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

https://doi.org/10.1016/j.htct.2025.106191

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.

https://doi.org/10.1016/j.htct.2025.106192

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.

https://doi.org/10.1016/j.htct.2025.106193

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.

https://doi.org/10.1016/j.htct.2025.106194

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.

https://doi.org/10.1016/j.htct.2025.106195