the only feasible option, in line with World Federation of Hemophilia (WFH) recommendations. **Conclusion:** Despite recent paradigm shifts in the treatment of pediatric hemophilia, factor replacement remains indispensable. Gene therapies hold promise for the future, but biological and ethical constraints currently prevent their application in children. Non–factor-based agents have facilitated prophylaxis but are insufficient in emergencies and lack long-term safety data, particularly in major surgical procedures and severe acute bleeding episodes. Factor replacement therapies, with their proven efficacy, predictable pharmacokinetics, established safety, and global accessibility, continue to stand as the gold standard treatment option for both today and the foreseeable future. *"A reference to a Turkish idiomatic saying, originally 'Introducing a new custom to an old village' (bringing new ways to an old place), which means introducing a revolutionary, unusual, or unexpected innovation or behavior into a traditional, clichéd order or way of doing things."

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Abstract 004

IRON CHELATİON İN MYELODYSPLASTİC SYNDROMES: WHO AND WHEN?

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Red blood cell (RBC) transfusions are the cornerstone of supportive care in patients with myelodysplastic syndromes (MDS). While transfusions alleviate symptomatic anemia, they inevitably lead to progressive iron accumulation in patients. This transfusional iron overload may exert toxic effects on the heart, liver, endocrine system, ultimately contributing to increased morbidity and mortality. Timely initiation of iron chelation therapy has become an important consideration in the comprehensive management of MDS. Chelation is primarily indicated for patients with lower-risk MDS (IPSS low or Int-1) who are expected to have longer survival, who remain transfusion-dependent. In such patients, iron overload not only threatens organ function also worsens prognosis. Multiple studies have shown that transfusion dependence is a negative prognostic factor, and retrospective analyses suggest that iron chelation may improve overall survival. Chelation is also particularly important in patients who are candidates for allogeneic stem cell transplantation, since excess iron has been associated with inferior transplant outcomes. By reducing systemic iron burden, chelation help optimize organ function and improve transplant eligibility. The decision is usually guided by transfusion history and serum ferritin levels. Most guidelines recommend considering chelation after approximately 20–30 units of RBC transfusions or when serum ferritin persistently exceeds 2500 ng/mL. The therapeutic goal is to maintain ferritin below 1000 ng/mL, minimizing iron-mediated oxidative stress and tissue damage. While serum ferritin is an imperfect surrogate, it remains a practical marker. More advanced techniques such as MRI T2* or SQUID can provide direct estimates of hepatic iron, but their availability is limited. Three chelators are currently in clinical use. Deferoxamine, administered subcutaneously or intramuscularly, is effective but limited by its parenteral route. Deferasirox, an oral once-daily agent, has become the preferred choice in many cases and is FDA-approved for transfusion-related iron overload. Randomized trials in lower-risk MDS demonstrated that deferasirox reduced ferritin, improved event-free survival, and even enhanced hematologic response in some patients. However, renal, hepatic toxicity require careful monitoring. Deferiprone, another oral agent, is mainly approved for thalassemia, can be considered when other chelators fail, though its use in MDS remains limited due to risk of agranulocytosis. Chelation has been associated with improved overall survival in observational studies, prospective trials provide encouraging evidence. Beyond survival, reversal of some iron-related cardiac, hepatic damage has been documented, underscoring its importance. Monitoring should include serial ferritin, renal, liver function, vigilance for adverse events. Individualization is critical: patients with advanced or high-risk MDS, limited life expectancy are less likely to benefit, and chelation is generally not recommended in such settings. Iron chelation therapy plays a vital role in selected MDS patients. It should be considered in lower-risk individuals with substantial transfusion requirements and elevated ferritin, especially in those with preserved organ function or who are candidates for transplantation. As evidence grows, iron chelation continues to evolve from a supportive measure into a prognostically meaningful intervention in the management of MDS.

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Abstract 005

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

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Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening thrombotic microangiopathy caused by severe ADAMTS-13 deficiency due to either autoantibodies (immune TTP, iTTP) or biallelic mutations (congenital TTP, cTTP). The first International Society on Thrombosis and Haemostasis (ISTH) guidelines were issued in 2020. Since then, substantial advances in therapeutic strategies and real-world evidence have prompted an ISTH 2025 focused update. The most significant change relates to cTTP prophylaxis. A new strong recommendation was issued in favor of recombinant ADAMTS-13 (rADAMTS-13) over fresh frozen plasma (FFP) in patients in remission. This decision, supported by a phase 3 randomized crossover trial, demonstrated that rADAMTS-13 provides higher and sustained ADAMTS-13 activity and fewer TTP-related manifestations, with a favorable safety profile [1]. Where rADAMTS-13 is unavailable, the panel conditionally recommends FFP over a watch-and-wait strategy, shifting from the neutral stance in 2020 [1,2]. Pregnancy-related cTTP remains a high-risk setting, and prophylactic therapy—preferably rADAMTS-13, or intensified FFP when rADAMTS-13 is

not accessible—is emphasized due to high maternal and fetal morbidity and mortality [1]. For iTTP, no major directional changes were made. Therapeutic plasma exchange (TPE) with corticosteroids remains standard of care. The addition of rituximab is conditionally suggested for both initial and relapsed events. Caplacizumab continues to be conditionally recommended, supported by real-world registry and cohort data showing faster platelet recovery, fewer exacerbations, reduced TPE sessions, shorter hospitalization, and mortality consistently below 5% [3,4]. Evidence highlights that early initiation, ideally within three days of diagnosis, maximizes benefit [4]. The update also provides revised good practice statements on antithrombotic therapy. Prophylactic anticoagulation (most often low-molecular-weight heparin) may be considered once platelet counts recover above 50×10^9/L in patients at elevated thromboembolic risk, while antiplatelet agents remain discouraged during the acute phase [1]. Importantly, registry data highlight the long-term morbidity of cTTP, including ischemic stroke, end-stage renal disease, and cardiac dysfunction, as well as pregnancy complications. These findings strengthen the rationale for early and consistent prophylaxis. Regulatory approval of rADAMTS-13 in the United States, Europe, and Japan for both prophylaxis and acute treatment represents a transformative milestone in cTTP management [5]. Conclusion: The ISTH 2025 focused update establishes rADAMTS-13 as the new standard for prophylaxis in cTTP and reaffirms the existing evidence-based triple therapy (TPE, corticosteroids, and caplacizumab ± rituximab) in iTTP. These recommendations, integrating randomized trial results, real-world data, and international consensus, provide globally harmonized, evidence-based guidance to improve outcomes and quality of life for patients with TTP.

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Abstract 006

THE TREATMENT ALGORITHM FOR SICKLE CELL DISEASE

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Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy characterized by the polymerization of Hemoglobin S (HbS), which results from a point mutation in the β-globin gene. The clinical heterogeneity of the disease is dictated by a complex interplay of three core pathophysiological mechanisms: vaso-occlusion (VOC), driven by erythrocyte rigidity secondary to deoxy-HbS polymerization; chronic hemolytic anemia, resulting from a shortened erythrocyte lifespan; and a state of chronic sterile inflammation and ischemia-reperfusion injury, triggered by the scavenging of nitric oxide (NO) by cell-free hemoglobin. While HbSS and HbS/β^0-thalassemia genotypes constitute the most severe phenotypes, therapeutic algorithms are designed to target these fundamental molecular underpinnings. **Foundational Management and Prevention in SCD:** The cornerstone of modern SCD management is rooted in proactive and preventive medicine. Early diagnosis through newborn screening programs facilitates the immediate initiation of penicillin prophylaxis (from 2 months to 5 years of age) and comprehensive vaccinations (against *Pneumococcus*, *Meningococcus*, and *H. influenzae*), which dramatically reduce the risk of invasive pneumococcal disease secondary to functional asplenia. Primary stroke prevention in the pediatric population (ages 2-16) relies on annual Transcranial Doppler (TCD) screening. A time-averaged mean of maximum velocity exceeding 200 cm/sec is an absolute indication for initiating a chronic transfusion program, a measure proven to reduce stroke risk by over 90%. Hydroxyurea remains the cornerstone of this foundational care, recommended for all patients with severe genotypes over the age of 9 months. When titrated to the maximum tolerated dose (MTD), its pleiotropic effects—including the induction of fetal hemoglobin (HbF) and its anti-inflammatory and anti-adhesive properties—significantly modify the disease course. **Management of Acute Complications:** Acute complications warrant standardized and aggressive intervention. The management of vaso-occlusive crises (VOCs) necessitates rapid, multimodal analgesia, featuring the administration of parenteral opioids and non-steroidal anti-inflammatory drugs (NSAIDs) within 30 to 60 minutes of presentation. Acute Chest Syndrome (ACS), a leading cause of mortality, is managed with broad-spectrum antibiotics, supplemental oxygen, and transfusion support. In cases of severe ACS, the 2020 American Society of Hematology (ASH) guidelines recommend exchange transfusion over simple transfusion to rapidly decrease the HbS fraction to less than 30%. Similarly, acute ischemic stroke constitutes a hematologic emergency that mandates immediate exchange transfusion to reduce the HbS level to below 30%. **Chronic Complications and Disease-Modifying Therapies:** For patients with a suboptimal response to or intolerance of hydroxyurea, therapy is personalized with phenotype-specific agents. In the vaso-occlusive-dominant phenotype, options include the P-selectin inhibitor crizanlizumab and the oxidative stress-targeting agent L-glutamine. However, the role of crizanlizumab in the treatment algorithm has become contentious following the failure of its post-approval STAND study to meet its primary endpoint. For the hemolysis-dominant phenotype, voxelotor, a direct inhibitor of HbS polymerization, is effective in increasing hemoglobin levels. Nevertheless, its use has become debatable following the non-renewal of its marketing authorization by the European Medicines Agency (EMA) due to insufficient evidence of clinical benefit and the company's subsequent global withdrawal decision. **Transfusion Support and Associated Management:** Chronic transfusion therapy is a life-saving intervention, particularly for stroke prophylaxis, but inevitably leads to iron overload. Iron chelation therapy should be initiated when serum ferritin levels exceed 1000-1500 ng/mL. The gold standard for monitoring chelation efficacy is the quantitative assessment of hepatic and cardiac iron burden via T2* MRI. To minimize iron accumulation and more precisely achieve target HbS levels, the 2020 ASH guidelines advocate for automated red cell exchange (RCE) over simple transfusions for patients on chronic transfusion regimens. **Conclusion:** The management paradigm for SCD has evolved from reactive care to a multifaceted approach encompassing proactive foundational

therapies, phenotype-specific treatments, and curative strategies. Allogeneic hematopoietic stem cell transplantation and the recently approved gene therapies based on CRISPR-Cas9 (Exa-cel) and lentiviral vectors (Lovo-cel) have ushered in a new era, offering curative potential for eligible patients. The future therapeutic algorithm is anticipated to become even more personalized through the integration of these revolutionary treatments.

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Abstract 007

WALDENSTRÖM MACROGLOBULINEMIA

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Waldenström Macroglobulinemia (WM) is a rare disease. The median age at diagnosis is 70 years and approximately 60 percent of patients are male. The etiology of WM is not fully understood. Approximately 90-95% of WM patients have mutations in the MYD88 L265P gene and 40% have recurrent mutations in the CXCR4 gene. The clonal B cell population leads to abnormal monoclonal IgM production. The pentameric configuration of IgM molecules increases serum viscosity, slowing blood flow through capillaries. In patients with WM, clonal B cells can directly infiltrate hematopoietic tissues, causing cytopenias (e.g., anemia, thrombocytopenia, neutropenia), lymphadenopathy, hepatomegaly, and/or splenomegaly. Rarely, plasmacytoid lymphocytes may infiltrate the central nervous system or meninges. Most patients with WM present with nonspecific constitutional symptoms but up to a quarter of patients may be asymptomatic at diagnosis. Common symptoms include weakness, fatigue, weight loss, and nose and gum bleeding. Bone marrow aspiration and biopsy demonstrating lymphoplasmacytic lymphoma is an important component of the diagnosis of WM. The biopsy specimen is usually hypercellular and densely infiltrated with lymphoid and plasmacytoid cells. Intranuclear vacuoles containing IgM monoclonal protein (Dutcher bodies) are common in the malignant cells of WM. The following criteria must be met for a diagnosis of WM: • IgM monoclonal gammopathy (any level) must be present in the serum. • ≥10% of the bone marrow biopsy specimen must show infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation (lymphoplasmacytic features or lymphoplasmacytic lymphoma) and an intertrabecular pattern. • The infiltrate should express a typical immunophenotype (e.g., surface IgM +, CD5-/+, CD10-, CD11c-, CD19+, CD20+, CD22+, CD23-, CD25 +, FMC7+, CD103-, CD138-). The plasmacytic component will be CD138+, CD38+, and CD45- or less prominent. The differential diagnosis includes chronic lymphocytic leukemia, marginal zone and mantle cell lymphoma. Not every VM patient requires treatment. For asymptomatic patients, follow-up without treatment every 3-6 months is recommended. Treatment is indicated for patients with symptomatic WM if any of the following are attributable to WM: • Systemic symptoms: B symptoms such as recurrent fever, severe night sweats, fatigue and/or unintentional weight loss • Cytopenias: Hemoglobin ≤10 g/dL or platelet count <100,000/microL; cold agglutinin anemia, immune hemolytic anemia, and/or thrombocytopenia • Symptomatic or large (≥5 cm) lymphadenopathy, symptomatic splenomegaly and/or tissue infiltration • End-organ damage: Hyperviscosity, peripheral neuropathy, immunoglobulin light chain (AL) amyloidosis with organ dysfunction, symptomatic cryoglobulinemia, pleural effusions or nephropathy due to WM Symptomatic hyperviscosity in a patient with an indication for treatment requires urgent plasmapheresis. Signs and symptoms associated with hyperviscosity include oronasal hemorrhage, blurred vision, headache, dizziness, paresthesia, retinal vein occlusion, papilledema, stupor, and coma. In patients with treatment indications but without symptoms of hyperviscosity, options include rituximab plus bendamustine or Bruton's tyrosine kinase inhibitors (such as ibrutinib, zanubrutinib, or acalabrutinib). Treatment of relapsed or refractory disease may include Bruton's tyrosine kinase inhibitors, bendamustine plus rituximab, nucleosome analog-based regimens, and venetoclax, if not previously used. High-dose chemotherapy and autologous or allogeneic hematopoietic cell transplantation (HCT) are rarely used in the treatment of WM.

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Abstract 008

REFRACTORY CHRONIC MYELOID LEUKEMIA: A REVIEW OF CURRENT THERAPEUTIC LANDSCAPE AND EMERGING CHALLENGES

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Chronic myeloid leukemia (CML) has become a paradigm of targeted therapy success; however, a proportion of patients develop refractory disease, marked by failure or intolerance to multiple TKIs. Optimal management requires integrating molecular, clinical, and patient-related factors into therapeutic decision-making [1,2]. **Mechanisms of Resistance and Genetic Complexity:** Resistance is commonly mediated by BCR::ABL1 kinase domain mutations. While second-generation TKIs (dasatinib, nilotinib, bosutinib) address many resistant clones, the T315I substitution remains uniquely sensitive to ponatinib [3,4]. Beyond kinase domain changes, clonal evolution with mutations in ASXL1, RUNX1, IKZF1, TP53, and DNMT3A has been increasingly recognized. These lesions, frequently encountered in advanced phases, are associated with poor response to TKIs, higher risk of progression, and inferior survival [5,6]. **Current Therapeutic Approaches:** Ponatinib remains the agent of choice for patients harboring T315I or compound mutations, with careful risk management to mitigate vascular events [4]. Asciminib, a first-in-class STAMP inhibitor targeting the myristoyl pocket of BCR::ABL1, has emerged as a major advance. By restoring kinase autoinhibition, asciminib demonstrated superior efficacy and tolerability over bosutinib in the ASCEMBL trial [3] and has shown promising results in real-world refractory populations. **TKI Selection Considerations:** In clinical practice, TKI selection is

guided by a combination of mutational status and comorbidities. Specific mutations confer resistance to certain TKIs, making mutation-directed sequencing essential. At the same time, patient comorbidities such as cardiovascular, pulmonary, or metabolic disease influence drug tolerability and safety, thereby shaping the optimal therapeutic choice [1,7]. **Beyond TKIs:** For patients failing multiple TKIs, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative approach, particularly in younger and high-risk patients [1,2]. Novel strategies under investigation include rational TKI combinations (e.g., asciminib plus ponatinib), immunotherapeutic approaches, and targeted inhibition of epigenetic regulators [8]. **Conclusion:** Refractory CML reflects the biological and clinical complexity of disease progression beyond BCR::ABL1 dependence. While ponatinib and asciminib have redefined therapeutic opportunities, additional high-risk mutations highlight the need for precision medicine strategies. Tailored TKI sequencing, integration of comorbidity profiles, and timely transplantation remain central pillars, while ongoing translational research promises to expand future options [7,8].

