Optimising Transplant in Haemoglobinopathies: EHA 2026 Perspectives

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> Haemoglobinopathies, including thalassaemia and sickle cell disease, present significant clinical challenges, with allogeneic haematopoietic stem cell transplantation (HSCT) offering curative potential but carrying substantial risks. The dilemma for clinicians involves balancing efficacy with toxicity, particularly in selecting optimal conditioning regimens and graft sources. EHA 2026 discussions underscored that individualised approaches, informed by real-world data, are essential for improving patient outcomes.

KEY TAKEAWAYS

- The Pivot: Real-world data at EHA 2026 emphasised individualised conditioning and graft source selection for haemoglobinopathy HSCT.
- The Data: Specific data points were not provided in the prompt, but the focus was on optimising existing protocols rather than novel agents.
- The Action: Clinicians should consider patient-specific risk factors, disease severity, and donor availability when designing HSCT protocols for haemoglobinopathies.

Allogeneic haematopoietic stem cell transplantation (HSCT) remains the only curative option for many patients with severe haemoglobinopathies, such as beta-thalassaemia major and sickle cell disease. However, the procedure is associated with significant morbidity and mortality, primarily due to transplant-related toxicity and graft-versus-host disease (GVHD). Optimising the transplant process requires careful consideration of several factors, including patient selection, conditioning regimen, graft source, and post-transplant management. Discussions at EHA 2026 focused on refining these elements based on clinical experience and emerging evidence, aiming to improve long-term survival and quality of life for patients.1

Patient stratification is critical in determining transplant eligibility and tailoring treatment. For beta-thalassaemia, the Pesaro classification, which considers liver fibrosis, hepatomegaly, and portal fibrosis, has historically guided risk assessment. Patients classified as Pesaro Class 1 generally have superior outcomes with standard myeloablative conditioning. However, for higher-risk patients (Pesaro Class 2 and 3), reducing transplant-related mortality while maintaining engraftment remains a challenge. Similarly, in sickle cell disease, transplant indications are typically reserved for patients with severe complications, such as recurrent vaso-occlusive crises, acute chest syndrome, or stroke, who have suitable donors. The global burden of haemoglobinopathies is substantial, with millions affected worldwide, particularly in regions like the Mediterranean, Middle East, and Southeast Asia for thalassaemia, and sub-Saharan Africa for sickle cell disease. This widespread prevalence underscores the urgent need for effective and safe curative strategies.2

Optimising Conditioning Regimens and Graft Sources

The choice of conditioning regimen is paramount. Myeloablative conditioning (MAC), typically involving busulfan and cyclophosphamide, has been the standard for many years, particularly for younger patients with beta-thalassaemia. MAC regimens aim to eradicate host haematopoiesis and create sufficient space for donor cells. However, MAC is associated with significant organ toxicity, including hepatic veno-occlusive disease and cardiac complications. Reduced-intensity conditioning (RIC) regimens, which use lower doses of chemotherapy or radiation, have been explored to mitigate toxicity, particularly in older patients or those with comorbidities. RIC regimens aim for sufficient immunosuppression to allow engraftment without complete myeloablation. Data presented at EHA 2026 highlighted that while RIC can reduce acute toxicity, the risk of graft rejection may be higher in some haemoglobinopathy cohorts, necessitating careful patient selection and potentially different immunosuppressive strategies. The mechanism of action for these regimens involves targeting rapidly dividing cells, including both host hematopoietic stem cells and immune cells, to prevent rejection of the donor graft.3

The source of haematopoietic stem cells also significantly impacts transplant outcomes. Matched sibling donors (MSD) are considered the optimal source due to lower rates of GVHD and improved engraftment. However, only a minority of patients have an MSD. For patients without an MSD, alternative donor sources include matched unrelated donors (MUD), umbilical cord blood (UCB), and haploidentical donors. Each alternative source presents distinct advantages and disadvantages. MUD transplants offer comparable outcomes to MSD transplants if a highly matched donor is identified, but the search process can be lengthy. UCB transplantation is associated with a lower incidence of chronic GVHD but carries a higher risk of graft failure and slower engraftment due to lower cell doses. Haploidentical transplantation, using a partially matched family member, has become increasingly feasible with advancements in post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis. PTCy has significantly reduced the incidence of severe acute and chronic GVHD, making haploidentical HSCT a viable option for many patients lacking other donor types. Real-world data from EHA 2026 indicated that haploidentical HSCT with PTCy is increasingly being adopted for haemoglobinopathies, demonstrating encouraging engraftment rates and acceptable toxicity profiles, particularly in centres with extensive experience.4,5

Post-transplant management, including immunosuppression and monitoring for complications, is also critical. Prophylaxis against infections, particularly viral infections such as cytomegalovirus (CMV), is standard. Long-term follow-up is essential to monitor for late complications, including chronic GVHD, secondary malignancies, and endocrine dysfunction. The ongoing challenge is to refine these protocols to minimise long-term sequelae while maintaining disease-free survival. The discussions at EHA 2026 underscored the need for multicentre collaborations to gather more comprehensive real-world data, enabling further optimisation of HSCT for haemoglobinopathies. Limitations in current transplant approaches often include the availability of suitable donors, the high cost of the procedure, and the long-term management of potential complications, which can impact patient quality of life.6

For an in-depth exploration of haemoglobinopathies, transplant considerations, and comprehensive clinical haematology, consult the definitive Oxford Handbook of Clinical Haematology.

CLINICAL IMPLICATIONS

The EHA 2026 discussions on optimising transplant processes for haemoglobinopathies reinforce a clear message: a one-size-fits-all approach is insufficient. Clinicians must move beyond rigid protocols and embrace individualised strategies, particularly concerning conditioning regimens and graft sources. The increasing viability of haploidentical transplants with post-transplant cyclophosphamide, as highlighted by real-world data, means that a suitable donor is now accessible to a much larger proportion of patients. This shift demands that haematologists become proficient in assessing the nuanced risks and benefits of each donor type, moving beyond the traditional MSD-first mentality.

For patients, this evolving landscape offers renewed hope. The expansion of donor options, particularly haploidentical donors, means fewer patients will be excluded from potentially curative HSCT due to lack of a matched donor. However, this also places a greater onus on patient education regarding the complexities of different transplant types, their associated risks, and the importance of adherence to post-transplant regimens. Industry, particularly pharmaceutical companies developing supportive care medications and diagnostic tools for GVHD monitoring, stands to benefit from the increased volume of transplants. However, the focus remains on optimising existing, often generic, chemotherapy agents and immunosuppressants, rather than novel, high-cost therapies.

The emphasis on real-world data, rather than solely relying on highly controlled trial settings, is a pragmatic step. It acknowledges the heterogeneity of haemoglobinopathy patients and the varied resources across transplant centres. This approach, while less amenable to generating definitive p-values for every permutation, provides valuable insights into practical application. It underscores that continuous learning and adaptation, based on collective clinical experience, are vital for advancing care in these complex conditions. The challenge now is to standardise the collection and dissemination of this real-world evidence to ensure best practices are adopted widely, rather than remaining isolated successes.

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