DOI:10.46765/2675-374X.2021v2n2p132

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH HEMOGLOBINOPATHIES: BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANTATION CONSENSUS

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INTRODUCTION

Hemoglobinopathies are the most common monogenic diseases worldwide. There are approximately 300,000 to 400,000 newborns with hereditary hemoglobinopathies yearly. In Brazil it is estimated that there are around 70,000 – 100,000 people living with hemoglobinopathies, the most common being sickle cell disease[1].

Sickle cell disease (SCD) is a severe genetic disorder caused by a single point mutation in the adult β-globin (HBB) gene that causes a Glu > Val aminoacid substitution in the β-globin chain (βS-globin)[2]. The sickle hemoglobin (HbS, α2βS2) has the propensity to polymerize under deoxygenated conditions, resulting in the production of sickle-shaped red blood cells (RBCs). In your turn, sickle RBCs causes hemolytic anemia and occlusions of small blood vessels, leading to impaired oxygen delivery to tissues, multiple organ damage, severe pain, and early mortality[3]. Stand of care treatments, such as transfusions, hydroxyurea and L-glutamine still are associated to reduced life expectancy and quality of life[4]. More recently developed targeted therapies, voxelotor, and crizanlizumab, although able to reduce the number of VOC, have not been tested in the long term and are associated with high costs[4]. Currently, the only available curative treatment for SCD patients is allogeneic hematopoietic cells transplantation (allo-HCT), with overall survival superior to 90% and event-free survival higher than 85%[5]. Nevertheless, allo-HCT is limited by the availability of compatible donors and transplant-related mortality and long-term toxicities[4,5].

Thalassemias are a heterogeneous group of recessive hereditary diseases that present a decreased synthesis of the alpha or beta chains of hemoglobin (Hb). It is considered a quantitative defect of hemoglobin synthesis and is characterized by a hypochromic microcytic anemia[6]. The spectrum of disease severity is varied and depends not only on the subtype of thalassemia but also on the treatment provided such as splenectomy, transfusions, and iron chelation[6]. Similar to SCD, HSCT is considered the only curative option for patients with thalassemia[7].

In thalassemia, the main complications are due iron overload secondary to chronic blood transfusion while in sickle cell disease, the main complications arise from vaso-occlusion. Neurological events like seizures, stroke and silent ischemia and damage to several organs, reduces life expectancy by 20 years when compared to that of the normal population, according to a Brazilian study[1].

In Brazil, the treatment of hemoglobinopathies in the public health system (Sistema Unico de Saude – SUS) is regulated by the Joint Ordinance No. 05 of February 19, 2018. The protocol established by this ordinance regarding SCD, includes newborn screening, antibiotic prophylaxis, hydroxyurea and monitoring of neurological disease with transcranial Doppler. In 2015 hematopoietic stem cell transplantation (HSCT), the only curative option for hemoglobinopathies currently available, was incorporated as a procedure reimbursed by SUS. Reimbursement for allogeneic HSCT in thalassemia has been approved since 1999.

THALASSEMIA MAJOR

The greatest experience in HSCT for thalassemia is from the Pesaro group, which defined a risk stratification as early as 1994. The classification should be followed in patients under the age of 17 years (8) and basically involves the quality of iron chelation and its consequences (Table I).

TABLE 1. Pesaro Risk Classification

Risk factors	Class 1	Class 2	Class 3
Inadequate iron chelation	No	Yes/No	Yes
Hepatomegaly > 2 cm from RCM	No	Yes/No	Yes
Portal fibrosis	No	Yes/No	Yes

RCM, right costal margin

With this stratification thalassemia-free survival (TFS) was 90%, 80% and 65% for class 1, 2 and 3 patients, respectively. Transplant-related mortality (TRM), as expected, was also related to risk classification, being higher in class 3 patients[8].

RELATED HLA IDENTICAL DONORS (BONE MARROW OR CORD BLOOD)

Most of the data are from identical HLA related donors of Pesaro's group and two large retrospective analyses from the U.S. and Europe. The most used conditioning regimen in these studies, for patients under the age of 17 years and Pesaro classes 1 and 2, was myeloablative with Bussulfan (14 mg/kg), Cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (ATG) (8). In patients with Pesaro class 3, due to high transplant-related mortality (TRM) and graft failureit appears to be better adopt a regimen with pre-HSCT immunosuppression with azathioprine, hydroxyurea, fludarabine and transfusion, with the objective of suppression of erythropoiesis, followed by reduced BuCy (cyclophosphamide of 120 mg/kg)[9]. With this new regimen, overall survival (OS) was 87% and thalassemia-free survival (TFS) was 82% in a group of 73 patients[10]. In patients over 16 years, this same regimen with pre-HSCT immunosuppression and reduced BuCY has been used[11].

