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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMOGLOBINOPATHIES

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INTRODUCTION

In 2021 the Brazilian society of stem cell transplantation and cell therapy published the consensus guidelines regarding hematopoietic stem cell transplantation (HSCT) for hemoglobinopathies[1] (Costa et al., 2021). The current recommendations are detailed in table 1.

THALASSEMIA MAJOR

No changes have been added for thalassemia. HSCT with a matched sibling donor (MSD) or a related cord blood is the treatment of choice for young patients with transfusion dependent thalassemia[2-4]. Matched unrelated and haploidentical HSCT, using bone marrow graft, are a clinical option. Pre-transplant immunosuppression should be considered for Pesaro class 3[5-7].

SICKLE CELL DISEASE

Indications for HSCT in sickle cell disease (SCD) are summarized in table 2. Conditioning regimen should be myeloablative for patients ≤ 16 years old. For adults, fludarabine, busulfan and ATG is a safe and effective regimen[1,8,9]. The chemo-free regimen with alemtuzumab and TBI, pioneered by the NIH group, was successfully reproduced by other centers and is a good option for adults and patients with established organ damage[10]. Haploidentical HSCT with post-transplant cyclophosphamide has been used worldwide for almost all diseases and, in SCD, showed high rejection rates in the beginning. Improvements in the conditioning regimen were performed, including the use of pre-transplant immunosuppression, the increase in TBI dose from 2 cGy to 4 cGy and the addition of thiotepa, which significantly reduced rejection rates[5,11-13]. We consider haploidentical transplant as a clinical option in children with significant neurological alteration and in adults with the established indications.

SHOULD HSCT BE OFFERED TO ALL YOUNG CHILDREN WITH AN HLA IDENTICAL SIBLING DONOR?

The optimal timing for HSCT in SCD with MSD is not well established. Previous international reports showed excellent outcomes in young children. Patients younger than 5 years old had a 12% increase in overall survival (OS) and event free-survival (EFS) compared to those undergoing HSCT with 15 years or older. The risk of grade 2-4 acute graft-versus-host disease (GVHD) and chronic GVHD is significantly higher in patients older than 15 years old[14,15]. Despite potential complications of HSCT (GVHD, gonadal dysfunction), transplantation at an earlier age may prevent organ dysfunction, strokes, iron overload and improve patients' quality of life[16-19]. Therefore, an early referral to HSCT is strongly recommended.

HOW TO BALANCE THE RISK OF THE HSCT AND DISEASE IN ADULTS WITH SICKLE CELL DISEASE?

The medical dilemma in older SCD patients will be the assessment of established organ damage and the risk of transplantation. Timing of transplant will also be important for choosing the best available donor. The clinical course of SCD is extremely variable and no validated genetic risk score has been established so far. Most of the risk scores use phenotypic characteristics together with laboratory biomarkers and imaging parameters to define outcomes in SCD[20].

Several adult-specific risk models have been more recently described. One model was based on ***SCD-related multiple chronic conditions***. This model includes several established clinical complications of the disease and considers any of them to define high-risk disease. Patients with one complication (stroke any significant neurological event, pulmonary hypertension, recurrent priapism, retinopathy, chronic arthritis, leg ulcers or psychiatric diseases) had a lower OS and should be carefully evaluated before indication of HSCT[21]. Another model is the ***Phenotypic risk score for prediction of mortality in sickle cell disease (PReMSCD).*** An online risk score calculator is available at https://dir.nhlbi.nih.gov/lab/echo/PReMSCD/. The authors included 600 patients with ≥ 18 years old (median age of 33.5 years). With this model it has been possible were able to divide the patients in 4 well defined risk scores. These risk scores can help when considering HSCT for adults with SCD[22]. Considering the transplant related mortality, only one specific risk score was published. Wich score considers only age and type of donor. Children < 12 years old and MSD are considered in the low-risk category (EFS of 92%). Patients over 16 years with an MSD donor are considered as intermediate risk. All other types of donors and age older than 16 years are considered high risk[20]. This again favors an early referral to a transplant center for children with SCD. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI), validated for hematological malignancies, were never validated for SCD, but should also be applied and can help guide transplant decisions[23].

TABLE 1. Hematopoietic stem cell transplantation for hemoglobinopathies.

	HLA identical sibling donor (bone marrow or cord blood graft)	Unrelated donor (bone marrow graft)	Haploidentical donor (bone marrow graft)
Transfusion dependent thalassemia	Standard of care	HLA identical (10/10) AND HLA DPB1 identical or with permissive mismatch	Clinical option
Sickle cell disease	Standard of care	Not recommended	Clinical option

TABLE 2. Indications for allogeneic HSCT in sickle cell disease.

CHILDREN	ADULTS
Patients who are using hydroxyurea and/or chronic transfusion and present at least one of the following complications: 1) Neurological alteration due to stroke, any neurological alteration persisting for more than 24 hours, altered imaging or cerebrovascular disease associated with sickle cell disease 2) Two or more severe vaso-occlusive crises (including acute chest syndrome) in the last year 3) More than one episode of priapism 4) Presence of more than one antibody in patients on a hypertransfusion regimen 5) Osteonecrosis in more than one joint	Same general indications for children. Consider also: 1) Administration of regular RBC transfusion therapy, defined as receiving 8 or more transfusions per year for 1 year to prevent vaso-occlusive clinical complications (ie, pain, stroke, and acute chest syndrome) 2) An echocardiographic finding of tricuspid valve regurgitant jet > 2.7 m/s
Absence of severe comorbidities that can increase transplant related mortality.	

HSCT, hematopoietic stem cell transplantation; RBC, red blood cell.

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