Hematopoietic stem cell transplantation in children with thalassemia: Brazilian Society of Bone Marrow Transplantation Consensus

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ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) represents a critical therapeutic option for patients with transfusion-dependent thalassemia (TDT), with thalassemia-free survival rates exceeding 90% in cases involving HLA-matched sibling donors. Due to the limited availability of matched donors, alternative sources such as HLA-matched unrelated donors, haploidentical donors, and umbilical cord blood have broadened HCT eligibility. Despite its potential for cure, HCT involves risks like graft-versus-host disease, graft rejection, and transplant-related mortality. Recent improvements in conditioning regimens have enhanced patient outcomes and quality of life. Factors affecting HCT success in TDT include recipient age, disease complications, effective chelation therapy, Pesaro score, and donor compatibility. This article aimed to update the Brazilian consensus established by the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation in 2021, incorporating the latest advances in treating and managing TDT patients undergoing transplantation.

Keywords: Thalassemia. Hematopoietic Stem Cell Transplantation. Hematology. Pediatrics.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) plays a crucial role in treating transfusion-dependent thalassemia (TDT), offering a potentially curative approach. The procedure involves replacing the patient's defective hematopoietic system with healthy stem cells from a donor, which can lead to thalassemia-free survival rates

exceeding 90% in HLA-matched sibling donors (MSD)[1]. However, availability of such donors is limited, prompting exploration of alternative donor sources, such as HLA-matched unrelated donors (MUD), haploidentical (HAPLO) donors, and umbilical cord blood (UCB), which have expanded the pool of patients eligible for HCT[1,2]. Despite its curative potential, HCT is associated with significant risks, including graft-*versus*-host disease (GVHD), graft rejection, and transplant-related mortality. Advances in conditioning regimens have mitigated some of these risks, improving patient outcomes and quality of life[3]. The success of TDT HCT is influenced by factors such as recipient age, disease-related complications, adequate chelation, Pesaro score, and availability of a histocompatibility donor[4].

The aim of this article was to update the Brazilian consensus previously published by the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation in 2021, highlighting the latest development in the treatment and monitoring of patients with TDT undergoing HCT[5].

PESARO RISK CLASSIFICATION

In the late 90s, the Pesaro group proposed a risk classification for pediatric patients based on the analyses of 222 patients categorized into three distinct groups according to the presence of specific clinical and pathological features (Table 1). The authors observed that portal fibrosis, hepatomegaly (> 2 cm from the right costal margin), and inadequate chelation therapy were significantly associated with lower probabilities of survival and event-free survival[6].

Table 1. Pesaro risk classification.

Risk classes	Hepatomegaly	Liver fibrosis	Irregular chelation
Class 1	No	No	No
Class 2 (minimum 1, maximum 2)	Yes/no	Yes/no	Yes/no
Class 3	Yes	Yes	Yes

Source: Strocchio and Locatelli[2].

However, this stratification is not easily applicable when liver biopsy analyses are not routinely conducted. Therefore, alternative risk group assignments independent of liver biopsy have been proposed. One such risk stratification scheme, focused primarily on age and liver size, reported cure rates exceeding 70% for MSD HCT in children under 7 years old with hepatomegaly < 5 cm, regardless of chelation history or liver fibrosis[7]. A report from the Center for International Blood and Marrow Transplant Research (CIBMTR) on the results of MSD HCT for TDT confirmed that age at transplantation and liver size are independent predictors of mortality following transplantation. In patients younger than 7 and without hepatomegaly (defined as hepatomegaly > 2 cm), the 5-year probabilities of overall survival and disease-free survival were 98 and 94%, respectively[8].

PRE-TCT EVALUATION

Individuals eligible for HCT should undergo routine evaluations for organ function and any thalassemia-related complications, as demonstrated in Table 2[5].

