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Perspective

HLA-matched related donor transplantation in children with transfusion-dependent thalassaemia: A single-centre experience in a resource-limited setting – Sri Lanka

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Abstract

Transfusion-dependent thalassaemia (TDT) is a significant health burden in low- and middle-income countries (LMIC) such as Sri Lanka. In LMIC, haematopoietic stem cell transplant (HSCT) remains the only curative option as it's a low-cost treatment modality compared to gene therapy. We present the outcomes of the first government-funded HSCT programme for TDT at the Lady Ridgeway Hospital for Children (LRH), Colombo.

A retrospective analysis includes 14 children with confirmed TDT who underwent matched family donor transplants at LRH between December 2021 and June 2025.

The median age at transplant was 10 years and 2 months. Nine children were in Pesaro class 2 and three were in class 3. Myeloablative conditioning regimens used included Bu/Cy/ATG and Treo/Thio/Flu. All patients achieved neutrophil and platelet engraftment, with median times of 17 and 20 days, respectively. The most common complication was neutropenic fever, followed by sinusoidal obstructive syndrome (n=6), more frequent in the Bu/Cy/ATG group. Two patients developed grade 2-3 acute gut GVHD; no chronic GVHD was observed. At a median follow-up of 387 days, transplant-related mortality was 0%, with 100% overall and thalassaemia-free survival. Twelve patients maintained full donor chimerism; two had mixed chimerism, with one requiring donor lymphocyte infusion.

This single-centre experience demonstrates that HLA-matched sibling HSCT is a safe and effective curative treatment for TDT, even in a resource-limited government setting. With careful patient selection, appropriate conditioning and international mentorship, HSCT can be successfully implemented and scaled in LMICs as part of national thalassaemia strategies.

Introduction

Thalassaemia is a group of inherited blood disorders characterised by reduced or absent production of one or more normal globin chains[1]. Depending on which chain's synthesis is impaired, the thalassaemias are classified as α, β, γ, δ, $\delta\beta$, or $\varepsilon\gamma\delta\beta$ thalassaemia. The most clinically significant types are α and β thalassaemia.

Based on their clinical severity and transfusion requirements, thalassaemia syndromes are phenotypically classified into two main groups: transfusion-dependent thalassaemia (TDT) and non-transfusion-dependent thalassaemia (NTDT). TDT is defined by lifelong dependence on regular blood transfusions, with the most common examples being beta thalassaemia major and E/β thalassaemia[1].

Incidence and health burden from TDT

The World Health Organisation reports that

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globally, 40,000 infants are born with thalassaemia annually, the majority being β thalassaemia[2]. Of these, over 25,000 infants born annually have transfusion-dependent thalassaemia.

In Sri Lanka, an ongoing prevention programme promoting "safe marriage" has been functioning for the last 15 years[3]. Despite this, around 2,000 patients with severe thalassaemia are currently living in the country, and approximately 80 new cases are born annually[4].

These children should adhere to a comprehensive blood transfusion and chelation therapy to achieve meaningful survival[5]. However, it will only alleviate symptoms, and not cure the disease. It's a significant health burden in a resource-limited setting, and the average cost per patient-year in Sri Lanka to deliver this care is USD 2601[6].

Regular transfusion became the standards of treatment in the 1960s[7]. It helps to maintain haemoglobin at normal levels, leading to a good quality of life in the short term. Still, it leads to death from transfusional iron overload at between 12 and 24 years of age[8]. The advancement in medical therapy has reduced morbidity and mortality, but life expectancy is still lower. Since 2000, over 80% of patients have a life expectancy of 40 years[8]. The thalassaemia registry data from England showed a continuous decline in survival, with fewer than 50% of thalassaemics surviving beyond 35 years due to poor compliance with comprehensive optimal chelation therapy[5]. An Indian study also confirms this, only 50% of thalassaemia patients survive by 26.9 years of age[9]. Comparatively, Sri Lanka has a much shorter average life span of around 20 years[10]. In Italy, the health-related quality of life is greatly affected by the disease, in both physical and psychological well-being[9]. These figures indicate the need for a cure for this disease.

Transfusion or transplant

The curative options available are haematopoietic stem cell transplantation (HSCT) and gene therapy. Gene therapy is only available in some high-income countries due to its high cost. According to Coquerelle S et al, the approximate cost of HSCT is Euro 215,571 when compared to Euro 608,086 for gene therapy in Europe[11].

Since the first transplant for TDT in 1981, nearly 10,000 transplants have been conducted worldwide with outstanding results. As a result, this therapy is now widely accessible in many parts of the world, including developing countries, due to its low cost compared to gene therapy.