The results with related HLA identical umbilical cord are similar to those of HLA identical bone marrow, both sources being currently recommended as standard of care for patients with transfusion-dependent thalassemia[12].

Some groups have associated Thiotepa with classic BuCY to reduce the rejection rate, especially in children under the age of 4 years[11]. A recent study compared data on BuCYATG versus BuCYThio and found no differences even in children under 4 years[13].

UNRELATED HLA IDENTICAL DONORS

Unrelated HSCT data in patients under 16 years and with HLA-identical donors (10/10) are similar to results with related HLA-identical donor (14). It is important to reinforce that, for hemoglobinopathies, typing should include HLA DPB1, considering that incompatibilities in this locus are associated with inferior outcome[15,16].

Data with unrelated umbilical cord blood, although restricted, resulted in high graft failure rates and, consequently, reduction in overall survival[17,18]. For this reason, we do not recommend the use of unrelated umbilical cord blood.

Haploidentical donors

Two strategies have been employed: *ex vivo* lymphocyte depletion and *in vivo* depletion. *Ex vivo* depletion comprises CD34 selection or CD3+/CD19+ depletion[19]. With overall survival of 100%, the data are encouraging, despite slow immune recovery and frequent viral infections[20].

Initial data on the use of post-transplant cyclophosphamide as T-cell depletion *in vivo* resulted in high rates of graft failure. Modifications such as increased TBI dose (200 cGy to 400 cGy) and inclusion of preconditioning immunosuppression, as that used in patients with Pesaro class 3, improved results significantly[21]. These transplants should be performed only in controlled clinical studies at this time.

SICKLE CELL DISEASE

Allogeneic Stem Cell Transplant indications

Currently, advances in conditioning regimens, graft-versus-host disease (GVHD) prophylaxis and better knowledge related to major complications of HSCT have made indications for HSCT broader, allowing both patients with severe disease and patients considered to be at higher risk for complications to be eligible for transplantation[22]. However, the decision to perform HSCT should be considered within a scenario in which each case should be individualized, since the clinical evolution is usually very variable

and the presence or absence of clinical symptoms in the first years of life does not predict how the patient will evolve in the future[23].

Thus, young patients with symptomatic sickle cell disease who have a compatible HLA sibling donor should be referred for evaluation at a transplant center, preferably at preschool age[5]. In adults, the risks and complications of HSCT have gradually decreased, so that symptomatic patients with an identical HLA sibling donor can also benefit from an evaluation at a transplant center[22].

Table 2 shows the main indications for HSCT for patients with SCD who are using hydroxyurea or under chronic transfusion and present at least one of the conditions described below. We highlight that in the recommendations of this consensus there is no contraindication associated with the patient's age.

TABLE 2. Indications for HSCT with HLA-identical sibling donors for sickle cell disease

Neurological alteration due to stroke, any neurological alteration persisting for more than 24 hours or altered imaging
Cerebrovascular disease associated with sickle cell disease
Two or more severe vaso-occlusive crises (including acute chest syndrome) in the last year
More than one episode of priapism
Presence of more than one antibody in patients on a hypertransfusion regimen
Osteonecrosis in more than one joint

PRE-TRANSPLANT CARE

Patients eligible for HSCT should be evaluated for their organic function and the presence of complications related to SCD (Table 3)24.

There is no contraindication for transplantation in patients with vascular alteration with Moyamoya's disease patter. Besides, we do not recommend pre-transplant surgical correction of this complication. In such cases, the decision to perform transplant shall be discussed and evaluated by the transplant center.

TABELA 3. Pre-TCTH evaluation

Organ/System	Exams
Lung	Pulmonary function test (PFT)
Heart	Echocardiogram with tricuspid valve evaluation
Central Nervous System	Brain MRI Transcranial Doppler ultrasound (Up to 16 years) Neuropsychiatric evaluation if possible
Liver	Liver MRI T2* (according to the number of transfusions and serum ferritin)
Kidney	Glomerular filtration rate Urinalysis Microalbuminuria-creatinine ratio
Hematological system	Anti-HLA antibody test (mismatch) Extended erythrocyte phenotype Number of transfusions received Ferritin Keep HbS% < 30% before transplantation with simple transfusion or erythrocytapheresis
Multidisciplinary evaluation	Social worker Psychology Hemotherapy Endocrinology (discussion on risk of infertility) Gynecology-obstetrics (if considering fertility preservation) Pain team - anesthesia (if chronic pain) Psychiatry (if pre-existing psychiatric disease)