RELATED HUMAN LEUKOCYTE ANTIGEN IDENTICAL DONORS

The earliest studies on MSD HCT for TDT used a myeloablative conditioning regimen that included busulfan (Bu), cyclophosphamide (Cy), and anti-thymocyte globulin (ATG), demonstrating successful outcomes, particularly in patients classified as Pesaro classes 1 and 2[6,9]. However, due to hepatic and cardiac toxicity caused by iron overload and its association with Bu and Cy, particularly in Pesaro 3, there has been a change towards using myeloablative conditioning regimens with reduced toxicity, primarily based on fludarabine (Flu). The use of a less toxic myeloablative regimen with Flu, Bu, and ATG showed promising results, achieving a 95% event-free survival (EFS)[10]. Further alterations include adding thiotepa (TT) to intravenous Bu and Cy or treosulfan with Flu and/or TT, which also results in favorable outcomes[4].

Table 2. Pre-hematopoietic cell transplantation evaluation.

Organ/system	Exams
Overall assessment	History, physical examination, height, and weight Lansky / Karnofsky performance status
General laboratory tests	Complete laboratory tests, including blood count, blood chemistries, kidney and liver function, serum ferritin, and other exams of iron profile, hormones, serology, urine and stool tests, β-HCG serum pregnancy test for females of childbearing potential
Lung	Pulmonary function test
Heart	Echocardiogram with tricuspid valve evaluation Electrocardiogram Heart MRI T2* to evaluate increased iron deposition
Liver	Liver MRI T2* to evaluate increased iron deposition Liver elastography or liver biopsy to assess portal fibrosis (if available)
Kidney	Glomerular filtration rate, urinalysis, microalbuminuria-creatinine ratio
Hematological system	Anti-HLA antibody test (if donor with mismatch), extended erythrocyte phenotype, and the number of transfusions received
Multidisciplinary evaluation	Social worker, psychologist, hemotherapy, endocrinology (risk of infertility), gynecology-obstetrics (if considering fertility preservation), dentist, nutritionist

Source: Elaborated by the authors.

Recently, a multicenter retrospective study conducted by the CIBMTR in conjunction with Asian centers demonstrated that Bu/Cy/Flu conditioning was associated with better overall survival and EFS and reduced graft failure incidence compared to Bu/Cy alone[10]. The major challenge is the preparatory regimen for Pesaro 3 patients, due to the high transplant-related mortality and graft failure. Different groups have been developing strategies to overcome this risk. The Pesaro group has developed a modified regimen that includes an immunosuppression phase (PTIS), adding hydroxyurea and azathioprine starting 45 days before the conditioning phase, which consists of Flu, Bu, Cy, and TT, resulting in an excellent outcome with a thalassemia-free survival rate of 92%. All patients received intensive pre-transplant hypertransfusion and chelation to suppress erythropoiesis[11,12]. Another effective strategy, developed by Anurathapan et al.[13], includes PTIS, which consists of two cycles of Flu and dexamethasone (starting two months before conditioning), followed by Flu, Bu, and ATG during the conditioning phase.

The results with related HLA-identical UCB are similar to those of HLA-identical bone marrow; both sources are currently recommended as standard of care for patients with TDT[14]. The gold standard for GVHD prophylaxis in most published reports of MSD is the combination of cyclosporine and a short course of methotrexate (MTX). Like sickle cell disease transplants, the addition of ATG for MSD and MUD has significantly improved outcomes and is now mandatory[15].

Therefore, considering the previously published consensus[5], we recommend either BuCy or FluCyBu-based myeloablative conditioning (Table 3), along with using bone marrow or related UCB as sources of hematopoietic stem cells for patients with MSD. GVHD prophylaxis should be administered with cyclosporine and MTX. For UCB, MTX should be replaced with another immunosuppressive drug.

Table 3. Preferred conditioning regimen to transfusion-dependent thalassemia.

	Preferred conditioning regimen
MRD*	Fludarabine 35–40 mg/m²/day 11 to 7 Busulfan** (dose based on body weight—kg) day 10 to 7 Cyclophosphamide 50 mg/kg/day 5 to 2 rATG (cumulative dose 4.5–7 mg/kg, according to institutional protocol)
MRD***	Busulfan** (dose based on body weight—kg) day 10 to 7 Cyclophosphamide 50 mg/kg/day 5 to 2 rATG (cumulative dose 4.5–7 mg/kg, according to institutional protocol)

Source: Elaborated by the authors. rATG: rabbit anti-thymocyte globulin; *busulfan should be administered immediately after the fludarabine; **for dose based on body weight (kg), see Table 4; ***may reverse the order of administering BusulfanCyclophosphamide to CyclophosphamideBusulfan to potentially reduce the risk of sinusoidal obstruction syndrome. It is recommended to have a 48-hour interval between busulfan and cyclophosphamide to lower the risk of veno-occlusive disease.