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Abstract 009

HYPERCOAGULABILITY: ETIOLOGY, DIAGNOSIS AND TREATMENT PRINCIPLES

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Thrombosis occurs when the delicate balance between prothrombotic and anticoagulant forces is impaired. It usually develops due to multiple factors. When multiple risk factors come together, the anticoagulant systems cannot resist procoagulant forces and thrombosis may develop as a result. Thrombosis due to hypercoagulability is usually seen clinically as venous thromboembolism (VTE) and rarely as arterial thrombosis. VTE can be seen as deep vein thrombosis (DVT) or pulmonary embolism. DVT most often manifests itself in the legs and rarely in the abdominal or intra-pelvic veins. The hereditary or acquired factors are involved in the etiology of venous thromboembolism. Clinically, VTE is observed in those who are due to hereditary factors, while venous or arterial thromboses may be observed in those who are due to acquired causes. Hypercoagulability due to acquired causes is observed more often (70%) and they have a greater risk of thrombosis. Venous thromboembolism is reported to occur in 1/10,000 people per year under the age of 40 and 1/1000 people per year over the age of 75. Hereditary thrombophilia causes are rare in the population. Although different rates are reported according to the world geography, The R506Q mutation in coagulation factor V, also known as the Factor V Leiden (FVL) mutation is the most common among them (3-8%). It is rare in far east countries. FVL mutation is the most common cause among hereditary hypercoagulabilities (50%). Clinically, young age, idiopathic thrombosis, thrombosis in an unusual place (upper extremity, mesenteric vein, portal vein, renal vein, cerebral vein) are noteworthy. Recurrence of thrombosis and a family history of venous thromboembolism are common. Since the findings are not specific in the diagnosis of venous thromboembolism, the patient's medical history, family history and examination findings should be evaluated together. Determination of thrombosis risk scores, D-Dimer test, blood chemistry, lung X-ray and ECG are included as the first examinations in the patient. In patients with a negative D-Dimer test, a further examination is usually not needed. The subject of which tests to perform and when to perform in VTE cases requires expertise. In cases of idiopathic thrombosis, occurring at a young age, or recurrent, genetic or coagulation tests may be planned. Since test results may be misleading during the acute thrombosis period, it is more appropriate to schedule the tests a few weeks later or after the end of treatment. In patients with a high thrombosis risk score and elevated D-dimer levels, extremity vein Doppler ultrasonography and computed pulmonary angiography are used as imaging studies. Oral or parenteral anticoagulants are used in the treatment of venous thromboembolism. These include low molecular weight heparin, FXa inhibitors (apixaban, rivaroxaban), and vitamin K antagonist (warfarin). The most commonly used are low-molecular-weight heparin, FXa inhibitors (apixaban, rivaroxaban), and vitamin K antagonists (warfarin). Anticoagulant therapy should last at least 3 months, after which patients should be evaluated based on their risk status. Anticoagulant therapy should be longer-term in patients with ongoing diseases or conditions that trigger thrombosis (such as antiphospholipid syndrome, active autoimmune disease, cancer). Patients should be carefully monitored for bleeding during anticoagulant therapy. Thrombolytic or interventional treatments may be administered to patients presenting with acute heart failure and hypotension. Patients should continue to be monitored after anticoagulant therapy, and physical therapy should be provided for patients with postthrombotic syndrome.

Key words: Hypecoagulability, venous tromboembolism, anticoagulant therapy.

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Abstract 010

THE PLACE OF IMMUNOTHERAPY IN ALL

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In patients with acute lymphoblastic leukemia (ALL), although 80-90% of adult patients achieve a complete response (CR), cure rates are only 40% with initial treatment and 10%-20% with subsequent salvage treatments. Ten percent of patients are refractory to initial treatment, and 40%-70% relapse. Allo-HCT is the standard of care for a fit and eligible group. Immunotherapies are an important choice in improving treatment success and reducing side effects. The primary immunotherapies include bispecific antibodies (BsAbs), antibody-drug conjugates, CAR T-cell, and CAR NK-cell therapies. Blinatumomab activates T cells by binding to

CD19 on B-ALL cells and CD3 on T cells, leading to polyclonal expansion of cytotoxic T cells, T-cell activation, and the release of cytokines and cytotoxic granules. thus causing lysis of CD19+ lymphoblasts. It is approved for the treatment of Ph (-) Relapsed/Refractory (R/R) B-ALL and has received FDA approval for consolidation therapy in patients with MRD-positive disease and for MRD-independent consolidation therapy. The Alcantara study demonstrated sustained responses in patients with Ph(+) R/R ALL. Inotuzumab is an antibody-drug conjugate containing calicheamicin, an anti-CD22-targeted, DNA-binding cytotoxic antibiotic. It received FDA approval after inotuzumab monotherapy demonstrated superiority over standard chemotherapy for relapsed/refractory CD22(+) B-ALL. The most common Grade ≥3 adverse events were hematologic and liver-related and included an 11% VOD, mostly seen after sequential allo-HSCT. Inotuzumab monotherapy has shown high CR and MRD negativity rates when used in combination with reduced-intensity chemotherapy in the first-line setting in elderly patients. Cell-based therapies have demonstrated efficacy in R/RB-ALL with CD19-targeted therapies such as tisagen-lecleucel (tisa-cel) for patients aged ≤25 years and brexucabtagene autoleucel for adults, despite the side effects that limit CAR T cells. Side effects include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), and B-cell aplasia. Studies of CD5-CART, CD7-CART, and NS7CAR are ongoing for relapsed/refractory T-cell leukemia. Although experimental, CAR-NK therapies, which use NK cells isolated from peripheral blood and do not pose a risk of GVHD, show promise with fewer side effects, fewer relapses, and longer survival. Studies of immune checkpoint inhibitors combined with other immunotherapies may be important for B-ALL, while combinations of BCL-2 and BCL-XL inhibitors with chemotherapy may be important for T-ALL, for which no antibody therapy is currently available. Difficulties continue to arise in the treatment of T-ALL and Ph-like ALL. Immunotherapy and cellular therapies are being studied in optimal combinations.

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Abstract 011

DIAGNOSIS AND MANAGEMENT OF EOSINOPHILIA

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Eosinophilia is defined as an absolute eosinophil count greater than 500/μL in peripheral blood and is characterized by a broad clinical spectrum, ranging from transient, benign processes to severe, life-threatening hematologic malignancies. The severity of eosinophilia has been classified into three categories: mild (500–1,500/μL), moderate (1,500–5,000/μL), and severe (>5,000/μL). Persistent elevations above 1,500/μL, particularly when accompanied by tissue infiltration, are defined as hypereosinophilia. This condition can progress to hypereosinophilic syndromes (HES), with multisystem organ damage. The most frequently involved are the skin, lungs, gastrointestinal tract, cardiovascular system, and central nervous system. A stepwise and comprehensive diagnostic approach is essential for the evaluation of eosinophilia. A comprehensive medical history and physical examination should address the following: allergic and atopic disorders, travel to endemic regions for parasitic diseases, drug exposures, and family history suggestive of hereditary conditions. Initial laboratory evaluation includes complete blood count and peripheral smear to verify eosinophilia and identify dysplastic features. The diagnostic evaluation should begin with the exclusion of secondary causes, which comprise parasitic and fungal infections, allergic or atopic conditions (e.g., asthma, atopic dermatitis), drug hypersensitivity, autoimmune/connective tissue diseases, and certain solid tumors. When secondary causes are excluded, primary or clonal eosinophilia must be considered. Bone marrow aspiration/biopsy, cytogenetic analyses, flow cytometry, and molecular assays (e.g., FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2, BCR-ABL mutations) are essential for differentiating neoplastic eosinophilia. When organ involvement is clinically suspected, assessment often includes imaging modalities (CT, MRI), echocardiography, pulmonary function testing, and endoscopic procedures. The approach to treatment depends on the underlying pathology, disease severity, and the presence or absence of organ involvement. In secondary eosinophilia, management includes targeted therapy such as anti-parasitic agents, discontinuation of causative drugs, or treatment of underlying autoimmune or malignant disorders. Systemic corticosteroids remain the first-line intervention for many patients, particularly those with symptomatic hypereosinophilia or organ-threatening disease, due to their rapid effect in lowering eosinophil counts and mitigating tissue injury. In primary or clonal eosinophilia, treatment varies with molecular findings. Patients with FIP1L1–PDGFRA–positive myeloproliferative variants typically respond dramatically to tyrosine kinase inhibitors such as imatinib. Other cytoreductive agents, including hydroxyurea and interferon-α, may be used in refractory or steroid-intolerant cases. In acute eosinophilic leukemia, intensive chemotherapy or hematopoietic stem cell transplantation may be indicated. Monoclonal antibodies directed against interleukin-5 (mepolizumab, reslizumab) or its receptor (benralizumab) have demonstrated significant efficacy in reducing blood and tissue eosinophil counts, improving clinical outcomes in HES, eosinophilic asthma, and other eosinophil-mediated disorders. These agents provide a more targeted approach with fewer systemic toxicities compared to traditional immunosuppressants, representing a paradigm shift in long-term disease management. In conclusion, eosinophilia is not a diagnosis in itself but a clinical finding requiring careful evaluation to distinguish reactive from clonal causes. Early recognition of hypereosinophilia and prompt assessment of target organ involvement are vital to prevent irreversible complications. Advances in molecular diagnostics and targeted biologic therapies have markedly improved the ability to personalize treatment and enhance prognosis. Future research will likely further explain the causes of the disease and expand the available treatments, which will in turn improve long-term results for patients with eosinophilia.

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Abstract 012

TREATMENT-FREE REMISSION IN CHRONIC MYELOID LEUKEMIA: CURRENT EVIDENCE, PREDICTORS, AND FUTURE DIRECTIONS

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Background: The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the management of chronic myeloid leukemia (CML), transforming it into a chronic condition with near-normal life expectancy. In this context, treatment-free remission (TFR)—defined as the maintenance of deep molecular response after discontinuation of TKIs—has emerged as a new therapeutic milestone beyond survival and disease control. While multiple clinical trials and real-world cohorts have demonstrated the feasibility and safety of TFR, several biological, molecular, and clinical factors continue to shape patient selection and long-term outcomes. **Content:** This presentation synthesizes evidence from pivotal discontinuation trials (STIM, EURO-SKI, ENESTfreedom, ENESTop, DASFREE, DESTINY) as well as real-world studies from Europe, Asia, and North America. Updated recommendations from international guidelines (ELN 2020/2025, NCCN 2025) are reviewed alongside emerging biological insights, including immune surveillance, transcript types, and microenvironmental regulation of leukemia stem cells. Novel approaches such as dose de-escalation, immunotherapy combinations, and predictive modeling are critically examined to delineate future directions in TFR research. **Results:** Clinical evidence consistently shows that sustained TFR is achievable in approximately **40–60%** of patients after ≥3 years of TKI therapy and ≥2 years of stable deep molecular response (DMR). Higher success rates have been reported in Japanese cohorts (up to 63%), underscoring the influence of patient selection and monitoring intensity. 1. **Relapse dynamics:** Most relapses occur within the first 6–12 months, with >95% of patients regaining major molecular response (MMR) after restarting TKIs. Late relapses are rare but underscore the necessity of lifelong molecular monitoring. 2. **Predictors of success:** Longer TKI duration (≥5 years), sustained MR4.5, and the e14a2 transcript type are consistently associated with improved outcomes. Immunological parameters, particularly increased NK cell activity and reduced regulatory T-cell frequencies, also correlate with durable remission. 3. **Therapeutic strategies:** Dose de-escalation (e.g., DESTINY trial) has been shown to reduce relapse risk and mitigate withdrawal symptoms. Second TFR attempts, as demonstrated in DAstop2, are feasible and safe for selected patients. 4. **Adverse effects:** Approximately 30–40% of patients experience musculoskeletal discomfort—termed "TKI withdrawal syndrome"—which is typically mild and self-limiting. **Discussion:** TFR represents a paradigm shift in CML care, reflecting both biological disease control and patient-centered goals such as quality of life and long-term safety. While most relapses are molecular and rapidly reversible, careful patient selection and standardized monitoring remain essential to ensure safety. Regional differences highlight the importance of infrastructure: countries with frequent PCR monitoring and strong patient compliance report superior outcomes. Immunological studies suggest that durable TFR depends on effective immune surveillance, with NK cells and T-cell subsets emerging as potential biomarkers. Moreover, mathematical modeling of leukemia stem cell–microenvironment interactions provides new insights into relapse biology. Future research will likely integrate these biomarkers into predictive algorithms to personalize TFR eligibility. Importantly, novel combinations—such as TKI with interferon-α or immune checkpoint blockade—are under active investigation and may enhance remission durability. **Conclusion:** TFR is now established as a safe and realistic treatment goal in selected CML patients, particularly those with prolonged TKI exposure and stable deep molecular responses. Success rates of 40–60% can be expected, with >95% of relapsed patients regaining response upon retreatment. Ongoing efforts should focus on refining patient selection through biomarkers, enhancing durability with immunotherapy-based combinations, and harmonizing monitoring practices globally.

Keywords: CML, TFR, Tyrosine Kinase Inhibitors, Deep Molecular Response, Immunotherapy.