CONDITIONING REGIMENS

The conditioning regimen currently recommended for HSCT-candidates with an HLA-identical sibling donor is myeloablative (MAC). This regimen is based on the use of busulfan (Bu) 14-16 mg/kg (total dose) and cyclophosphamide (Cy) 200 mg/kg (total dose) with ATG[7]. Studies published using BuCy have demonstrated an OS in the pediatric population of 95 to 97%, and EFS of 85%[25-27]. It is important to highlight the role of the addition of ATG in conditioning regimens, since its inclusion decreases the incidence of GVHD, in addition to reducing the rejection rate from 22.6% to 3% in one study[27]. Another recommended scheme is the use of fludarabine and busulfan, with results similar to those of BuCy[28]. There is a clear relationship between age at the moment of HSCT and the result obtained, which is superior in pediatric patients[29]. It is important to highlight that, despite the excellent results, myeloablative regimens are associated with higher morbidity and mortality due to the risk of infertility, secondary neoplasia, besides hindering transplantation in some cases in adults with important comorbidities and organic dysfunction[30]. The use of a less toxic myeloablative regimen with fludarabine (Flu), busulfan and ATG showed promising results with 95% EFS[31].

HSCT with reduced intensity conditioning (RIC) or non-myeloablative (NMA) in the pediatric population resulted in high graft failure rate, thus not being recommended for this age group[32]. In adults, conditioning containing alemtuzumab associated with low radiation dose (TBI 300 cGy) and sirolimus as prophylaxis for GVHD showed promising results[33]. However, the data are restricted, and we do not routinely recommend non-myeloablative regimens.

So, we recommend, for patients with a compatible sibling donor, myeloablative conditioning:

A) Cell source: Bone marrow or related umbilical cord

B) Busulfan 14 - 16 mg/kg IV + Fludarabin 150 mg/m^2 + rabbit ATG 4.5 – 7.5mg/kg

C) Busulfan 14-16 mg/kg IV + Cyclophosphamide 200 mg/kg + rabbit ATG 4,5 – 7,5 mg/kg

D) GVHD prophylaxis with cyclosporine and methotrexate. In the case of umbilical cord blood, methotrexate should be replaced by another immunosuppressive medication.

ALTERNATIVE DONORS

Although indications with alternative donors did not differ from indications with HLA-identical sibling donors, only the use of HLA-identical related umbilical cord blood showed results similar to those of bone marrow from HLA-identical siblings[12]. HSCT with matched unrelated donors are limited. A recent retrospective EBMT register study with 73 transplants showed that this is an important option for patients with severe complications (stroke) and non-responding to hydroxyurea[34]. The HSCT with haploidentical donors is an important option but with few cases published so far[19,35]. Haploidentical transplants should be performed only in the context of clinical trials at this time[19,36].

We emphasize that all patients (or their parents) diagnosed with sickle cell disease should receive information about all therapeutic options, including HSCT, as soon as possible. If they have siblings, they should be submitted to HLA typing. Patients with alterations indicating HSCT should be referred for evaluation as soon as possible at a transplant center.

TRANSFUSION SUPPORT

Patients with hemoglobinopathies usually arrive for transplant after a long period of exposure to red blood cell (RBC) transfusions. These patients have a higher rate of RBC alloimmunization than patients with cancer. Alloimmunization occurs in 10-20% of transfusion-dependent patients with thalassemia[17], while in patients with sickle cell disease, this rate varies between 20-50%[37]. Planning transfusion must involve the hemotherapy service. The number of previous transfusions, the history of transfusion reactions, information about the presence of acquired anti-erythrocyte antibodies (AEA) and red cell phenotyping data are essential for a good HSCT planning.

The tests to be performed pre-HSCT are, in addition to ABO and Rh typing, the search for AEA, antibody titration, in case of ABO incompatibility between donor and recipient, direct antiglobulin test and extended RBC phenotyping. This must include at least the following antigens: C (RH2), E (RH3), c (RH4), and (RH5), K (KEL1), k (KEL2), Jka (JK1), Jkb (JK2), Fya (FY1), Fyb (FY2), S (MNS3), s (MNS4). Genotyping is recommended to elucidate complex cases and to identify RHCE variants, common in patients with sickle cell disease[38].

All patients with hemoglobinopathies undergoing HSCT should receive leukocyte reduced and irradiated cellular blood products. It is advisable to initiate irradiation in the pre-conditioning period. Washed blood products are indicated for patients with previous severe allergic / anaphylactic reactions and may

be indicated in ABO-incompatible transplants to minimize the amount of antibodies infused[39] .