Patients with a liver size > 2 cm (Pesaro class 2–3), any palpable spleen larger than 2 cm, or ferritin levels exceeding 1,000 ng/mL should receive hydroxyurea (Hu) before conditioning to reduce erythropoietic hypertrophy (Table 4).

Table 4. Busulfan dose*.

Body weight (kg)	Dose per day	Total dose
< 9	4	16
9–16	4.8	19.2
16–23	4.4	17.6
23–34	3.8	15.2
> 34	3.2	12.8

Source: adapted from the Busilvex Leaflet. *From the Busilvex Leaflet. Monitoring serum busulfan levels is strongly recommended, with a targeted AUC of 3.600 to 4.440 mcMol*min/L[16].

ALTERNATIVE DONORS

Matched unrelated donors and umbilical cord blood

In cases in which a matched family donor is unavailable, alternative donor HCT has become the standard of care. Recent years have shown that the outcomes of MUD HCT are comparable to those of MSD, with five-year EFS rates approaching 90%, and even better outcomes in patients under 6 years old. Major challenges to achieving optimal results in MUD transplants include graft failure, regimen-related toxicity, and GVHD[10,17]. Concerning conditioning, FluBu-based conditioning that includes cyclophosphamide ± thiotepa and introducing drugs like alemtuzumab or ATG has effectively reduced GVHD in all cases of HLA disparity or non-related donors[10,18]. Similar to the findings in MSD HCT, patients with Pesaro 3 and MUD donors also benefit from PTIS and Flu-based conditioning[13]. Currently available evidence suggests that unrelated UCB transplantation is a suboptimal strategy for managing TDT since graft failure rate could be as high as 57%[19].

Haploidentical donors

In recent years, there has been a potential improvement in accessibility and outcomes of HAPLO HCT. A recent review[20] examined 10 studies on HAPLO transplant for TDT patients, finding an EFS rate of 84.5% and a graft failure rate of 8.1%. Transplantation-related mortality was reported at 7.4%, with infections identified as the primary cause of death. The pooled proportions of acute GVHD were 29.6%, with 22.3% for grades 2 to 4 and 9.1% for grades 3 to 4.

Some excellent results have been published from the Thailand group, utilizing a PTIS phase, Flu Bu conditioning, and PTCy GVHD prophylaxis, with outcomes approaching MSD and MUD[21]. Due to regular transfusions, patients with thalassemia are at high risk of developing donor-specific antibodies (DSA) and graft failure.

Several studies suggest that the sequential use of certain medications and procedures, such as immunoglobulin, plasmapheresis, mycophenolate mofetil, bortezomib, and buffy coat, can effectively desensitize highly sensitized patients and help prevent graft failure[13,21,22]. Thus, we recommend for HAPLO transplant the protocol used by Anurathapan et al.[22], with special attention to the PTIS phase and the management of high DSA titers. Table 5 summarizes the main indications for transplantation for TDT, considering the type of donor.

Table 5. Hematopoietic cell transplantation indications for pediatric patients: Brazilian Society of Cellular Therapy and Bone Marrow Transplantation's consensus recommendations for thalassemia.

Allogeneic			
Familiar		Unrelated	
MSD	HAPLO	MUD	MMUD
Yes	Clinical option	Yes HLA identical (10/10) and HLA DPB1 identical or with a permissive mismatch	No

Source: Elaborated by the authors. MSD: matched sibling donors; HAPLO: haploidentical; MUD: matched unrelated donors; MMUD: mismatch unrelated donor.