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Abstract 013

THE PAST, PRESENT, AND FUTURE OF TRANSFUSION

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Blood has attracted human interest since the dawn of history. The human spirit, strength, and character have been identified with blood. The first known human-to-human blood transfusion (1492) was performed on Pope Innocent VIII with the aim of rejuvenating him, using blood from three young men. This procedure ended with the death of the Pope and the young donors. Initially, blood transfusions were attempted from animal to animal, followed by attempts at blood transfusions from animal to human. A blood transfusion from a lamb to a human was performed to calm a person with mental disorders, followed by attempts at blood transfusions from various animals to humans. Following acute hemolysis cases that ended in death, the Paris Medical Association declared this practice illegal and banned it. The first human-to-human transfusion was performed by American Dr. Philip Syng Physick. Another significant example in the field of transfusion is James Blundell's blood transfusions from husbands to women with postpartum hemorrhage. Five of the ten transfusions performed by Blundell were successful. The discovery of blood groups by Karl Landsteiner (1901) marks a turning point in the history of transfusion. The A, B, and O blood groups were discovered first, followed by the AB blood group a year later, and the Rh blood group in 1939. The subantigens of the Rh blood group were discovered in 1944. In 1942, Bernstein discovered that blood groups are inherited in humans according to Mendel's laws. In 1946, the Kell, Duffy,

and Kidd blood group systems were discovered. Today, there are over 360 different blood group antigens within 48 blood group system. Landsteiner won the Nobel Prize in 1930 for his discovery of blood groups. In 1907, it was recognized that blood group compatibility between donor and patient was necessary, and the first cross-matching tests were performed by Ruben Ottenberg. With these studies, Ottenberg demonstrated that the O blood group is a universal donor. A milestone in blood banking was the use of sodium citrate, an anticoagulant, in blood transfusions (1914-1915) (Hustin, Agote, Levishon). Prior to this discovery, transfusions were performed by transferring blood from the donor to the patient using syringes or vascular anastomoses. However, with the ability to store blood without clotting, transfusions began to be performed by transferring blood from the donor into a glass bottle containing citrate and then to the patient. The world's first blood bank was established in England in 1921 by Oliver Percy. Later, with the addition of dextrose, phosphate, adenine, and mannitol mixtures, blood could be stored for up to 42 days in four-degree blood refrigerators. In 1930, Russian Shamov performed the first transfusion of cadaver blood to a living person. In the following years, transfusions were performed on 2,500 people using this method. In 1935, the International Society of Blood Transfusion (ISBT) was founded. At its 1937 congress, the ISBT adopted the ABO terminology for blood grouping. In 1950, plastic blood bags were developed. In 1953, blood components were obtained using a refrigerated centrifuge method. In 1968, the first apheresis devices were developed. In Turkey, the first human-to-human transfusion was performed at Haydarpaşa Numune Hospital in 1932. Starting in 1945, small blood units were established in some hospitals. In 1957, Red Crescent blood banks were established first in Ankara and then in Istanbul. In 1983, Law No. 2857 on Blood and Blood Products was enacted in Turkey. In ....., a new blood law and related regulations were enacted in light of scientific developments. Accordingly, Red Crescent Regional Blood Centers and Hospital Transfusion Centers were established. Guidelines were developed. Mandatory screening tests were initiated for diseases transmitted through transfusion, including HBV, syphilis, malaria, HIV, and most recently HCV. In 1996, the Blood Centers and Transfusion Association (KMTD) was established. In 1997, a donor screening form was created and its use was made mandatory throughout Turkey. When KMTD was established, whole blood usage in Turkey was over 95%. KMTD, in collaboration with the Ministry of Health, held 118 educational meetings in 74 provinces, explaining blood components, transfusion indications and complications, and blood bank-clinic relationships. As a result, component usage was adopted throughout the country. Annual courses and conferences were held to keep pace with developments worldwide and in Turkey. Recently, training has focused particularly on Hemovigilance (blood monitoring system) and Patient Blood Management. Currently, components are used not only for component requirements but also for various treatment options. For this purpose, platelets, mesenchymal stem cells, and plasma are used in regenerative medicine and wound healing. In light of scientific and technological developments, the following developments are expected in the field of transfusion in the future: Artificial blood (oxygen-carrying hemoglobin derivatives and engineered products), Universal blood production and conversion of erythrocytes from various blood groups to O-type erythrocytes (cell tissue engineering), digital and automation systems, and artificial intelligence will enable fast and accurate data analysis, reduction of human error, reduction of infection risk, and the use of advanced bioprinters.

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Abstract 014

PLATELET FUNCTION DISORDERS: CONTEMPORARY INSIGHTS AND FUTURE DIRECTIONS

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Platelet function disorders (PFDs) represent a diverse group of qualitative platelet defects that often remain underdiagnosed despite normal platelet counts. Their clinical relevance extends beyond hematology, as undetected PFDs contribute to perioperative bleeding, complications in oncology, and challenges in balancing hemostasis with cardiovascular protection during antiplatelet therapy. For hematologists, timely recognition of these disorders is critical for optimal patient care. Inherited PFDs (IPFDs) include Glanzmann thrombasthenia, Bernard–Soulier syndrome, and RUNX1-associated familial platelet disorder, each characterized by distinct receptor or signaling abnormalities. These range from impaired fibrinogen binding (αIIbβ3 defects) to defective adhesion (GPIb–IX–V complex deficiencies). Syndromic forms such as Wiskott–Aldrich syndrome illustrate the intersection of platelet dysfunction, immune dysregulation, and malignancy predisposition. The spectrum of bleeding can vary considerably. Acquired PFDs are more frequent and clinically impactful. Drugs such as aspirin and P2Y12 inhibitors, uremia, advanced liver disease, myeloproliferative neoplasms, and xtracorporeal circulation all compromise platelet activation or secretion. Given their prevalence, distinguishing pharmacologic platelet inhibition from true dysfunction is a practical challenge in routine hematology. Diagnosis requires a structured, tiered approach. Clinical history and bleeding scores remain the foundation, but must be complemented by laboratory assays. Initial testing should exclude von Willebrand disease, while light transmission aggregometry, flow cytometry, and secretion assays provide functional insights. Next-generation sequencing now allows precise molecular classification of many IPFDs, though accessibility remains uneven. Novel technologies, including microfluidics and whole-blood shear assays, ... Therapeutic strategies depend on etiology and severity. Antifibrinolytics and desmopressin are often sufficient for mild bleeding; platelet transfusions and recombinant factor VIIa are mainstays for severe inherited forms, particularly Glanzmann thrombasthenia complicated by alloimmunization. Hematopoietic stem cell transplantation offers curative potential in selected syndromic disorders. In acquired dysfunction, correcting underlying disease or adjusting medications is essential. Personalized perioperative

pla... Future challenges include diagnostic delays, variability in laboratory availability, and unequal global access to advanced therapies. However, rapid integration of genomics, standardized testing protocols, and emerging hemostatic agents promise to redefine clinical management. Collaborative registries and international networks will be essential to accelerate discovery and translate innovation into equitable care. In conclusion, PFDs embody a nuanced and evolving frontier in hematology. By integrating advanced diagnostics with personalized management strategies, hematologists can reduce morbidity, anticipate complications, and contribute to reshaping the future of bleeding disorder care., Türkiye

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Abstract 015

CNS INVOLVEMENT IN PRIMARY AND SECONDARY ALL AND TREATMENT STRATEGIES

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Abstract Central nervous system (CNS) involvement is an important prognostic factor in acute lymphoblastic leukemia (ALL). Both primary and secondary CNS disease are associated with increased relapse risk and inferior survival. In adults, CNS involvement at diagnosis occurs in 5–10% of cases, with relapse rates of 4–15%. Before the introduction of prophylaxis in the 1980s, CNS relapse rates were as high as 30–40%. The pathophysiology of CNS involvement in ALL is complex, involving early migration of leukemic blasts across the blood –brain barrier, facilitated by adhesion molecules, integrins, and vascular endothelial growth factor (VEGF). VEGF-mediated endothelial disruption increases vascular permeability and plays a pivotal role in the development of posterior reversible encephalopathy syndrome (PRES). Targeting VEGF with monoclonal antibodies has been shown to reduce CNS leukemic burden, suggesting a promising future strategy in both pediatric and adult ALL. The immune-privileged microenvironment of the CNS provides a sanctuary for leukemic cells, supporting their persistence and relapse risk. Traditionally, cerebrospinal fluid (CSF) cytomorphology has been considered the gold standard for assessing CNS involvement. However, this method has low sensitivity and specificity, particularly in samples with low cell counts or technical artifacts. In recent years, flow cytometric immunophenotyping of CSF has demonstrated superior sensitivity, identifying CNS disease more frequently and serving as a strong biomarker for relapse prediction. Minimal CNS involvement not only increases the risk of relapse but is also associated with treatment-related neurotoxicities. Data from the NOPHO group indicate that minimal CNS involvement in pediatric ALL is linked to higher rates of seizures and PRES. Standard treatment approaches continue to rely on intrathecal chemotherapy (methotrexate, cytarabine, corticosteroids) and high-dose systemic agents. However, repeated intrathecal administration and cranial irradiation carry substantial risks of long-term neurotoxicity, highlighting the need for more selective and less toxic strategies. Radiation therapy may still be considered in selected cases, particularly in the context of hematopoietic stem cell transplantation (HSCT). HSCT remains a potentially curative option, especially when preceded by effective cytoreduction with immunotherapy. In conclusion, CNS involvement in ALL represents a biologically and clinically distinct entity requiring tailored management. Primary involvement demands sensitive diagnostics and a careful balance between efficacy and neurotoxicity, while secondary CNS relapse necessitates aggressive multimodal therapy, often incorporating novel immunotherapies and HSCT. Advances in CNS-directed diagnostics and therapeutics are expected to further individualize treatment, aiming to reduce relapse risk while minimizing late toxicities.

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Abstract 016

GAUCHER DISEASE

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Gaucher disease is an autosomal recessive lysosomal storage disorder caused by pathogenic variants in the GBA1 gene on chromosome 1q21, resulting in reduced or absent activity of the enzyme glucocerebrosidase. Consequently, glucosylceramide accumulates primarily in macrophages, leading to the formation of Gaucher cells. The disease most commonly presents with anemia, thrombocytopenia, bleeding tendency, hepatosplenomegaly, fatigue, and skeletal involvement. Bone pathology includes decreased mineral density, bone marrow infiltration, infarction, and fibrosis, all of which contribute to impaired hematopoiesis and cytopenias. From a hematological standpoint, bone marrow aspiration may reveal Gaucher cells with the typical “wrinkled tissue paper” cytoplasm; however, this finding is not pathognomonic and may be seen in other lysosomal storage disorders. Definitive diagnosis therefore requires demonstration of deficient glucocerebrosidase activity or identification of pathogenic GBA1 variants through molecular analysis. In clinical practice, hematological parameters remain essential both for diagnosis and longitudinal monitoring. Complete blood counts provide information on cytopenias and treatment response, while coagulation studies and platelet function tests assist in evaluating bleeding risk. Biomarkers such as chitotriosidase and glucosylsphingosine, together with organomegaly assessment, are increasingly employed in follow-up. Historically, hematopoietic stem cell transplantation was considered a potential curative approach but was limited by high morbidity, mortality, and donor-related challenges. With the advent and efficacy of enzyme replacement therapy and substrate reduction therapy, hematopoietic stem cell transplantation is now reserved only for rare, severe cases without access to standard treatment. In summary, Gaucher disease is a multisystemic disorder with prominent hematological manifestations. Early recognition, accurate diagnosis, and systematic monitoring

underscore the central role of hematology in the comprehensive management of this condition.

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Abstract 017

OPTIMIZATION OF TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA

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In the treatment of chronic myeloid leukemia (CML), first-line tyrosine kinase inhibitor (TKI) choice should be individualized. According to current guidelines, not only risk scores (Sokal, Hasford, ELTS) but also patient-specific factors must be considered. In young patients with high-risk disease, second-generation TKIs (dasatinib, nilotinib, bosutinib) are recommended to achieve deeper and faster responses, thereby increasing the likelihood of future treatment-free remission (TFR). For elderly or low-risk patients, first-generation imatinib remains a safe and effective option.Comorbidities significantly influence drug choice The type of BCR-ABL1 transcript should also be considered; while common variants do not consistently affect outcomes, rare atypical transcripts may influence monitoring and drug selection.Molecular response must be closely monitored with RT-qPCR (international scale, %IS) every three months. Achieving BCR-ABL1 targets of ≤10% at 3 months, ≤1% at 6 months, and ≤0.1% at 12 months (major molecular response, MMR) strongly predicts better long-term outcomes and TFR achievement.BCR-ABL1 >10% at 3 months is considered a warning, while failure to achieve MMR by 12 months is an adverse prognostic sign. Once stable MMR is achieved, monitoring can be extended to every 3–6 months, but in potential TFR candidates or in cases of suspected relapse, more frequent testing is recommended.For patients with primary or secondary resistance, mutation analysis of the BCR-ABL1 kinase domain is strongly recommended. Mutations determine TKI sensitivity and guide therapeutic choices. The T315I “gatekeeper” mutation confers resistance to all first- and second-generation TKIs; in such cases, ponatinib or the novel allosteric inhibitor asciminib is preferred. Other mutations, such as P-loop (Y253H, E255K/V, F359), reduce nilotinib sensitivity but may still respond to dasatinib, bosutinib, or ponatinib. Conversely, mutations like F317L reduce dasatinib efficacy. Thus, therapy must be tailored to the patient’s mutational profile.In cases of intolerance, dose reduction is the first strategy rather than immediate drug substitution.Persistent grade 3–4 toxicities, however, necessitate switching to another TKI. Ponatinib should be initiated at the lowest effective dose, with further reductions once major molecular response is achieved, in order to mitigate cardiovascular risks. The favorable safety profile of asciminib makes it an important option for patients intolerant to multiple TKIs. TFR is feasible in patients with durable deep molecular responses (MR^4 or MR^4.5) after at least 4–5 years of TKI therapy. Eligibility criteria include:chronic-phase disease only, no history of accelerated/blast phase, no prior resistance, and reliable PCR monitoring. Following TKI discontinuation, BCR-ABL1 should be monitored monthly for the first 6–12 months and every 2–3 months thereafter. Loss of MMR (≥0.1%) requires immediate TKI reinitiation, and responses are typically regained quickly. Longer duration of TKI therapy and prolonged deep response increase the likelihood of durable TFR. TKI optimization in CML must be individualized, balancing risk scores, comorbidities, transcript types, molecular milestones, and mutation status. Intolerance can often be managed with dose reduction or switching to alternative TKIs, while TFR remains an attainable and important quality-of-life goal for appropriately selected patients.

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Abstract 018

Mastocytosis

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Mastocytosis is a rare, heterogeneous myeloid neoplasm characterized by clonal proliferation and abnormal accumulation of mast cells. It is classified into cutaneous mastocytosis (CM), systemic mastocytosis (SM), mast cell sarcoma (MCS), and extracutaneous mastocytoma. SM comprises indolent and smouldering variants as well as advanced forms, including aggressive SM and mast cell leukemia. Clinical manifestations range from asymptomatic disease to life-threatening presentations with cytopenia, malabsorption, hepatosplenomegaly, lymphadenopathy, ascites, or osteolytic bone lesions. Mediator-related symptoms such as flushing, diarrhea, and anaphylaxis are common. The KIT D816V gain-of-function mutation represents the central pathogenic driver, leading to ligand-independent KIT activation and uncontrolled mast cell proliferation. Diagnosis relies on WHO and ICC criteria, integrating histopathology, immunophenotyping, and KIT mutation analysis. Management depends on disease subtype: non-advanced forms are treated symptomatically with antihistamines, mast cell stabilizers, and trigger avoidance, while advanced SM requires cytoreductive agents and KIT inhibitors. Midostaurin and avapritinib, potent inhibitors of KIT D816V, have demonstrated significant improvements in mediator-related symptoms, overall survival, and quality of life, whereas imatinib is ineffective in D816V-positive patients but may benefit other KIT genotypes (e.g., K509I, V560G, F522C). Emerging inhibitors such as bezuclastinib and elenestinib show promising efficacy. Allogeneic hematopoietic stem cell transplantation remains the only curative option for aggressive SM. In summary, mastocytosis is a clinically heterogeneous disease in which early-stage treatment focuses on symptom control and anaphylaxis prevention, whereas advanced disease benefits from targeted therapy that has markedly improved prognosis.