HSCT is an expensive, highly specialised medical procedure requiring expertise and good support systems to achieve a good outcome. However, when considering the lifetime cost of blood transfusion and iron chelation and the irreversible organ damage caused by iron overload, the only cost-effective curative option for a low-resource setting would be HSCT[12].

In the late eighties, Guido Lucarelli and the Pesaro group developed a well-recognised scoring system to predict the outcome of allogeneic hematopoietic stem cell transplantation in thalassemia[13]. This scoring system stratified patients <16 years of age into statistically significant three risk groups using hepatomegaly (≤ 2 cm versus >2 cm from the costal arch), liver fibrosis (absent versus present at any degree), and duration of exposure to iron chelation[13]. The overall survival and thalassemia-free survival were 94% and 87%, 84% and 81%, and 50% and 47% in Class 1, 2, and 3, respectively. This clearly shows the excellent outcomes in class 1 and 2 and the poor outcomes in class 3 patients. Mathews et al. further subdivided the class 3 into low and high-risk groups using an age cut off >7 years and liver size of 5 cm. These class 3 high-risk children have a high risk of graft rejection, around 34%[14]. This emphasises the strategy of early transplant in thalassaemia before irreversible organ damage sets in.

Sri Lankan experience

Establishment of infrastructure

Lady Ridgeway Hospital for Children (LRH) established the inaugural government-funded paediatric allogeneic bone marrow transplant centre and opened it publicly in 2020. The unit includes two high-efficiency particulate air (HEPA) -filtered positive-pressure rooms.

A total of 268 TDT children were referred to LRH from 2017 to June 2025. After the initial transplant

in December 2021, there was a pause due to Sri Lanka's economic crisis in 2022. The programme was restarted in January 2023 and continued uninterrupted. Between December 2021 and June 2025, twenty-six allogeneic transplants were carried out at LRH. Out of the total 26,14 children with TDT successfully underwent matched family donor transplants, while others remain on the waiting queue due to limited bed capacity. Many bone marrow failure syndromes (BMFS), primary immune deficiencies (PID), and inherited metabolic diseases requiring early transplants are also being referred. Hence, priority is also given to these children who require urgent transplants.

Patient selection

As we are in the initial phase of establishing the national paediatric transplant programme, we have carefully selected children for haematopoietic stem cell transplants. During the early phase, we adopted selection criteria to achieve good outcomes and build confidence in the team. Because failures during the foundational stage have a profound impact on the progress of the transplant programme.

The first transplant was performed on a 7-year-old girl with Pesaro class 2, low-risk TDT. Initially, we selected "good risk" thalassaemic children – under 14 years old, with a liver size less than 2 cm from the costal margin, and serum ferritin <1000 ng/L before proceeding with the transplant. Liver fibrosis was assessed using liver elastography, as liver biopsy is not routinely performed. Iron levels were evaluated with serum ferritin and T2*MRI of the liver and the heart. All initial transplants were reviewed with our mentors at the Christian Medical College (CMC) – Vellore until the team gained confidence. As the team – built experience and confidence in managing complex post-transplant scenarios, the team was able to undertake high-risk thalassaemia transplants.

Pre-transplant evaluation

All patients were evaluated with a complete blood count (CBC), biochemical profile and serology for syphilis, HIV, HBV, HCV, CMV and malaria parasite. Donors and patients were typed using high-resolution human leukocyte antigen (HR-HLA) for class 1 and class 2. All cases were confirmed to have beta thalassaemia, either through high-performance liquid chromatography (HPLC) or genetic analysis.

Conditioning regimen and graft source

Two types of myeloablative (MAC) conditioning regimens were used. Seventy-two per cent (72%) received anti-thymocyte globulin (ATG), either horse ATG 90 mg/kg or rabbit ATG 4.5 mg/kg, busulfan (Bu) 16 mg/kg, and cyclophosphamide (Cy) 200 mg/kg, the balance twenty-eight per cent (28%) received fludarabine (Flu) 180 mg/m^2, thiotepa (Thio) 8 mg/kg, and treosulfan (Treo) 14 g/kg. The choice of the regimen depended on the Pesaro class, with classes 1 and 2 receiving Bu/Cy/ATG and class 3 receiving Flu/Treo/Thio.

While bone marrow (BM) was the preferred source of stem cells in these non-malignant conditions, granulocyte colony-stimulating factor (G-CSF) primed peripheral blood stem cells (PBSC) were used in some cases, particularly when using Flu/Treo/Thio to enhance engraftment and to reduce mixed chimerism. In our cohort 72% (n=10) and 28% (n=4) received bone marrow and Granulocyte colony-stimulating factor (G-CSF) primed PBSC as grafts, respectively.