GENE THERAPY

Gene therapy (GT) involves the potential for genetic enhancement by correcting altered (mutated) genes or site-specific modifications. In TDT patients, GT relies on the *ex-vivo* genetic modification of autologous stem cells to restore β-globin production or induce an increase in γ-globin, thus reducing the imbalance between α and non-α chains and increasing absolute hemoglobin levels. Several techniques have been recently highlighted, particularly lentiviral transduction, which replaces the β-globin gene with lentiviral vectors (gene addition). Another method, gene editing, allows for the introduction of specific DNA sequences into the genome of autologous stem cells using nucleases such as zinc finger nucleases and CRISPR-Cas9 nucleases. This process enhances fetal hemoglobin expression by reactivating gamma chain production, often through the inactivation of genes like BCL11A or ZBTB7A, which are potent inhibitors of γ-globin synthesis.

Lastly, base editing has shown promising results despite being in a more preliminary stage due to its precision in gene correction[23]. In GT, the patient undergoes an autologous transplant that includes mobilization, cell collection, and myeloablative chemotherapy, followed by the infusion of laboratory-corrected hematopoietic stem cells. Approved in 2015 in the United States of America, betibeglogene autotemcel (Zynteglo) promoted transfusion independence in 20 of the 22 patients analyzed (91%)[24]. This product is indicated in the package insert for patients aged 12 years old or older with β-TDT who do not have the β0/β0 genotype, for whom HCT would be indicated, but no HLA-identical donor is available. The estimated cost is $ 2.8 million per patient, significantly limiting access to this treatment worldwide. In a recent study, Frangoul et al.[25] demonstrated promising gene editing results by infusing autologous CD34+ cells edited using the CRISPR/Cas9 technique to target the BCL11A gene.

It is important to emphasize that GT may present potential genotoxicity associated with myeloablative conditioning and an increased risk of developing myelodysplastic neoplasms and leukemias, as previously described in clinical studies involving patients with sickle cell disease undergoing gene therapy[26].

CHIMERISM SURVEILLANCE

About 35–45% of post-transplant patients develop mixed chimerism (MC), but those with stable MC are transfusion-independent and show no signs of ineffective erythropoiesis[27]. The risk of progression to secondary failure is associated with the timing of detection of MC and its degree[27]. A proposed classification of the degree of MC considers the amount of residual host cells (RHC):

- Level 1 < 10%;
- Level 2 = 10–25%;
- Level 3 > 25%.

Patients who develop level 3 RHC in the first month after transplantation are at the most significant risk for SGF[4,27]. For those patients with complete chimerism, a proposed follow-up is evaluation on D+30, D+60, D+90, D+180, and D+360. For those with MC, a more frequent evaluation should be performed with the inclusion of

D+120 and D+150 assessment[5]. Most patients with MC will eventually develop persistent mixed chimerism in the long term[27]. Strategies for managing progressive loss of chimerism include immunosuppression tapering, immunosuppression improvement, and donor lymphocyte infusion[28,29]. None of these strategies has an adequate level of evidence.

IRON OVERLOAD THERAPY

Pre-transplant iron overload is associated with several complications, such as hepatic veno-occlusive disease, graft failure, GVHD, and decreased overall survival[30,31]. Ferritin, transferrin saturation index, and T2* MRI of the liver and heart are essential for assessing iron overload status before HCT. Iron overload therapy is a gradual process that should be organized before HCT. Effective iron chelation relies on evaluating adherence, optimizing doses, and sometimes experimenting with a combination of chelators[30].

Iron overload after transplant is also associated with increased morbidity. Therefore, iron overload therapy should continue in those with inadequate iron chelation before the transplant. During the early post-transplant phase, phlebotomy and iron chelators are acceptable treatment options[5,30].

TRANSFUSIONAL SUPPORT

Before HCT, patients should be on a regular transfusion regimen that helps suppress ineffective erythropoiesis. They should receive transfusions of leukoreduced red blood cells with an extended phenotype to prevent alloimmunization to HLA antigens and red cell antigens. Planning for post-transplant transfusion support relies on evaluating transfusion history, the extent of alloimmunization, and any prior transfusion reactions. Ideally, the hemotherapy team should participate in this process[5].

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Conception and design:** Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Analysis and interpretation of data:** Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Technical procedures:** Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Statistics analysis:** Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Manuscript writing:** Darrigo Junior LG, Vieira AK, Kuwahara C, Gouveia RV, Klinger P, Antunes AA and Garcia JL. **Final approval:** Darrigo Junior LG.

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