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Abstract 019

INNOVATIVE TREATMENTS FOR MYELOFIBROSIS

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Myelofibrosis (MF) is a Philadelphia chromosome-negative chronic myeloproliferative neoplasm characterized by fibrosis in the bone marrow, cytopenias and extramedullary hematopoiesis (1). In the 2022 International Consensus Classification (ICC) and the 5th edition of the World Health Organization (WHO) classification, myelofibrosis is subclassified as prefibrotic and overt primary myelofibrosis (2). The 2022 WHO or ICC criteria should be used for PMF diagnosis. The disease is a clonal stem cell disorder, with the most common genetic mutations are JAK2 V617F (60%), MPL (13.6%) and calreticulin (CALR) (22-35%). Approximately 90% of PMF patients have these mutations, while triple-negative cases have non-driver mutations. Chromosomal abnormalities may also be observed in PMF (1, 3-5). After diagnosis, prognostic risk scoring is performed for the treatment and management of patients. Symptoms are assessed using the myeloproliferative neoplasm symptom assessment form. IPSS, DIPSS, DIPSS Plus, MIPSS70, MIPSS70+v2, and GIPSS are the scoring systems used in PMF. Patients are divided into low/high risk groups, the reatment planning is based on this and patient's symptoms (6-7). The only curative and survival-enhancing treatment method in PMF is allogeneic hematopoietic stem cell transplantation (ASCT), which has high mortality and morbidity rates. In high-risk PMF patients, the treatment decision is primarily shaped by whether the patient is a candidate for ASCT. Treatments other than ASCT are currently aimed more at palliative care, controlling symptoms, and reducing spleen size (2). In patients with low-risk PMF who are asymptomatic, they may be observed only or included in a clinical trial. In symptomatic patients, hydroxyurea, ruxolitinib, or interferon may be used, or enter a clinical trial (2). In PMF, treatment decisions related to symptoms are made by considering anemia, splenomegaly, and constitutional symptoms. Especially in patients with prominent anemia, androgens, prednisolone, lenalidomide, thalidomide, and pomalidomide may be preferred if the patient does not have splenomegaly. New studies are investigating the efficacy of combining ruxolitinib with immunomodulatory agents. The efficacy of erythropoiesis-stimulating agents is limited, and studies show that luspatercept has a low effect in PMF patients. Momelotinib and pacritinib are also other treatment options for these patients and they have positive effects on increasing erythropoietic activity, splenomegaly and constitutional symptoms (2,3,8,9). In patients with anemia, splenomegaly, and constitutional symptoms, momelotinib should be the first choice. If splenomegaly is present alone, hydroxyurea, interferon, or ruxolitinib may be preferred. In patients resistant to ruxolitinib, fedratinib or momelotinib is preferred, while pacritinib is recommended in thrombocytopenic cases (2,10-13). There are studies on many agents planned for use alone or in combination with ruxolitinib in PMF patients. Studies exist on pelabresib, navitoclax, parsaclisib, pegylated interferon alpha, selinexor and luspatarcept in combination with ruxolitinib, and ongoing studies exist on the use of navtemadlin, bomedemstat, RUV120, and imetelstat as single agents in PMF treatment. The preliminary analysis report of these studies at the 2022 American Society of Hematology annual meeting. There is also a preclinical study on monoclonal antibody therapy (INCA 033989) specifically targeting mutant CALR, which has been shown to be effective in thrombocytosis (2).

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Abstract 020

CURRENT TREATMENT APPROACHES IN ELDERLY PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with a median age at diagnosis of 68 years. Estimated 5-year survival differs significantly by age and is <10% for patients older than 60 years (1). Older patients represent highly heterogeneous group and require careful evaluation of comorbidities and frailty. When selecting a treatment plan for older patients, physicians must carefully weigh the risk of adverse events and the potential impact on quality of life (QOL) against possible survival benefits. They are generally unsuitable for curative treatment options such as intensive chemotherapy and hematopoietic stem cell transplantation. Consequently, treatment strategies aimed at improving outcomes and patient compliance continue to evolve. Lower intensity regimens include hypomethylating agents (HMA), such as azacitidine or decitabine, or low-dose cytarabine (LDAC). The introduction of azacitidine in 2012 and decitabine in 2015 significantly transformed the treatment landscape for these patients (2-4). However, HMA monotherapy has been associated with remission rates of 30% or less and survival of under one year (2, 5). As HMA therapy is considered the standard backbone for AML patients unfit for intensive chemotherapy, the majority of phase III trials have been designed to evaluate novel agents in combination with HMA versus HMA alone. In 2018, azacitidine and venetoclax combination was approved for patients with newly diagnosed AML aged ≥75 years old or ineligible for intensive chemotherapy (6). The VIALE-A trial demonstrated improved overall survival (OS) with venetoclax-azacitidine versus plasebo-azacitidine (14.7 and 9.6 months, respectively). Moreover, with long term follow-up, patients achieving CR/CRi with measurable residual disease (MRD) negativity had a longer median OS (34.2 months) compared to those without MRD response (18.7 months) (7). Profound cytopenias accompanied by concurrent infections, bone marrow evaluations during treatment cycles to evaluate cellularity, treatment delays, and prolonged hospitalizations are frequently observed. Nevertheless, due to its manageable side effect profile and a protocol allowing dose and schedule modifications,

venetoclax-azacitidine has become a first-line treatment for elderly AML patients worldwide who are unfit for intensive therapy. Similarly, the VIALE-C trial, which randomized patients to LDAC/venetoclax versus LDAC/placebo, demonstrated improved CR/Cri (48% vs 13%) and OS (8.4 vs 4.1 months) in the venetoclax arm.(8) The combination of HMAs with other agents, together with the establishment of genetic risk profiles and identification existing mutations, underscores the importance of individualized therapy. Among promising agents, Ivosidenib monotherapy or its combination with HMA has shown superiority in OS, CR/Cri, and EFS for IDH- 1mutated de novo AML (AGILE trail) (9). Patients with TP53 alterations, however, continue to experience significantly worse survival outcomes (10). The CD47 monoclonal antibody magrolimab has demonstrated clinical efficacy when combined with azacitidine or with azacitidine/venetoclax (11).Several multiple novel agents and combinations are under investigation, including fromtline FLT3i, oral HMAs, and triplets combining HMA, venetoclax and targeted agents (12). Considering that none of these regimens are curative, it remains a matter of debate whether dynamically assessing patient frailty and using non-intensive therapies can provide a bridge to allogenic stem cell transplantation.

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Abstract 021

HEPATIC VENO-OCCLUSIVE DISEASE

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Hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (VOD/SOS), is a severe complication which usually occurs due to conditioning regimens used for hematopoietic stem cell transplantation (HSCT). It is characterized by hepatomegaly, hyperbilirubinemia, ascites and right upper quadrant pain and usually develops within the first 20-30 days after transplant. It is accepted to be a result of endothelium and hepatocyte damage caused by chemotherapy and radiotherapy of the conditioning regimen. Current studies suggest that the primary site of toxic injury is the hepatocyte, subsequently followed by damage to the central veins in zone 3 of the hepatic acinus and sinusoidal endothelial cells. Early changes include fibrin deposition, venous occlusion, progressive venous micro-thrombosis and sinusoidal occlusion. These changes lead to severe clinical problems including portal hypertension, hepatorenal syndrome and hepatocellular necrosis, which may ultimately result in multiorgan dysfunction (MOD) and death. Previously, the Baltimore and Seattle criteria were used for VOD/SOS diagnosis; however, the limitations of these criteria for VOD/SOS diagnosis (especially in anicteric children and those who have symptom onset after 21 days), led to establishment of the EBMT (European Society for Blood and Marrow Transplantation) 2017 VOD/SOS criteria which evaluates pediatric and adult patients separately. The EBMT 2017 criteria is comprised of laboratory and clinical findings such as transfusion-resistant thrombocytopenia, unexplained weight gain, hepatomegaly, ascites and elevation in bilirubin levels. Despite the advantages brought by this criteria, it is still difficult to diagnose VOD/SOS. Several approaches to prevent its development of VOD/SOS were put forth, including individualized dosing of chemotherapy, reduction of the intensity of the conditioning regimens, close monitoring of the levels of busulfan and cyclophosphamide and also reducing their use. Prostaglandin E1 and tissue-plasminogen activator with or without concurrent heparin have been explored in VOD/SOS treatment; however, these approaches have shown little success, as is the case with supportive treatments. Defibrotide (DF) emerged as the most promising medication for both prophylaxis and treatment in patients with VOD/SOS. DF is a single-stranded polydeoxyribonucleotide with anti-inflammatory, anti-ischemic, anti-thrombotic, and thrombolytic properties in addition to its protective effects on endothelial cells. DF is approved for adult and pediatric patients with VOD/SOS with renal or pulmonary dysfunction after HSCT in the United States, and for severe VOD/SOS post-HSCT in patients aged >1 month in the European Union. In addition, several studies have examined DF prophylaxis can reduce the incidence of VOD/SOS in high-risk patients. Although the literature is unanimous for the use of DF in patients diagnosed with VOD/SOS, its use as a prophylactic agent has not been approved; even though many studies have reported reduced VOD/SOS incidence and severity with DF prophylaxis.

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Abstract 022

TREATMENT OF RELAPSED/REFRACTORY DLBCL

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Fifteen percent of DLBCL patients are refractory to the first line of therapy, while 25% experience relapse after response. The management of these patients is planned according to the patient's suitability for high-dose chemotherapy and whether the disease is refractory/early relapse (BSH guideline, 2025). While HSCT provides long-term survival in patients who are suitable for treatment and are chemosensitive (CORAL study), long-term survival compared to HSCT has been achieved in non-chemosensitive patients with CAR-T therapies ZUMA-7 and TRANSFORM studies. CAR-T therapies are approved as first-line treatment for patients with refractory/early relapse. However, some r/r DLBCL patients are not suitable for HSCT and CAR-T treatments due to age and comorbidities, and some are resistant to these treatments or relapse after these treatments. Tafasitamab – Lenalidomide combination is approved for patients with relapsed DLBCL, NOS who are not eligible for HSCT or CAR-T therapies (L-MIND study). The efficacy of Glofitamab – GemOx has also been proven in patients with relapsed DLBCL, NOS who are not suitable for HSCT or CAR-T therapy in the STARGLO study. Loncastuximab is a single-agent ADC used in r/r DLBCL. Due to its cumulative toxicity, long-term use is not suitable, and a one year treatment was planned in the LOTIS-

2 study. This study also included a significant number of patients with refractory and high-grade lymphoma, making it one of the limited treatment options in this high-risk patient group. Polatuzumab-BR was compared with BR in a phase II trial. Pola-BR demonstrated superiority in r/r DLBCL patients who were not suitable for HSCT and CAR-T therapies, and it should be considered an option, particularly in patients with < 60 years, IPI<2, ABC phenotype, non-bulky, and relapsed patients.Glofitamab and epcoritamab are a treatment option for r/r DLBCL patients. CAR-T therapies are costly and have high side effects, leading to treatment delays, especially in patients with rapid progression, and requiring specialized centers. BiTE therapies, with fewer side effects, lower costs, and easier access, may be an alternative for patients unable to access CAR-T therapies. The inclusion of high-grade lymphoma cases in trials provides an alternative in this group with limited treatment options. Its use will also increase as an important part of combination treatments. The XPO1 inhibitor Selinexor has been tested in SADAL study in patients with R/R DLBC lymphoma who have no treatment options. Although response rates are low, it may increase the effectiveness of these treatments as part of combination therapies. The SADAL study demonstrated greater efficacy in the GCB phenotype. Since there are no randomized studies of TL, Loncastixumab, BiTE treatments, Pola-BR and XPO1 inhibitors with each other, the choice of these treatments can be determined based on subgroup analyses in the studies. Allogeneic stem cell transplantation, a treatment with high NRM and morbidity, remains an alternative treatment for DLBCL patients. Although prospective studies have not compared it with CAR-T therapies, retrospective studies have not found any significant differences (Blood 2020, Dreger et al)

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Abstract 023

MODULATION OF INEFFECTIVE ERYTHROPOIESIS IN THALASSEMIA

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Introduction: Thalassemia comprises inherited disorders characterized by reduced globin chain synthesis, leading to an imbalance between α- and β-globin chains. Ineffective erythropoiesis (IE) is the long-term outcome of a complex interaction of molecular mechanisms, primarily involving the bone marrow and its intricate bidirectional communication with the liver, spleen, and gut, ultimately leading to the production of pathological RBCs. IE is the primary driver of thalassemia and the main contributor to most of the clinical manifestations of this disorder. In patients with β-thalassemia, the bone marrow contains approximately six times more erythroid precursors than in healthy individuals, and the rate of apoptotic cell death is nearly four times higher than normal (1). In thalassemia, the altered differentiation of erythroid progenitors appears to worsen IE, coupled with increased proliferation and apoptosis, ultimately leading to anemia, extramedullary hematopoiesis, splenomegaly, and systemic iron overload. Therefore, advanced characterization of the molecular foundations of these complex processes is crucial for developing effective disease-modifying therapies. Therapeutic approaches seek to modulate pathways that reduce iron absorption (for example, activating hepcidin through Tmprss6 antisense oligonucleotides—ASOs) or pathways that increase erythropoiesis (e.g., erythropoietin [EPO] administration or modulating red blood cell (RBC) synthesis via control of transferrin receptor 2 [Tfr2]) or activin II Receptor Ligand Traps (2). **Pathophysiology of Ineffective Erythropoiesis:** Erythropoiesis is a tightly regulated process producing billions of functional red blood cells (RBCs) daily. In thalassemia, this process is disrupted. The hallmark is the substantial expansion of early-stage erythroid precursors in the bone marrow in response to elevated erythropoietin, coupled with premature death of late-stage precursors, resulting in a low output of mature RBCs. Therapeutic Strategies Targeting IE Building on the mechanistic understanding of IE, therapies aim to address the underlying pathology rather than merely treating anemia or iron overload. 1. Activin II Receptor Ligand Traps Luspatercept is a leading therapeutic that traps TGF-β superfamily ligands (including GDF11 and Activin A). By sequestering these ligands, luspatercept prevents receptor binding, promoting terminal erythroid maturation and reducing IE. Clinical trials show that luspatercept significantly increases hemoglobin and reduces transfusion requirements in β-thalassemia. 2. Targeting Iron Metabolism Novel agents modulate iron metabolism to reduce iron overload and improve erythropoiesis. Ferroportin inhibitors (e.g., VIT-2763) aim to block iron export from cells. Other strategies aim to enhance hepcidin activity or inhibit erythroferrone (ERFE) (4). 3. Gene Therapy and Gene Editing Emerging approaches include gene-based strategies to correct globin imbalance or regulate erythropoiesis, with potential to reduce IE. 4. Combination and MicroRNA-Targeting Approaches indicates that combining Tmprss6-ASO with EPO or Tfr2 haploinsufficiency yields superior outcomes in Hb and splenomegaly reduction, compared with single therapies. Additionally, targeting dysregulated microRNAs may provide supplementary therapeutic avenues (5). **Conclusion:** IE remains a central feature of β-thalassemia, driven by iron dysregulation, oxidative stress, and impaired erythroid maturation via TGF-β signaling. Luspatercept and other activin receptor ligand traps have demonstrated clinical benefit. Emerging combinations that couple iron-restriction strategies with erythropoietic stimulation show promise for enhanced efficacy. Ongoing research is essential to optimize regimens, identify responders, and translate preclinical findings into durable clinical solutions.

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Abstract 024

STEM CELL MOBILIZATION: AUTOLOGOUS AND ALLOGENEIC

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In autologous HSCT, stem cells are collected from the patient following prior exposure to chemotherapy. The standard mobilization approach is granulocyte colony-stimulating factor (G-CSF) alone or in combination with chemotherapy, such as cyclophosphamide. While chemotherapy-based mobilization may increase CD34+ yields and contribute to disease cytoreduction, it is associated with increased infectious and hematologic complications. Plerixafor, a CXCR4 antagonist, has emerged as a highly effective adjunct in patients with poor mobilization, particularly those heavily pretreated or with impaired marrow reserve. Predictors of mobilization failure include advanced age, extensive prior therapy, and low baseline blood counts. In allogeneic HSCT, stem cells are obtained from healthy donors. G-CSF administration for 4 −5 days remains the standard strategy, providing sufficient peripheral blood stem cell (PBSC) yields and enabling rapid hematopoietic recovery. Compared with bone marrow harvest, PBSC collection is less invasive and results in higher CD34+ cell counts, but is associated with an increased incidence of chronic graft-versus-host disease. Plerixafor has been investigated as an alternative or adjunct in specific donor populations with inadequate mobilization, though its use remains limited. Donor safety, tolerability of mobilization agents, and long-term health implications are major considerations in the allogeneic context. Despite distinct indications, both autologous and allogeneic mobilization share key challenges: ensuring adequate stem cell yield, minimizing toxicity, and reducing the need for multiple apheresis procedures. Recent advances have improved mobilization outcomes, yet the problem of poor mobilizers persists. Novel mobilizing agents, optimization of dosing schedules, and risk-adapted strategies are under evaluation to enhance efficiency and safety. Stem cell mobilization remains a critical determinant of HSCT success. Autologous mobilization is challenged by prior therapy and patient-related factors, whereas allogeneic mobilization prioritizes donor safety and graft quality. The incorporation of agents such as plerixafor has significantly expanded the mobilization armamentarium. Future directions include individualized mobilization protocols, novel pharmacologic combinations, and strategies aimed at improving long-term transplant outcomes.