CHIMERISM EVALUATION

The evaluation of chimerism in the context of HSCT in hemoglobinopathies is of fundamental importance. The recommendation is that the evaluation starts on the D+30 post-HSCT and repeated on D+60, D+90, D+120 (if no complete chimera D+90), D+150, D+180 and D+365 post-HSCT. In sickle cell disease, Bernaudin et al. showed that 44% of patients submitted to an HLA-identical donor HSCT maintained mixed chimera one year after HSCT. This fact, however, did not result in graft failure or disease manifestations[27]. It is estimated that at least stable 25% donor mixed chimera is needed to prevent clinical manifestations of sickle cell disease after HLA identical sibling transplants[40]. Chimerism analysis should ideally be performed in specific cell populations (erythrocyte, myeloid and T cells) and not just in whole peripheral blood[40]. Mixed chimerism data in donors that are not HLA-identical siblings are scarce and cannot be extrapolated safely to these other scenarios. Approach to falling chimerism are not well established in the literature. Most authors recommend increasing immunosuppression, but no clear recommendation can be done.

IRON OVERLOAD

Patients with hemoglobinopathies usually present with iron overload for HSCT. We recommend, if possible, the best available iron chelation in the pre-HSCT period[41]. There are no prospective data in literature so far, if a period of intense iron chelation pre HSCT will improve long term outcome, since iron overload is a long-lasting process. Pre- and post-HSCT evaluation and approach of iron chelation are summarized in Table 5. Iron chelation options are phlebotomy 6-9 mg/kg each 2 weeks; if well tolerated, it can be done weekly (AIII); deferoxamine 40 mg/kg IV ou SC 5/7 days of the week (AII); deferasirox 10 mg/kg/day (AII).

TABLE 5. Recommendations regarding the evaluation and approach of iron overload.

	Iron overload evaluation	Toxicity evaluation of iron chelation
Before HSCT	Ferritin, Transferrin saturation Serum iron, MRI (LIC and T2*)	Kidney and hepatic function
6 months post-HSCT (from 6 months, if there is no GVHD or other complication that contraindicates it)	Ferritin Transferrin saturation MRI (T2* and LIC) (only if clinically indicated and in patients with pre-HSCT abnormalities)	Kidney and hepatic function every two weeks Most frequent assessments depending on clinical and laboratory assessment
12 months after the beginning of therapy and annually until normalization	Ferritin Transferrin saturation MRI (T2* and LIC)	

MRI, magnetic resonance imaging; LIC Liver iron concentration

LONG-TERM FOLLOW-UP

Long-term follow-up should be programmed according to the general recommendations for all HSCTs. However, some specific assessments, such as neurological, cardiac and hepatic, require special attention[31,42]. In relation to assessments of infections and immunizations, the recommendations of the corresponding chapters should be followed.

TABLE 6. Long-term follow-up after HSCT for hemoglobinopathies

Evaluation and Exams	Days		Months				Years	
	100	120	6	9	12	18	2 years	Annual
Disease evaluation	X	X	X	X	X	X	X	X
Chimera evaluation (VNTR or STR, ABO group if incompatibility, karyotype, Hb electrophoresis)	X	X	X	X	X	X	X	X
General exams (hepatic and kidney function, biochemistry exams)	X	X	X	X	X	X	X	X
Brain MRI (for SCD)					X		X*	X*
Transcranial Doppler (for SCD if abnormalities in previous exams)					X		X*	X*
Neurological and cognitive evaluation (if available)	X				X		X*	X*
Cardiac and hepatic MRI (if abnormalities in previous exams)					X		X*	X*
TSH					X		X	X
Ferritin and transferrin saturation			X		X		X*	X*
Echocardiogram					X			
PFT			X	X	X	X	X	
Lipidogram			X		X		X	X
Bone mineral density					X			
Vaccination (according to institutional protocol)								
Fertility evaluation (≥11 years): FSH, LH, Testosterone and sperm analysis (for men)					X			
Skin, mouth, eyes, gynecological evaluation					X		X	X
Screening for malignancy					X		X	X
Growth and hormonal evaluation (≥ 11 years)					X		X	X

HSCT, hematopoietic stem cell transplantation; VNTR, variable number tandem repeat; ST, short tandem repeat; Hb, hemoglobin; MRI, magnetic resonance imaging; SCD, sickle cell disease; TSH, thyroid-stimulating hormone; PFT, pulmonary function tests; FSH, follicular-stimulating hormone; LH, lutenizing hormone

TABLE 7. Recommendations

Transfusion-dependent talassemia	Recommendation
HLA-identical donor (bone marrow or umbilical cord) Age <16 years Pesaro classes 1 and 2	Standard
Unrelated donor 10/10 (preferably bone marrow), Age < 16 years, Pesaro classes 1 and 2 HLA DPB1 without mismatch or with permissive mismatch	Standard
Unrelated cord blood	Not recommended
Haploidentical	Experimental protocol
Sickle cell disease	Recommendation
HLA-identical sibling donor (bone marrow or cord blood)	Standard
Unrelated umbilical cord blood	Not recommended (NR)
Haploidentical	Experimental protocol (EP)

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