Graft vs host disease prophylaxis

All received graft versus host disease prophylaxis with a short course of intravenous methotrexate (MTX): 10 mg/m² on day +1 and 7 mg/m² on days +3, +6, and +11 and Intravenous cyclosporin A at 2.5 mg/kg BID.

Outcomes

All patients were under 14 years at the time of transplant, and 8% (*n*=1) were under 7 years, while 92% (*n*=13) were over 7 years. The median age of the patients at the transplant was 10 years and 2 month (range 6 years 6 months to 12 years 7 months).

Karnofsky-Lansky score before transplantation was > 90 in all patients. The male-to-female ratio was 1.3:1, and all were 10/10 HLA-matched donor transplants. 42% (n=6) of the patients received stem cells from their brothers, 50% (n=7) from their

sisters, and 8% (n=1) from their father. 35% (n=5) had sex-matched donors, while 72% (n=10) had blood group-matched donors. Of the four group-mismatched donors, two were major mismatches. Patients were classified into the Pesaro three groups based on liver size, duration, and adequacy of iron chelation, as well as elastography/Fibroscan estimation of fibrosis. None of the patients was in class 1. Nine children were in class 2, and 3 were in class 3. When class 3 is further classified according to age (>7 years) and liver size (> 5 cm) 11 one child was in the class 3 high-risk group.

All underwent T2* MRI of the heart and liver, and 3 had mild liver iron and 1 had moderate liver iron deposition. Only 2 had heart iron deposition.

The mean CD34 stem cell dose was 6.71 x 10^6/Kg. All patients engrafted, and the median time to engraftment was 17 days (range, 15-26 days). Platelet engraftment occurred at a median time of 20 days (range, 15-27 days). The median duration of follow-up was 539 days (range 83-1102 days).

Infective complications are the commonest complication during the transplant, and almost all patients received antibiotic therapy for neutropenic sepsis at some point during the transplant course. One child developed severe *Closterium difficile* infection. Cytomegalovirus reactivation occurred in one child, and it was treated with intravenous Ganciclovir. One child developed a Parvo virus-induced hepatitis requiring Intravenous immunoglobulin therapy. The next common complication that occurred is sinusoidal obstructive disease. The main reason for the high incidence is that the liver is already damaged by transfusion iron overload and the use of busulfan and cyclophosphamide. A total of 6 patients developed sinusoidal obstructive disease (SOS) of the liver. Five had clinically mild disease and 2 had severe SOS. Incidence of SOS in the Bu/Cy/ATG group is higher (5 children) compared to the Flu/Treo/Thio group (2 children). The severe SOS cases were seen in the Bu/Cy/ATG group.

Most patients developed oral mucositis. One child had typhlitis and received total parental nutrition. 2 children developed grade 2-3 acute lower gut GVHD. Both were steroid-responsive and confined to the lower gut. No incidence of cGVHD was reported at the time of writing.

Median donor chimerism was 99% (range 72.07-100%) at the last follow-up. Twelve patients achieved sustained full donor chimerism, and two had mixed chimerism. Only one child received a donor lymphocyte infusion at day 434 post-transplant for a slipping chimerism, and he is currently transfusion independent with a mixed chimerism of 72.07%.

Despite being a LMIC, 0% transplant-related mortality (TRM) and 100% overall survival (OS) rates, with a 100% thalassaemia-free survival rate at the time of writing. All 14 children are alive, transfusion-independent, and maintaining excellent quality of life.

Conclusion

This report represents a single-centre experience of HLA-matched sibling donor HSCT in children with TDT in a government-funded transplant centre in Sri Lanka. Our findings confirm that HLA-matched related donor HSCT is a safe, and cost-efficient curative option for children with TDT, even in low-resource settings. Careful patient selection, appropriate conditioning regimens, experienced multidisciplinary care, and international mentorship enabled excellent outcomes.

Scaling up access to HSCT for thalassaemia in Sri Lanka and similar settings will require increased infrastructure, training, and early identification of suitable patients before irreversible organ damage occurs. Given its curative potential and cost advantage over lifelong transfusion and chelation, HSCT should be prioritised in national thalassaemia management strategies.

Author contribution

The main contribution to this work was made by S. Vitharana, who is the first and corresponding author. N. Senadheera also contributed.

Conflict of interests

The authors declare that there are no conflict of interests.

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