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Abstract 025

LABORATORY EVALUATION IN MYELOMA: WHICH TESTS SHOULD BE PREFERRED DURING DIAGNOSIS AND FOLLOW-UP?

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of abnormal plasma cells, production of monoclonal immunoglobulins, and organ dysfunction, often defined by the CRAB criteria (hypercalcemia, renal impairment, anemia, and bone disease). Laboratory testing is central to diagnosis, risk assessment, and monitoring during therapy and remission. **Baseline Evaluation at Diagnosis: Hematology and Biochemistry** - CBC with differential → detection of anemia, leukopenia, or thrombocytopenia. - Biochemistry panel → creatinine, urea, calcium, albumin, LDH. - β2-microglobulin and albumin → incorporated into the Revised International Staging System (R-ISS). - CRP may reflect disease activity (IL-6 driven). **Monoclonal Protein Studies:** - Serum protein electrophoresis (SPEP): quantifies the M-spike. - Urine protein electrophoresis (UPEP, 24 h): detects Bence Jones proteinuria. - Immunofixation (serum and urine): confirms the type of heavy and light chain. - Serum free light chain (sFLC) assay: critical for light-chain, non-secretory, and oligo-secretory myeloma. **Bone Marrow Examination** - Morphology: percentage of plasma cells. - Multiparameter flow cytometry: demonstrates clonality and immunophenotype. - Cytogenetics/FISH: identifies high-risk abnormalities (del[17p], t[4;14], t[14;16]) that influence prognosis. **Laboratory Evaluation During Follow-Up Routine Monitoring** - M-protein quantification (SPEP/UPEP): mainstay of monitoring. - Immunofixation: required to confirm complete response. - sFLC assay: sensitive tool for relapse, especially in light-chain disease. - CBC, renal function, calcium, LDH, β2-microglobulin: routine for treatment toxicity and disease burden. **Advanced Monitoring** - Minimal Residual Disease (MRD): assessed via next-generation flow cytometry or next-generation sequencing. MRD negativity correlates with superior survival and is increasingly used as a response endpoint. - Mass spectrometry and liquid biopsy are promising future tools for detecting residual disease with high sensitivity. **Preferred Tests in Clinical Practice** - At diagnosis: a comprehensive panel including SPEP, UPEP, serum/urine immunofixation, sFLC, bone marrow studies (with cytogenetics/FISH), and advanced imaging is essential. - During follow-up: routine monitoring can be streamlined to SPEP and sFLC, supplemented by basic hematology and chemistry. UPEP is reserved for patients with baseline significant proteinuria. - In specialized centers: MRD testing should be incorporated, especially in clinical trials, to refine response evaluation. **Conclusion** Laboratory evaluation remains the cornerstone of myeloma diagnosis and long-term management. While a full diagnostic panel is indispensable at baseline, streamlined monitoring with SPEP and sFLC is sufficient in most patients during follow-up. Advanced tools such as MRD assessment and mass spectrometry are reshaping the landscape, providing unprecedented sensitivity in disease monitoring. The optimal combination of tests ensures accurate diagnosis, appropriate risk stratification, and effective treatment monitoring in multiple myeloma.

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Abstract 026

ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE: INSIGHTS INTO ETIOPATHOGENESIS

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Graft-versus-host disease (GvHD) remains one of the most significant complications following allogeneic hematopoietic stem cell transplantation (HSCT), contributing substantially to morbidity and mortality despite advances in conditioning regimens, donor selection, and prophylactic strategies. Understanding the etiopathogenesis of acute and chronic GvHD is essential for improving risk stratification, tailoring prophylaxis, and designing novel targeted therapies. Acute GvHD (aGvHD) typically develops within the first 100 days post-transplant and arises from a multi-step immunopathological cascade. Conditioning regimens induce extensive tissue damage, releasing danger-associated molecular patterns (DAMPs) and pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which activate host antigen-presenting cells (APCs). Activated APCs prime donor T cells, leading to the expansion of alloreactive effector T cells. These T cells infiltrate target organs—most prominently the skin, gastrointestinal tract, and liver—mediating tissue destruction via cytotoxic molecules (perforin, granzyme) and further amplification of the inflammatory milieu. Regulatory T cell (Treg) dysfunction, microbial translocation from intestinal damage, and loss of epithelial integrity amplify these effects. Emerging evidence highlights the contribution of innate immune cells, the microbiome, and cytokine networks in shaping the severity and trajectory of aGvHD. Chronic GvHD (cGvHD), in contrast, is a complex, multifactorial syndrome that shares features with autoimmune and fibrotic disorders. It generally manifests beyond day 100, although temporal overlap with aGvHD is increasingly recognized. The pathogenesis of cGvHD involves sustained immune dysregulation, including aberrant thymic recovery, impaired central and peripheral tolerance, and persistence of autoreactive and alloreactive T and B cells. B cell hyperactivity, autoantibody production, and activation of germinal center–like reactions contribute to chronic inflammation. Crosstalk between T follicular helper cells, pathogenic B cells, and fibroblasts drives tissue remodeling and fibrosis. Key target organs include the skin, lungs, liver, eyes, and mucous membranes, with progressive organ dysfunction severely impacting quality of life. Recent studies underscore the importance of profibrotic cytokines (e.g., TGF-β, PDGF) and aberrant tissue repair pathways in perpetuating cGvHD. Advances in molecular and cellular profiling have provided novel insights into both acute and chronic disease mechanisms. High-throughput sequencing, proteomic analyses, and microbiome studies have identified candidate biomarkers for early diagnosis, disease monitoring, and therapeutic stratification. These findings are paving the way toward precision medicine approaches, including selective inhibition of JAK/STAT pathways, B cell depletion strategies, adoptive Treg therapy, and microbiota modulation. Despite these promising developments, challenges remain in balancing graft-versus-host effects with graft-versus-leukemia (GvL) activity, underscoring the need for therapeutic interventions that preserve antitumor immunity while mitigating alloreactivity. In summary, both acute and chronic GvHD arise from complex, overlapping yet distinct immunopathological processes that reflect dysregulated interactions between donor-derived immune cells, host tissues, and the microenvironment. Ongoing research continues to refine our understanding of GvHD biology, which is critical for developing innovative therapies and improving long-term outcomes in allogeneic HSCT recipients.

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Abstract 027

CHELATION THERAPY IN THALASSEMIA

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Thalassemia major is a severe hereditary hemoglobinopathy characterized by ineffective erythropoiesis and transfusion-dependent anemia. Regular red blood cell transfusions remain the cornerstone of supportive treatment; however, they inevitably result in progressive iron overload due to the absence of physiological mechanisms for iron excretion. Iron accumulation predominantly affects the liver, heart, and endocrine organs, leading to cirrhosis, cardiomyopathy, arrhythmias, and multiple endocrinopathies. Consequently, iron chelation therapy constitutes a fundamental component of long-term management in patients with thalassemia major. The first clinically available chelating agent was deferoxamine (DFO) promotes urinary and fecal iron excretion. Long-term use of DFO has significantly improved survival by reducing iron-related cardiac mortality. Nevertheless, its administration—via subcutaneous or intravenous infusion for 8–12 hours on most days of the week—poses substantial challenges to adherence, particularly in pediatric and adolescent populations. To address these limitations, oral chelators were developed. Deferiprone (DFP) is effective in reducing myocardial iron burden and preventing cardiac dysfunction, although it carries the risk of agranulocytosis, requiring strict hematological monitoring. Deferasirox (DFX) has demonstrated efficacy in maintaining negative iron balance and reducing hepatic iron concentration, thereby improving adherence and overall patient satisfaction. In cases of severe or refractory iron overload, combination therapy has been employed. The concurrent use of DFO and DFP exhibits synergistic effects, particularly in the clearance of cardiac iron. Emerging data also support the potential benefits of combining DFO with DFX in select clinical scenarios. These strategies allow for individualized treatment based on iron burden, organ involvement, and patient tolerance. Monitoring of chelation efficacy is essential. Serum ferritin is widely utilized as a surrogate marker of body iron, though it may be confounded by inflammation or hepatic injury. T2-star magnetic resonance imaging provides a more reliable and non-invasive quantification of cardiac and hepatic iron, enabling timely therapeutic adjustments and prevention of irreversible organ damage. Chelation therapy has transformed the prognosis of thalassemia major, shifting the natural history from early mortality to survival into adulthood with improved quality of life. Nevertheless, challenges persist, including variability in drug availability, treatment adherence, and adverse event profiles. Future perspectives include optimization of chelation regimens, development of safer agents, and curative

approaches such as gene therapy and hematopoietic stem cell transplantation, which may ultimately reduce or eliminate the lifelong requirement for transfusion and chelation.

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Abstract 028

RELAPS/REFRACTORY MANTLE CELL LYMPHOMA TREATMENT

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Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL) characterized by the overexpression of cyclin D1 due to the chromosomal translocation t(11;14)(q13;q32). Despite advances in therapeutic approaches, MCL remains a significant clinical challenge, particularly in relapsed and refractory (R/R) cases. Relapse occurs when the disease reappears after an initial response to therapy, while refractory MCL refers to cases where the disease fails to respond adequately to standard treatment regimens. Both conditions are associated with poor prognosis and limited treatment options, reflecting the need for novel therapeutic strategies. Relapsed MCL is characterized by clonal evolution and the emergence of more aggressive phenotypes, including resistance to previously administered therapies. Refractory cases, on the other hand, exhibit intrinsic or acquired resistance mechanisms, such as mutations in the B-cell receptor (BCR) signaling pathway, TP53 abnormalities, and alterations in DNA damage response genes. Recent therapeutic advances have improved outcomes for R/R MCL patients. Targeted therapies, including Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib, have demonstrated significant efficacy by disrupting BCR signaling. Ibrutinib, the first BTK inhibitor approved for R/R MCL, has shown durable responses in clinical trials, although resistance to BTK inhibitors is a growing concern. Lenalidomide, an immunomodulatory agent, and venetoclax, a BCL-2 inhibitor, have also shown promise in heavily pretreated patients. Furthermore, chimeric antigen receptor (CAR) T-cell therapy targeting CD19, such as brexucabtagene autoleucel, represents a groundbreaking approach for patients with chemorefractory disease. While these therapies offer hope, their application is often limited by adverse events, accessibility, and high costs. Biological heterogeneity within MCL further complicates the management of R/R cases. The proliferation index (Ki-67), TP53 mutation status, and the presence of blastoid or pleomorphic variants are critical prognostic factors influencing treatment decisions. Additionally, the integration of next-generation sequencing (NGS) and molecular profiling enables the identification of actionable mutations and pathways, paving the way for personalized medicine. Despite these advancements, challenges remain in optimizing the sequencing of therapies, managing toxicities, and overcoming resistance. Clinical trials continue to explore novel agents, including bispecific antibodies, proteasome inhibitors, and checkpoint inhibitors, as well as combination strategies to enhance efficacy and minimize resistance. Moreover, the role of minimal residual disease (MRD) monitoring in guiding treatment remains an area of active investigation. In conclusion, relapsed and refractory MCL represents a complex clinical entity with significant unmet needs. While recent therapeutic innovations have improved outcomes, the heterogeneity of the disease necessitates a personalized approach to treatment. Future research should focus on elucidating resistance mechanisms, refining therapeutic strategies, and improving access to novel treatments to enhance the prognosis for this challenging patient population.

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Abstract 029

SUMMARY: OPTIMIZATION OF TREATMENT IN PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL)

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Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is a high-risk subtype of ALL, historically associated with poor outcomes. The introduction of tyrosine kinase inhibitors (TKIs) has dramatically changed its therapeutic landscape. Current optimization strategies focus on integrating TKIs with chemotherapy, immunotherapy, and, in selected cases, allogeneic stem cell transplantation (allo-HSCT), while tailoring treatment according to minimal residual disease (MRD) status and patient characteristics. Induction therapy now commonly consists of a TKI combined with corticosteroids and/or reduced-intensity chemotherapy, aiming to achieve remission with lower toxicity compared to traditional intensive regimens. Commonly used TKIs include imatinib, dasatinib, and ponatinib, with the latter being preferred in cases with the T315I mutation due to its broader activity. Consolidation therapy is designed to eradicate residual disease. Achieving MRD negativity is the primary goal, as it strongly predicts long-term survival. Strategies include continued TKI administration combined with short chemotherapy blocks or novel agents such as blinatumomab, a CD19-targeted bispecific T-cell engager. Allo-HSCT remains an important option for younger, fit patients, especially those with persistent MRD or high relapse risk. However, accumulating evidence suggests that deep and durable remissions may be achievable without transplantation when combining TKIs with immunotherapies. Maintenance therapy typically involves prolonged TKI treatment, often for at least two to three years, with ongoing MRD monitoring to guide adjustments. In the relapsed or refractory setting, therapeutic options expand to include next-generation TKIs such as ponatinib, immunotherapies including blinatumomab and the CD22-targeted antibody-drug conjugate inotuzumab ozogamicin, and chimeric antigen receptor T-cell (CAR-T) therapies targeting CD19, which have shown promising results in heavily pretreated patients. The core principles of treatment optimization in Ph+ ALL include: 1. MRD-directed decision-

making, as MRD negativity is the strongest predictor of favorable outcomes. 2. Reducing treatment-related toxicity, particularly in elderly or frail patients, by minimizing intensive chemotherapy and incorporating TKIs with immunotherapy. 3. Individualizing the role of allo-HSCT, reserving it primarily for patients with persistent MRD, high-risk features, or early relapse. 4. Integrating novel agents such as blinatumomab, inotuzumab, and CAR-T therapies earlier in the treatment course to improve long-term survival and potentially reduce the need for transplantation. In summary, modern management of Ph+ ALL emphasizes TKI-based regimens, MRD-guided therapeutic decisions, and the incorporation of targeted immunotherapies. While allo-HSCT remains relevant for selected patients, emerging evidence suggests that long-term remission may increasingly be achievable without transplantation, especially when potent TKIs and immunotherapies are combined. This evolving paradigm reflects a shift toward personalized, less toxic, and more effective treatment strategies for Ph+ ALL.

