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.

https://doi.org/10.1016/j.htct.2025.106213

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.

https://doi.org/10.1016/j.htct.2025.106214

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

https://doi.org/10.1016/j.htct.2025.106215

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)