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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