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Abstract 030

CRS AND ICANS MANAGEMENT

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CRS (Cytokine Release Syndrome) CRS is an exaggerated systemic inflammatory response triggered by treatments such as Bispecific Antibodies (BsAb), which activate T cells and cause the release of inflammatory cytokines. CRS symptoms range from mild flu-like symptoms to severe multiorgan failure. Symptoms: Fever, hypotension, hypoxia, tachycardia, organ dysfunction. Physical Examination - Temperature, blood pressure, pulse oximetry or arterial blood gas (or mixed venous blood gas/O2 saturation), skin, heart, and lung examination Laboratory Tests - Complete blood count with differential diagnosis; Coagulation (PT/PTT, fibrinogen, fibrin D-dimer); Chemistry (serum electrolytes, kidney and liver function, uric acid, lactate, LDH; C-reactive protein and ferritin (inflammation); Microbiological tests, especially in neutropenic patients (blood and urine cultures); cardiac markers are clinically indicated. Do not await laboratory results. Laboratory findings: Cytopenias, elevated creatinine, elevated liver enzymes, irregular coagulation parameters, elevated C-Reactive Protein • Management of CRS (see Management Section below) does not require laboratory testing and should not be delayed pending laboratory results. **Management by grade:** • Grade 1: Support only (antipyretic, fluid support, close monitoring). • Grade 2: Low-dose oxygen, IV fluids, low-dose vasopressors if necessary. Tocilizumab may be initiated. • Grade ≥3: High-dose oxygen, intensive care support, vasopressor requirement. **Medical Treatment:** • First choice: Tocilizumab (anti-IL-6 monoclonal antibody) • If no response: Corticosteroids (e.g., dexamethasone, methylprednisolone) are added. • Other support: Antibiotic prophylaxis/treatment, electrolyte balance, close monitoring of organ functions. **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** Neurological toxicity caused by the inflammatory effects of cytokines released after BsAb treatment results in disruption of the blood-brain barrier and accumulation of inflammatory cytokines in the central nervous system. ICANS is a diagnosis of exclusion after other possibilities have been excluded. Neurological toxicity develops after immune activation. Flu-like symptoms: Fever (≥38.0°C/<100.4°F) (unattributable to another cause); nausea; fatigue; headache; rash; diarrhea, arthralgia, myalgia Hypotension Systemic inflammatory response syndrome (circulatory collapse; vascular leakage; peripheral and/or pulmonary edema; renal failure; cardiac dysfunction; multiorgan failure) Respiratory symptoms: cough; tachypnea; hypoxia, ARDS Rash and Urticaria (allergic reaction) Low-grade CRS is common and high-grade is rare **Diagnosis:** • ICANS should be suspected if there are new or worsening neurological symptoms following recent immune effector cell (IEC) therapy, such as CAR-T cell therapy or BsAb therapy. • Initial symptoms may be mild, such as loss of attention and/or slurred speech or tremors. • Further evaluation to investigate other possible causes should include review of concomitant medications or recent use of CNS-active drugs (e.g., opiates, benzodiazepines). Investigation may include a head CT or brain MRI, and a lumbar puncture to investigate infectious causes. Management: It may occur with or without CRS. **Treatment:** • Grade 1 (mild): Close neurological monitoring, supportive care. • Grade ≥2: Corticosteroids (Dexamethasone or Methylprednisolone) are initiated. • Tocilizumab is generally not effective for ICANS (because the IL-6 antibody does not cross the blood-brain barrier well). • Seizure prophylaxis/treatment: Levetiracetam is preferred. • Intensive care support in severe cases.

Keywords: CRS, ICANS, management, treatment.

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Abstract 031

GRAFT VERSUS HOST DISEASE PROPHYLAXIS

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Graft−versus−host disease (GvHD) is an important complication that can be observed after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The incidence of Acute GvHD (aGvHD) is around 30%-50% in HLA fully matched allo-HSCT. aGvHD is also common in haploidentical and matched unrelated donor transplantation. The mechanism underlying tissue damage in aGvHD is massive inflammatory cytokine secretion. Proinflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6] are seen, as well as the increased expression of the receptor repertoire (pattern recognition receptors) on antigen-presenting cells. The most important risk factor for GvHD is HLA mismatch. Other risk factors include sex disparity between donor and recipient, the intensity of the conditioning regimen, increased age, multiparous female donors, ineffective GvHD prophylaxis, and the source of the graft. A study showed that aGvHD was

significantly more common with total body irradiation involving a myeloablative regimen and peripheral stem cell transplantation from a fully matched related donor. GvHD can be acute or chronic based on the clinical presentation and its occurrence after or before 100 days after allo-HSCT. aGvHD may occur beyond this arbitrary cut-off of 100 days. The widely accepted National Institutes of Health consensus criteria havebeen used to classify GvHD. GvHD is divided into four subclasses: 1) Classic aGvHD: Diagnostic and distinctive features of chronic GvHD (cGvHD) are absent. Clinical features of aGvHD and present within 100 days of allo-HSCT or donor lymphocyte infusion (DLI). 2) Persistent and/or recurrent late-onset aGvHD: Features of classic aGvHD without diagnostic manifestations of cGvHD occurring beyond 100 days after allo-HSCT or DLI. 3) Classic cGvHD: Present at any time after HSCT. Diagnostic and distinctive features of cGvHD are present without aGvHD. 4) Overlap syndrome; Features of both cGvHD and aGvHD can be seen. The most commonly affected organsa are:Skin,eyes,oral mucosa,liver,GIS tract,genital organs,lungs,joints and fascia. The most important step for the prevention of GvHD is minimizing risk factors with donor selection and a preparative regimen. GvHD prophylaxis is essential for patients undergoing allo-HSCT. Guidelines for GvHD prophylaxis have been proposed by the European Group for Blood and Marrow Transplantation and European LeukemiaNet . The most common form of GvHD prophylaxis has been the combination of cyclosporine and a short course of methotrexate, which demonstrated improved survival compared to either drug alone. Both cyclosporine and tacrolimus decreased the proliferation of T-lymphocytes . Tacrolimus plus methotrexate is better in decreasing the risk for aGvHD than the combination of cyclosporine and methotrexate, particularly in unrelated HSCT. Both regimens are considered as cornerstones for most GvHD prevention strategies for patients receiving allo HSCT. The effects of the addition of corticosteroids to the combination of cyclosporine and a short course of methotrexate have shown conflicting results. Calcineurin inhibitors and Ruxolitinib, a JAK 1/2 inhibitor, are also used as prophylactic treatment. Unfortunately, there is no standard indication or timing for the initiation of therapy for GvHD. Many agents have been tested alone or in combination with corticosteroids. Extracorporeal photopheresis (ECP), mycophenolate mofetil, sirolimus, everolimus, rituximab, and ibrutinib are available options.

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Abstract 032

CHRONİC LYMPHOCYTIC LEUKEMIA (CLL): IMMUNOGENETICS AND DIAGNOSIS

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CLL is a monoclonal proliferation of mature B lymphocytes defined by an absolute clonal count $\geq 5 \times 10^9$/L in blood. CLL is clinically heterogeneous: some patients remain asymptomatic for years, whereas others need multiple lines of therapy. BCR biology and immunogenetics. A central driver of CLL biology is B-cell receptor (BCR) signaling. Compared with normal B cells, CLL cells display low IgM expression, variable responses to antigen, and tonic activation of anti-apoptotic pathways. Gene-expression and tissue array studies show up-regulation of BCR-pathway genes in lymph nodes and marrow versus blood, highlighting microenvironmental homing. The IGHV mutation status is a key immunogenetic marker: about 60% of patients have IGHV mutated ≥2% from germline (typically indolent course), while ∼40% have unmutated IGHV (<2%), associated with faster progression and shorter survival before the era of BCR-targeted therapies. Roughly 30% of cases carry stereotyped BCRs; certain stereotyped subsets (e.g., 1 and 2) predict higher-risk disease. Cytogenetic lesions. Recurrent abnormalities identified by FISH (and, when needed, stimulated metaphase karyotype) include del(13q14.3) (most common; favorable when isolated), trisomy 12 (intermediate risk), del(11q22.3) involving ATM (bulky nodes, aggressive disease in younger patients), and del (17p13.1) affecting TP53 (worst prognosis, poor response to traditional chemotherapy). Complex karyotype (≥3 abnormalities) adversely impacts time to treatment and overall survival. Because clonal evolution can occur even without therapy, FISH (± cytogenetics) should be reassessed before each line of treatment, particularly to detect new del(17p). Gene mutations and microRNAs. CLL genomes are relatively simple (≈20 nonsynonymous changes and ≈5 structural lesions on average) and lack a unifying driver. Recurrently mutated genes include SF3B1, NOTCH1, MYD88, ATM, and TP53. NOTCH1 mutations (∼15%) often co-occur with trisomy 12 and may confer reduced sensitivity to anti-CD20 antibodies and increased risk of Richter transformation; SF3B1 relates to DNA-damage responses; TP53 mutations rise from ∼5% in early untreated disease to ∼40% in advanced disease, frequently coexisting with del(17p). ATM mutations (10–15%) often accompany del(11q). MYD88 mutations are enriched in IGHV-mutated CLL and associate with a more indolent course. Non-coding alterations are also relevant: del(13q14.3) deletes the miR-15/16 cluster, derepressing anti-apoptotic programs (e.g., BCL2); loss of miR-181a and over-expression of miR-155 further support leukemic survival. Immune dysregulation. Beyond the malignant clone, CLL features innate and adaptive immune defects: reduced complement, qualitative neutrophil and NK-cell dysfunction, $CD4^+$ T-cell exhaustion with impaired cytotoxicity, Th1→Th2 polarization, and T-regulatory expansion. Hypogammaglobulinemia is common (≈85% over the disease course), with low IgG/IgA correlating with infections. Diagnosis and differential. CLL is most often detected incidentally via lymphocytosis. Flow cytometry confirms a characteristic phenotype—$CD19^+$, CD20 (dim), $CD22^+$, $CD23^+$, $CD200^+$, $CD5^+$, with dim surface Ig (kappa or lambda). When blood clonal B cells are $\geq 5 \times 10^9$/L, no additional testing is needed to confirm CLL. Take-home. Integrating flow cytometry, cytogenetics (FISH/karyotype), and targeted sequencing with IGHV status and non-coding lesions underpins modern risk stratification and sharpens diagnostic certainty in CLL.

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Abstract 033

INTERPRETATION OF GENETIC TESTING IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Chronic myeloproliferative neoplasms (MPNs) represent a group of clonal hematopoietic stem cell disorders characterized by uncontrolled proliferation of one or more myeloid lineages. The discovery of recurrent driver mutations has transformed the diagnostic, prognostic, and therapeutic landscape of these disorders. This article reviews the clinical relevance of genetic testing in MPNs, with a focus on driver and additional mutations, and their implications for patient management. **Introduction:** Chronic myeloproliferative neoplasms, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are defined by clonal proliferation of hematopoietic progenitors. The molecular era has revealed the critical role of somatic mutations in their pathogenesis. Genetic testing has now become integral to diagnosis, risk stratification, and therapeutic decision-making. Driver Mutations JAK2 - JAK2 V617F mutation is present in approximately 95% of PV cases and 50–60% of ET and PMF cases. - It leads to constitutive activation of the JAK-STAT signaling pathway, driving cytokine-independent proliferation. - Allele burden correlates with clinical phenotype and thrombotic risk. CALR - Detected in 20–30% of ET and PMF patients who are JAK2-negative. - Mutations, mostly frameshift in exon 9, generate novel C-terminal peptides. - CALR-mutated ET patients often present at a younger age, with higher platelet counts and relatively favorable prognosis. MPL - Mutations in the thrombopoietin receptor gene, most commonly W515L/K, occur in 3–5% of ET and PMF cases. - They lead to constitutive activation of thrombopoietin signaling and megakaryocyte proliferation. Additional Mutations - Genes such as ASXL1, EZH2, SRSF2, IDH1/2, and TP53 are frequently mutated, particularly in PMF. - These mutations are not disease-defining but provide prognostic information. - ASXL1 mutation, for instance, is associated with adverse prognosis and impacts decisions regarding allogeneic stem cell transplantation. Clinical Applications Diagnosis - The WHO (2022) and ICC (2022) classifications incorporate genetic testing into diagnostic criteria. - Identification of JAK2, CALR, or MPL mutations confirms clonality and assists in differentiating MPNs from reactive conditions. - Triple-negative patients (negative for JAK2, CALR, MPL) often exhibit more aggressive clinical behavior. Prognosis - Prognostic scoring systems such as MIPSS70, GIPSS, and DIPSS-plus include molecular findings. - The presence of high-risk mutations predicts increased risk of progression to acute leukemia and reduced overall survival. Therapeutic Implications - JAK2 allele burden informs thrombotic risk stratification and the need for cytoreductive therapy. - The detection of adverse mutations influences consideration for hematopoietic stem cell transplantation. - Targeted therapies, such as JAK inhibitors, have been developed based on the molecular pathogenesis of MPNs. Future Perspectives The integration of next-generation sequencing (NGS) panels into clinical practice allows for comprehensive molecular profiling. This facilitates the development of personalized treatment strategies, including targeted therapies beyond JAK inhibition. Ongoing clinical trials are exploring agents directed against epigenetic regulators and splicing factors. **Conclusion:** Genetic testing has revolutionized the approach to chronic myeloproliferative neoplasms. Driver mutations (JAK2, CALR, MPL) remain essential for diagnosis, while additional mutations provide prognostic and therapeutic guidance. The expanding role of molecular testing paves the way toward precision medicine in MPNs.

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Abstract 034

ATYPICAL HEMOLYTIC UREMIC SYNDROME: FROM PATHOPHYSIOLOGY TO THERAPEUTIC ADVANCES

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Introduction and Pathophysiology: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) distinct from Shiga toxin-producing Escherichia coli (STEC)-related HUS. It is primarily driven by genetic or acquired dysregulation of the complement system, with pathogenic variants in complement factor H (CFH), factor I (CFI), membrane cofactor protein (MCP/CD46), factor B (CFB), and C3 identified in nearly 60% of patients. The resulting uncontrolled activation of the alternative complement pathway leads to endothelial damage, platelet activation, and microvascular thrombosis, most prominently affecting renal function. Clinically, aHUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury, most commonly renal but often involving extrarenal systems such as cardiovascular, neurological, dermatological, and gastrointestinal organs. Diagnosis is challenging, requiring exclusion of other TMAs such as thrombotic thrombocytopenic purpura (TTP) and typical HUS. Early and accurate identification is essential to prevent irreversible organ damage. **Advances in Diagnosis and Treatment:** Diagnostic workup integrates clinical, laboratory, and genetic testing. ADAMTS13 activity measurement is critical to exclude TTP, while Shiga toxin assays help differentiate typical HUS. Complement biomarkers, including soluble C5b-9 and factor Ba, are under investigation for their diagnostic and prognostic utility. Genetic testing, employing next-generation sequencing and MLPA, provides prognostic insights and guides therapy, though penetrance remains incomplete and environmental triggers (infections, pregnancy, transplantation) play a pivotal role. Therapeutically, plasma exchange was historically the first-line option, but outcomes were poor with high rates of end-stage renal disease (ESRD). The advent of complement inhibitors has revolutionized management. Eculizumab, a monoclonal antibody targeting C5, effectively halts terminal complement activation, resulting in rapid

hematologic normalization and renal recovery, especially when initiated early. Ravulizumab, a long-acting C5 inhibitor requiring infusions every 8 weeks, offers comparable efficacy with improved quality of life. Real-world studies confirm their sustained safety and effectiveness, though concerns regarding meningococcal infections necessitate vaccination and antibiotic prophylaxis. The duration of therapy remains debated; relapse occurs in 20–30% after discontinuation, particularly in carriers of CFH and CFI mutations. Emerging biomarkers and genetic stratification may enable more personalized discontinuation strategies. **Challenges and Future Perspectives:** Despite therapeutic advances, significant challenges remain. Complement inhibitors impose a lifelong economic burden, raising questions of cost-effectiveness and accessibility. Health-economic analyses highlight the need for balanced strategies between clinical benefit and financial sustainability. Furthermore, gaps persist in standardized diagnostic criteria, access to genetic testing, and long-term outcome data for ravulizumab. Ongoing research focuses on refining biomarkers for risk stratification, identifying novel complement targets, and developing more affordable therapies. Special considerations arise in pregnancy-associated aHUS, post-transplant recurrence, and pediatric populations, where individualized management is critical. In conclusion, aHUS exemplifies a paradigm shift in the treatment of rare complement-mediated diseases. Early recognition, integration of genomic data, and targeted complement inhibition have transformed its prognosis. Future research must focus on optimizing therapeutic duration, expanding access to novel agents, and achieving a cost-effective, precision medicine approach for this devastating disorder.

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Abstract 035

CURATIVE TREATMENT APPROACHES IN THALASSEMIA

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Supportive therapies prolong survival in transfusion-dependent β-thalassemia (TDT), however they do not eradicate the disease. Advances in hematopoietic stem cell transplantation (HSCT), gene therapy, and gene editing technologies have transformed the therapeutic landscape and brought curative options into clinical practice. Allogeneic HSCT remains the most established curative treatment for thalassemia. In HLA-matched sibling transplantation, event-free and thalassemia-free survival exceed 80–90% in children transplanted at an early stage. Younger patients without advanced iron overload consistently achieve superior outcomes, highlighting the importance of early referral. Alternative donor strategies are being increasingly explored. Haploidentical HSCT using post-transplant cyclophosphamide (PTCy)-based regimens has improved survival rates to 60–70%, though graft failure and graft-versus-host disease (GVHD) remain major limitations. Umbilical cord blood transplantation, although feasible, is hampered by limited cell dose and delayed engraftment. Novel approaches such as α/β T-cell depletion or infusion of regulatory T-cells are under investigation to mitigate GVHD and reduce graft loss. Beyond allogeneic transplantation, lentiviral gene therapy represents a major breakthrough. Autologous $CD34^+$ hematopoietic stem cells can be transduced with a lentiviral vector encoding a functional βA-T87Q-globin gene. In early phase trials such as HGB-204 and HGB-205, 75–80% of patients achieved transfusion independence for ≥12 months. Phase III studies (Northstar-2 and Northstar-3) confirmed long-term transfusion independence in over 80% of non-$\beta0/\beta0$ genotypes and around 70% of $\beta0/\beta0$ patients. Toxicities are mainly conditioning-related, with busulfan causing cytopenias, hepatic veno-occlusive disease, and infertility. Importantly, no insertional leukemogenesis has been reported. Betibeglogene autotemcel (Zynteglo®) received EMA approval in 2019 and FDA approval in 2022, yet its high cost is a significant barrier to widespread adoption. Long-term safety and durability of benefit are being assessed in the ongoing LTF-303 follow-up study. CRISPR-Cas9 gene editing has introduced a paradigm shift in curative approaches. Exagamglogene autotemcel (Exa-cel) works by inactivating the BCL11A erythroid enhancer, thereby reactivating fetal hemoglobin (HbF) and providing a mutation-independent therapeutic effect. Regulatory agencies have rapidly recognized its impact: the MHRA in the UK approved Exa-cel in November 2023 for both TDT and SCD, while the FDA granted approval in December 2023 (SCD) and January 2024 (TDT). EMA approval is pending, with PRIME designation already granted. Safety data so far suggest that adverse events are primarily busulfan-related, with no evidence of genotoxicity or malignant clonal expansion. Additional curative strategies are under early investigation. Other gene editing platforms, such as TALENs and zinc-finger nucleases, may allow more controlled cleavage activity, though their clinical application remains experimental. Pharmacologic HbF induction is another promising avenue. Hydroxyurea has limited efficacy in TDT but modest benefit in HbE/β-thalassemia. Novel small molecules such as mitapivat, a pyruvate kinase activator, have shown hemoglobin improvement in non-transfusion-dependent patients, and Phase III trials are ongoing. LSD1 inhibitors and pomalidomide derivatives are in preclinical or early clinical development as pharmacologic HbF inducers. From a clinical perspective, HSCT remains the gold standard in eligible patients with a matched donor, while refined haploidentical protocols are expanding donor availability. Gene therapy offers a curative option for patients lacking suitable donors, though conditioning-related toxicity, accessibility, and cost limit its use. CRISPR-based genome editing has shown transformative efficacy, but long-term safety monitoring is essential before universal adoption. In conclusion, curative treatment for thalassemia has expanded far beyond traditional transplantation. Lentiviral gene therapy and CRISPR-based editing represent a paradigm shift, offering functional cures in the majority of treated patients.

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Abstract 036

NON-FACTOR APPROACHES AND NEW HORIZONS

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Hemophilia is an X-linked recessive disorder. It is divided into two different subtypes; hemophilia A (HA) and B (HB), which result from the deficiency or complete absence of clotting factors VIII (FVIII) and IX (FIX) respectively. Current management of HA and HB includes prophylactic factor replacement[1]. Neutralising antibodies, as inhibitors, can develop against the infused factor and that can complicate the management of hemophilia patients. If inhibitors develop, immune tolerance induction can potentially promote tolerance to exogenous FVIII or FIX, and bypassing agents (BPAs) such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCC) can be used to circumvent factor use[2]. Inhibitor development impacts negatively upon quality of life and treatment compliance, highlighting the need for improved therapies. Several novel pharmacological therapies developed for hemophilia aim to rebalance the clotting cascade. These therapies utilise a range of different mechanisms, namely: the extension of the circulating half-life of standard recombinant factors; the mimicking of factor VIII cofactor activity; rebalancing of coagulation through targeting of natural anticoagulants such as antithrombin and tissue factor pathway inhibitor; and inducing the production of endogenous factors with gene therapy. **Discussion:** Extended half−life products involves fusing FVIII or FIX to a protein with a long half-life[3]. Albumin and the constant region (Fc) of IgG have long plasma half-lives as they bind to the neonatal Fc receptor, which is critical for the endogenous recycling of both IgG and albumin. Another method is PEGylation, where one or more PEG chains are covalently linked to rFVIII or rFIX. PEG chains interfere with the recombinant factors binding to their clearance receptors, thereby prolonging circulating half-life. Emicizumab, a recombinant humanised bispecific IgG antibody, mimics the cofactor function of the missing FVIII in HA. It simultaneously binds activated FIX (FIXa) and factor X (FX), bringing them into spatial proximity to promote FIXa-catalysed FX activation, thereby restoring haemostasis[4]. Fitusiran, a novel therapy applicable to both HA and HB, consists of the amino acid, N-Acetyl- galactosamine, the ligand of the hepatic asialo-glycoprotein receptors, conjugated to a synthetic siRNA. It targets and degrades a region of the SERPINC1 gene mRNA, preventing antithrombin production and enhancing thrombin generation. Antithrombin is a potent anticoagulant which inactivates FIXa, activated factor X (FXa) and activated factor II (FIIa/thrombin). Therefore, fitusiran can correct the coagulation imbalance and prevent the bleeding phenotype[5]. Concizumab is an IgG4 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI). It presents an alternative therapy for HA and HB patients, both with and without inhibitors. TFPI is a coagulation inhibitor. It limits coagulation during the initiation of the coagulation cascade through inhibition of the tissue factor-activated factor VII (TF-FVIIa) complex and through FXa inhibition[6]. Gene therapy presents a novel and effective treatment modality for hemophilia, potentially bypassing complications of other therapies. Gene therapy regimens consist of single infusions of a viral vector, which result in transduction of a gene coding for the deficient factor into patient hepatocytes. Current gene therapy regimens for hemophilia predominantly utilise adeno-associated virus (AAV) vectors to deliver the required gene[7]. **Conclusion:** Current factor replacement poses numerous issues, resulting in poor adherence and reduced QoL. Inhibitor development presents a key limitation to factor replacement. EHL products, emicizumab, fitusiran, and concizumab (summarised in appear effective in patients with and without inhibitors, and their longer half-lives enable less frequent injections.

Keywords: Hemophilia A, Hemophilia B, Extended half-life, Emicizumab, Fitusiran, Concizumab, Gene therapy.

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Abstract 037

IMMUNE THROMBOCYTOPENİA: PATHOPHYSIOLOGY AND MOLECULAR BIOLOGY

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Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia. While traditionally explained by antibody-mediated platelet destruction, recent studies reveal a broader syndrome of immune dysregulation involving both platelet destruction and impaired thrombopoiesis. The best-established mechanism involves autoantibodies, primarily IgG1 and IgG3, against platelet glycoproteins GPIIb/IIIa and GPIb/IX. Antibody-coated platelets are phagocytosed by macrophages via Fcγ receptors in the spleen and liver. Anti-GPIb antibodies cause platelet desialylation and clearance by the hepatic Ashwell−Morell receptor. Autoantibodies also trigger complement activation, enhancing destruction through C3b deposition. Beyond humoral immunity, T-cell dysregulation is central. Th1 polarization, characterized by elevated IFN-γ, TNF-α, and IL-2, stimulates macrophage activation and autoreactive B-cell differentiation. In contrast, Th2 cytokines (IL-4, IL-10) are reduced, impairing tolerance. Increased Th17 cells and IL-17 further amplify inflammation and suppress regulatory T-cell (Treg) activity. Indeed, $CD4^+CD25^+FoxP3^+$ Tregs are both reduced in number and function, with diminished production of IL-10 and TGF-β. This promotes unchecked autoreactive B- and T-cell activity. $CD8^+$ cytotoxic T cells have emerged as key players. These cells directly induce apoptosis of platelets and bone marrow megakaryocytes through perforin−granzyme and Fas/FasL pathways, representing antibody-independent platelet destruction. Their expansion is particularly evident in refractory or chronic ITP. B-cell activation is driven by cytokines from Th1 and follicular helper T cells. The B-cell survival factors BAFF (B-cell activating factor) and APRIL (A proliferation-inducing ligand) are elevated in

ITP, allowing autoreactive B cells and long-lived plasma cells to persist. This explains resistance to rituximab, which depletes $CD20^+$ B cells but spares plasma cells. The BAFF/APRIL axis is therefore a promising therapeutic target. In addition to peripheral destruction, impaired thrombopoiesis is critical. Autoantibodies against GPIIb/IIIa and GPIb/IX disrupt megakaryocyte maturation and proplatelet formation. $CD8^+$ T cells induce megakaryocyte apoptosis, further reducing platelet production. Bone marrow stromal dysfunction, including reduced secretion of TGF-β, SCF, and CXCL12, exacerbates these defects. A hallmark of ITP is the paradoxically low thrombopoietin (TPO) level despite severe thrombocytopenia. Since TPO synthesis is regulated by megakaryocyte mass rather than platelet count, reduced megakaryocyte numbers and dysfunction result in insufficient TPO and inadequate platelet production. The cytokine milieu in ITP reflects a proinflammatory imbalance. Increased IFN-γ, TNF-α, and IL-17 reinforce autoimmunity, while decreased IL-10 reflects Treg dysfunction. These changes disrupt tolerance and promote disease chronicity. In conclusion, ITP is not merely an antibody-driven disorder but a complex immune dysregulation syndrome. Both humoral and cellular mechanisms contribute to platelet destruction, while megakaryocyte impairment and insufficient TPO hinder platelet production. Elevated BAFF/APRIL, Th1/Th17 polarization, Treg deficiency, and cytotoxic T-cell activity represent crucial pathogenic pathways. Advances in molecular biology are redefining ITP pathogenesis and identifying novel therapeutic targets that extend beyond conventional immunosuppression.

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Abstract 038

HIGH-RISK MDS TREATMENT AND INNOVATIONS

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Myelodysplastic syndrome (MDS) is a clonal neoplastic myeloid stem cell neoplasm characterized by ineffective hematopoiesis in the bone marrow and cytopenias in the peripheral blood. Prognostic scoring systems classify patients as low-risk or high-risk MDS. Various prognostic scoring systems have been developed to predict disease course and survival using markers such as cytopenias, bone marrow blast ratio, cytogenetics, age, and performance status. The most commonly used scoring systems are the IPSS and R-IPSS. In its 2022 classification, the WHO used the term myelodysplastic neoplasms instead of myelodysplastic syndromes. These clonal hematopoietic neoplasms were defined by cytopenias and morphological dysplasia, with a dysplasia threshold of 10% for all series. MDS subtypes were grouped into those characterized by genetic abnormalities and those defined by morphology. Although patients may be classified as low risk based on their current MDS risk scores, the disease is a blood cancer with a generally poor prognosis. Patients with high and very high IPSS-R risk can expect a median survival of 1.6 and 0.8 years, respectively, while those with intermediate, low, and very low IPSS-R risk have a median survival of 3, 5.3, and 8.8 years, respectively. The treatment approach for high-risk MDS is aimed at delaying leukemic transformation and prolonging survival. Currently, the only curative treatment for high-risk MDS patients is allogeneic stem cell transplantation (HSCT). Its application is limited by the advanced age and lack of vigor of many MDS patients. All "high-risk" MDS patients with good performance status and without serious comorbidities should be considered for curative allogeneic HSCT. Transplant-related factors have also been shown to play a role in determining post-transplant prognosis. Treatment options for patients ineligible for transplantation are limited, and HMA remains the standard of care. New agents are under development for high-risk MDS patients. In recent years, several new drugs have been tested in combination with 5-azacitidine to further improve patient outcomes, but these have been unsuccessful. A randomized phase II SWOG trial compared standard azacitidine with azacitidine combined with lenalidomide or vorinostat in 227 patients with HR-MDS, reporting an overall response rate of 38% in the azacitidine group, while no improvement in response or survival was seen in the combination group. The recent approval of venetoclax, a BCL-2 inhibitor, for use with 5-azacitidine in AML has prompted investigation of this combination in MDS. In particular, azacitidine + venetoclax, azacitidine + sabatolimab, and azacitidine + magrolimab have shown encouraging results in large, single-arm studies and have also improved in placebo-controlled, double-blind studies with OS as the primary endpoint. IDH1 or IDH2 mutations occur in 5–15% of MDS patients, and enasidenib and ivosidenib have been shown to produce responses in MDS patients with IDH2 mutations. It may be mentioned that the new ICC, which classifies previous WHO 2016 MDS with ≥10% blasts as MDS/AML, would potentially allow the use of AML-approved drugs also in higher-risk MDS

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Abstract 039

CURATIVE TREATMENT OPTIONS IN SICKLE CELL DISEASE

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Introduction: Sickle cell disease is the most commonly inherited hemoglobinopathy (1).Disease modifying drug therapies such as hydroxyurea,L-glutamine,voxelotor and crizanlizumab reduce pain crises and severe complications(2).Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option. In 1984, the first report of HSCT in a patient with SCD who was transplanted for AML demonstrated the efficacy of HSCT as a curative treatment option for SCD patients with severe disease.In 1996,Walters and colleagues first reported the curative benefits of treatment in a 22-year-old patient with severe sickle cell disease who had an HLA-identical sibling donor(3). INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION Indications for HSCT are summarized in the Table 1. According to the expert panel,(1)

any young patient with symptomatic SCD who has an HLA-identical sibling donor should be transplanted as early as possible, preferably at preschool age; (2)bone marrow and umbilical cord blood from HLA-identical sibling donors are the recommended stem cell sources;(3)for patients who need to use an alternate donor source,more stringent indications are still recommended, and these patients should only have HSCT under a clinical trial and at a center where the staff are experienced in the procedure(3). DONOR SELECTION AND STEM CELL SOURCES Current recommendations by the National Marrow Donor Program recommend high-level matching at the HLA-A,HLA-B,HLA-C and HLA-DRB1 loci for unrelated donors.20 Matching in all the loci is referred to as an 8/8 match (3).Unfortunately, <%20 of patients have HLA-matched donors.In the absence of a matched sibling donor, HLA-matched unrelated donors,HLA-identical sibling cord blood donors and haploidentical donors are alternatives.Two trials, Sickle Cell Transplant To Prevent Disease Exacerbation (STRIDE) and Sickle Cell Unrelated Transplant trial (SCURT), are evaluating the use of matched unrelated donors in different age groups and with different conditioning regimens.The STRIDE trial started in 2012 for reduced intensity myeloablative transplantation in patients with SCD aged 15-40 years and reported excellent outcomes (OS and EFS of %95) at 12-month follow-up.32 The SCURT trial opened in 2008 and demonstrated no difference in graft rejection rates with matched unrelated donors compared to HLA-identical sibling donors; however, significant morbidity from chronic GVHD (%62) was reported. CONDITIONING REGIMENS Conditioning regimens are categorized as being myeloablative,reduced intensity,or nonmyeloablative. **Myeloablative Conditioning Regimen** The most commonly used myeloablative conditioning regimen for SCD consists of busulfan 14-16 mg/kg and cyclophosphamide 200 mg/kg ± ATG.Cryopreservation of sperm and ovarian tissue is recommended in these types of HSCT(1). **Reduced Intensity and Nonmyeloablative Conditioning Regimens** Reports of SCD symptoms resolving even in patients with mixed chimerism suggest that complete donor chimerism is not necessary and have led to interest in using reduced intensity and nonmyeloablative conditioning regimens for this population(3).

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Abstract 040

DİAGNOSİS AND TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBİNURİA

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening clonal hematopoietic stem cell disorder characterized by hemolytic anemia, bone marrow failure, and thrombosis. The absence of glycosylphosphatidylinositol (GPI)-anchored complement regulatory proteins, such as CD55 and CD59, leads to uncontrolled complement activation, chronic intravascular hemolysis, and severe complications. Thrombosis remains the leading cause of mortality, accounting for 40–67% of deaths in PNH patients. **Diagnosis:** High-sensitivity flow cytometry is the gold standard for detecting GPI-deficient cell populations and remains essential for both diagnosis and follow-up. Laboratory evaluation includes complete blood count, hemolysis parameters (LDH, bilirubin, haptoglobin, reticulocytes), and bone marrow examination. Clinical indications for testing are hemolysis, cytopenias, unexplained anemia, aplastic anemia, and thrombosis in atypical sites such as hepatic or cerebral veins. International guidelines (IPIG, ICCS, BCSH) recommend screening all patients with aplastic anemia for PNH clones at diagnosis. **Treatment and Follow-up:** Regular monitoring of hemolysis-related parameters is critical to identify high disease activity, defined as LDH ≥1.5 × ULN plus at least one symptom (fatigue, dyspnea, abdominal pain, hemoglobinuria, anemia, thrombosis). Eculizumab, a C5 inhibitor, was the first targeted therapy to significantly reduce intravascular hemolysis and thrombotic risk. Vaccination against Neisseria meningitidis is mandatory before treatment initiation. Ravulizumab, a long-acting C5 inhibitor, offers extended dosing intervals with comparable efficacy. **Novel Therapies:** Recent therapeutic advances are transforming PNH management. Crovalimab, a next-generation C5 inhibitor, allows subcutaneous administration with longer dosing intervals. Biosimilar eculizumab (Bkemv) improves treatment accessibility. Proximal complement inhibitors, including iptacopan (oral Factor B inhibitor), danicopan (Factor D inhibitor), and pegcetacoplan (C3 inhibitor), target both intravascular and extravascular hemolysis, improving hemoglobin stabilization, transfusion independence, and quality of life. These agents are increasingly incorporated into personalized treatment strategies. **Bone Marrow Transplantation:** Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option but is associated with high treatment-related mortality. It should be reserved for patients with severe bone marrow failure or refractory disease when risks outweigh potential benefits. **Conclusion:** The therapeutic landscape of PNH is undergoing a paradigm shift, with novel long-acting and oral complement inhibitors improving disease control and patient convenience. Early diagnosis through flow cytometry and individualized treatment selection remain essential for optimal outcomes. Although HSCT offers potential cure, complement inhibitors currently represent the cornerstone of PNH management.

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Abstract 041

ALL IN ADOLESCENT AND YOUNG ADULTS

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Recent advances in the treatment of adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) highlight the critical role of pediatric-inspired regimens, molecular stratification, and novel immunotherapies. Historically, outcomes for AYA lagged behind children due to greater

treatment resistance and toxicity. However, intensification strategies adapted from pediatric protocols have significantly improved remission and survival rates. Despite this progress, survival in AYA remains inferior to pediatric patients, underscoring the need for more refined, biology-driven approaches (Siegel et al., 2018). One of the most important biological insights concerns the Philadelphia-like (Ph-like) ALL subtype, which is particularly prevalent in AYA (25–30%). Characterized by kinase-activating lesions, this subgroup exhibits high resistance to chemotherapy but offers opportunities for targeted therapy using tyrosine kinase inhibitors (TKIs) such as ruxolitinib or ABL-class inhibitors. Other genetic alterations, including MEF2D, ZNF384, and DUX4 fusions, also contribute to disease heterogeneity and prognosis. Identifying these lesions rapidly remains a major challenge, and the integration of genomic profiling with predictive algorithms and ex vivo drug sensitivity testing is expected to optimize individualized care (Pui et al., 2019). Minimal residual disease (MRD) monitoring has become a cornerstone of risk stratification in AYA ALL. Early MRD levels after induction and consolidation strongly predict relapse risk and guide decisions regarding allogeneic hematopoietic stem cell transplantation (allo-HSCT). Importantly, MRD thresholds differ between pediatric and adult-inspired protocols, highlighting the need for age-specific approaches. Furthermore, MRD is increasingly employed as a primary endpoint in clinical trials and as a trigger for introducing immunotherapies (Stock et al., 2019). Immunotherapeutic agents are transforming frontline therapy in AYA ALL. Inotuzumab ozogamicin (anti-CD22) and blinatumomab (CD3–CD19 bispecific antibody) have demonstrated superior response rates and MRD clearance compared with standard chemotherapy in relapsed/refractory settings. Both are now being evaluated earlier in therapy, particularly as consolidation strategies. Similarly, CD19-directed chimeric antigen receptor (CAR) T-cell therapy, notably tisagenlecleucel, has shown durable remissions in pediatric and AYA patients, although relapse due to antigen loss remains a challenge. Efforts are underway to improve CAR T-cell persistence and safety in this age group (Pui et al., 2019). Beyond targeted and immune-based therapies, novel small molecules such as BCL2 inhibitors (venetoclax, navitoclax) and menin inhibitors show promise in genetically defined subgroups. These agents may further reduce chemotherapy intensity while improving efficacy. Equally crucial is comprehensive supportive care for AYA patients. Fertility preservation, psychosocial support, and survivorship programs are essential to address long-term treatment burdens, particularly for those undergoing allo-HSCT. Late complications such as infertility, osteonecrosis, and prolonged immune dysfunction remain pressing issues that require multidisciplinary management (Siegel et al., 2018). In conclusion, the therapeutic landscape of AYA ALL is shifting from generalized intensification to precision medicine. Advances in understanding disease biology, the incorporation of MRD into decision-making, and the integration of immunotherapy and small molecules are reshaping standards of care. Future progress will depend on broad clinical trial participation and multidisciplinary support to optimize both survival and quality of life for AYA patients with ALL.

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Abstract 042

WHY I CHOSE HEMATOLOGY ?

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After graduating from Hacettepe University Faculty of Medicine in 1970, with the support of my professors I began corresponding with universities abroad to pursue residency training. During this period I met Prof. Faruk Özer, the head of the Hacettepe Faculty of Medicine Hematology Department, who made me love hematology and sparked my interest in the field., Türkiye On July 1, 1971, I started my straight medical internship at Newark Medical School Hospital/Jersey City Medical Center. At the beginning of 1972, I transferred to Thomas Jefferson University in Philadelphia (Jefferson Medical College), to which I had applied, and in 1974 I completed my internal medicine residency. While training in internal medicine, I met Prof. Allan J. Erslev, the head of the Hematology Department and director of the Cardeza Foundation for Hematologic Research, and I began attending the early-morning slide discussion sessions he organized for residents. He would put the peripheral smear and bone marrow slides of inpatients onto the microscope, have us read them, and ask us to interpret the findings. We received an excellent education in morphology. These morning sessions created a passion for hematology in me, because we could make diagnoses by directly examining morphology alongside the clinical and laboratory findings. No other subspecialty offered such a superb opportunity. This excited and motivated me., Türkiye With that excitement, I began my hematology fellowship in July 1974. Our department chair, Prof. Allan J. Erslev, had identified the hormone erythropoietin in 1953 while working at Harvard Medical School. In my second year as a clinical fellow, he suggested that I conduct research on erythropoietin. Thus, starting in 1976, I focused my research on extrarenal sources of erythropoietin and on immunology. One of Prof. Erslev's most important contributions to modern hematology is that the erythropoietin hormone he described was later produced recombinantly and is now widely used in clinical practice for many anemias, especially in chronic renal failure. At that time Prof. Allan J. Erslev was also preparing a new hematology textbook, and in 1972 he began serving as a co-editor—together with Williams, Rundles, and Beutler—of the book **HEMATOLOGY**, which went on to become the much-read **"Williams Hematology"**, now in its 10th edition. Prof. Erslev entrusted me with many tasks in the preparation of this book. I would go to the famous Saunders Publishing house next to Thomas Jefferson University and, working together with the responsible editors, proofread and revise the chapters I had corrected. This greatly contributed to my affection for hematology and to my training. Thus, even before the book's first edition in 1974, I had the opportunity to read the entirety of a very important text in hematology., Türkiye At the Hematology Department of Thomas Jefferson University, I had the opportunity to do both clinical and research fellowships until 1980. In my research, I examined the antigenic and immunologic characteristics of extrarenal erythropoietin. During this period, I received comprehensive

training in hematopoiesis and bone marrow physiology as well as cellular immunology. Encouraged by Prof. Erslev, I even completed a master's program in protein science at Temple University in my second fellowship year. Later, to better understand stem-cell biology, he arranged for me to work for a time at the Toronto Cancer Center, where Prof. Ernest McCulloch and Prof. James Till—who, in their 1961 publications, identified hematopoietic stem cells in mice—were based. All these experiences greatly helped me learn the fundamental principles of hematology in depth., Türkiye Together with my wife, Prof. Tülay Kansu, we completed our postgraduate training in Philadelphia between 1972 and 1980. During my years in Philadelphia, I had the opportunity to meet and work with many distinguished hematologists who made very significant contributions to the field. Prof. Peter C. Nowell of the University of Pennsylvania (who identified the Philadelphia chromosome), Prof. Sol Sherry of Temple University in the field of coagulation, Prof. Sandy Shapiro in antiphospholipid syndrome and Prof. James Holland the founder of CALGB, among many other esteemed hematologists. Through these collaborations, I gained highly valuable academic knowledge and experience from pioneers of the field., Türkiye Over the last 50 years, hematology has seen major scientific advances that have improved patients' quality of life and expanded treatment options. Among these are the development of cell-culture and genetic technologies; stem-cell transplantation; cancer immunotherapy and targeted therapies; checkpoint inhibitors; gene therapy; biotechnology; innovations in the treatment of sickle-cell disease and thalassemia and advances in imaging and diagnostic methods. In conclusion, I believe that the hematology subspecialty—which I chose with determination and affection in the final years of my internal medicine residency—has made very important contributions to my academic life. I sincerely recommend that our young colleagues choose hematology in their subspecialty training and academic careers.

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Abstract 043

DONOR SELECTION IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapeutic option for various malignant and non-malignant hematological disorders. Donor selection remains the most critical factor affecting transplantation outcomes, with human leukocyte antigen (HLA) compatibility being the cornerstone of this process. The traditional donor hierarchy begins with HLA-matched sibling donors (MSD), who provide the best outcomes with the lowest risk of graft-versus-host disease (GVHD) and transplant-related mortality (TRM). For patients without an MSD, matched unrelated donors (MUD) with 10/10 HLA compatibility are the next preferred option. Recent advances in high-resolution HLA typing have improved outcomes with unrelated donors, approaching results comparable to those of MSD. When multiple compatible donors are available, non-HLA factors guide selection. Donor age significantly impacts outcomes, with younger donors (18-35 years) yielding better results. Cytomegalovirus serostatus concordance between donor and recipient is crucial to prevent post-transplant complications. Male donors are generally preferred over female donors, particularly for male recipients, due to the increased risk of chronic GVHD associated with female-to-male transplants. ABO blood group compatibility, while not affecting survival directly, influences the risk of immediate post-transplant complications. Alternative donor sources have expanded transplantation possibilities for patients lacking conventional donors. Haploidentical family donors have seen remarkable improvements in outcomes with the introduction of post-transplant cyclophosphamide (PTCy), challenging the traditional donor hierarchy. Umbilical cord blood units provide another alternative, particularly beneficial in pediatric patients, despite limitations in cell dose. Donor selection strategies differ between pediatric and adult populations. In pediatric patients, the focus remains on minimizing long-term complications, particularly chronic GVHD, which can severely impact growth and development. In adults, stronger graft-versus-leukemia effects may be prioritized in high-risk malignancies, making alternative donors with potential for enhanced alloreactivity more attractive. Disease-specific considerations also influence donor choice. Benign hematological disorders require complete HLA matching to minimize complications, while in malignant diseases, partial HLA mismatches might be accepted to enhance graft-versus-tumor effects. Hodgkin lymphoma patients demonstrate superior outcomes with haploidentical donors compared to MUDs, challenging conventional hierarchies. Donor exclusion criteria encompass medical conditions that may increase donation-related risks or compromise graft quality. These include cardiovascular, pulmonary, hematological, and immunological disorders, active infections, and malignancy history. As transplantation practices evolve, personalized donor selection algorithms incorporating disease characteristics, patient factors, donor availability, and center experience are replacing rigid hierarchies, ultimately improving outcomes for patients requiring allogeneic HSCT.

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Abstract 044

GENE THERAPY IN HEMOPHILIA

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Symptomatic or prophylactic treatment of hemophilia began in the 1960s with fresh frozen plasma therapy. Over the years, treatment evolved through plasma-derived products, recombinant therapies, extended half-life products, and

subcutaneous treatments. However, achieving zero bleeding has remained elusive. In 2022, gene therapies received regulatory approval, offering hope for a definitive cure for hemophilia. Ege University joined gene therapy clinical trials in 2021. Our patient, MA, born in 1998 and diagnosed in 2000, had a childhood marked by frequent bleeding and target joint involvement despite starting prophylaxis. During gene therapy screening, he was found to be AAV5 seronegative and was invited to our clinic. Following gene therapy, it was as if he was reborn. His initial Factor VIII level of 0.1 IU/dL rose to 128 IU/dL by week 208. His HJHS score dropped from 15 to 8, and he experienced no bleeding episodes., Türkiye Hemophilia is an ideal candidate for gene therapy because it is a single-gene disorder with a simple expression loss, even low levels of expression are clinically effective, no specific tissue or cell targeting is required and the factor is secreted directly into plasma and can be easily measured. Initial preclinical studies (early 2000s) using both viral and non-viral methods showed limited efficacy but no significant side effects. Adequate FVIII expression was not achieved. AAV-based somatic gene therapy for hemophilia was approved and commercialized in 2022–2023. AAV is ideal for gene transfer due to its non-pathogenic nature, defective self-replication, long-term transgene expression, availability of different serotypes for different tissues. The goal of gene therapy is to insert normal FVIII/FIX genes into the liver, enabling liver cells to synthesize these clotting factors. In the HOPE-B study, mean FIX activity was 39.0 IU/dL at 6 months (±18.7; range 8.2–97.1), 36.7 IU/dL at 24 months (±19.0; range 4.7–99.2). In the GENEr2 study,75.4% of patients had FVIII activity >5 IU/dL at year 2. However, factor expression varied significantly among patients. Challenges in Hemophilia Gene Therapy are high sero-prevalence of AAV antibodies, potential reduction in factor synthesis due to antibody development and risk of liver damage. The limitations of gene therapy are variable treatment response between patients, durability and applicability of the therapy, many patients already have AAV antibodies, higher vector genome doses may be required, increasing toxicity risk, immune reactions against the capsid may lead to loss of transfected hepatocytes, uncertainty in children, inhibitor-positive patients, and those with liver disease, redosing is not possible due to antibody development and high cost. To overcome these limitations, new gene technologies are being explored.

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