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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC ACUTE MYELOID LEUKEMIA

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ABSTRACT

Acute myeloid leukemia (AML) represents 15%–20% of acute leukemias in children, and the risk of treatment failure is based on genetic risk and response to therapy1-4. Although the initial remission rate exceeds 90%, more than 30-40% of children with AML die of refractory/relapsed disease or treatment-related toxicity5. The best therapeutic results are achieved by integrating intensive chemotherapy, optimal supportive care, and hematopoietic stem cell transplant (HSCT) adapted to each patient's risk of relapse6–9. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to provide general guidance on HSCT for childhood AML to provide evidence-based guidance for the appropriate management of this disease.

Keywords: Hematopoietic Stem Cell Transplantation. Pediatric Acute Myeloid. Leukemia. Clinical Guidelines

Acute myeloid leukemia (AML) represents 15%–20% of acute leukemias in children, and the risk of treatment failure is based on genetic risk and response to therapy[1-4]. Although the initial remission rate exceeds 90%, more than 30-40% of children with AML die of refractory/relapsed disease or treatment-related toxicity[5]. The best therapeutic results are achieved by integrating intensive chemotherapy, optimal supportive care, and hematopoietic stem cell transplant (HSCT) adapted to each patient's risk of relapse[6–9]. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to review and update the main indications for HSCT for childhood AML based on previous guidelines, intending to provide evidence-based guidance for the appropriate management of this disease.

Currently, HSCT is not recommended for patients in first clinical remission (CR1) when they are classified as low or intermediate risk. Patients classified as high risk, either because of genetic/molecular factors or measurable disease after induction therapies, will be referred for HSCT in CR1.

With the evolution of methods for detecting genetic/molecular alterations, including the greater availability of gene sequencing techniques, novel genetic alterations have been correlated with different clinical

and prognostic characteristics. Recent studies have demonstrated new alterations and their clinical, morphological, immunophenotypic and prognostic correlates[10]. The implication of new genetic/molecular markers in AML is evolving. For example, AML with KMT2A rearrangements include AML subtypes with with disparate outcomesFor instance, AML cases with t (6; 11) (q27; q23), t (10; 11) (p12; q23) and t (10; 11) (p11.2; q23) have high relapse rates, while patients with t (1; 11) (q21; q23) have an excellent. outcomesThe t (9; 11) (p12; q23) is associated with intermediated risk when occurring in monoblastic or myelomonoblastic leukemia , but a high risk when associated with with acute megakaryoblastic.[6]. The table below show the abnormalities with a more consolidated prognostic impact.

TABLE 1 - Molecular genetic abnormalities with prognostic impact in Pediatric AML

FAVORABLE
t t(15;17)/PML-RARA
t(8;21)/RUNX1-RUNX1T1
inv(16)(p13.1;q22)/CBF β -MYH11
t(16;16)(p13.1;q22)/CBF β -MYH11
t(1;11) (q21;23)/ MLL AF1Q
NPM1 mutated without FLT3/ITD
Biallelic Mutation CEBPA
M6 or M7 with GATA-1 in Down Syndrome or mosaic for Down syndrome*1
UNFAVORABLE
-7
-5/del5q
t(6;11)(q27;q23)/MLLT4-KMT2A
t(10;11)(p12;q23)/MLLT10-KMT2A
t(10;11)(p11.2;q23)/ABI1-KMT2A
t(6;9)/DEK-CAN (NUP214)
t(8;16)(p11;p13)/MYST3-CREBBP
t(16;21)(q24;q22)/ RUNX1-CBFA2T3
t(5;11)(q35;p15.5)/NUP98-NSD1
t(9;22) (q34;q11)/ BCR/ABL
inv(16)(p13.3q24.3)/CBFA2T3-GLIS2 in megakaryoblastic LMA*2
t(11;15)(p15;q35)/NUP98-KDM5A
Complex karyotype (≥ 3 changes)
FLT3/ITD
FAB MO, M6 e M7 without t(1;22) or without GATA-1
Secondary AML (Myelodysplastic Syndrome or previous treatment)

*1 Mast KJ, et al. Pathologic Features of Down Syndrome Myelodysplastic Syndrome and Acute Myeloid Leukemia: A Report From the Children's Oncology Group Protocol AAML0431. Arch Pathol Lab Med. 2020 Apr;144(4):466-472.
*2 Gruber TA, et al. An inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia*Cancer Cell. (2012) 13; 22(5): 683–697.

In recent years, the measurement of residual disease (MRD) has been incorporated as an additional risk stratifier in the treatment of pediatric AML, usually after the induction cycles. Due to the different methodologies to assess residual disease, the clinical value of MRD is still evolving and should . interpreted within the context of specifictherapeutic protocols.

In countries with limited resources, there is great difficulty in reproducibility and standardization of the methodology used in flow cytometry to quantify low levels of residual disease in AML, which makes interpreting these results and determining their impact on clinical decisions very complex.

Considering the difficulties mentioned above, patients classified as low or intermediate risk, who are referred to HSCT only because they have detectable levels of residual disease after the induction phase, will be evaluated individually. If necessary, the review of MRD tests will be performed by immunophenotyping by the Brazilian Group of Flow Cytometry (GBCFlux) for further definition of the indication of HSCT by the Pediatric Group of SBTMO and by the Study Group on Acute Myeloid Leukemia (GELMAI) of the Brazilian Society of Pediatric Oncology (SOBOPE)5.

TABLE 2 - Risk classification based on diagnostic characteristics associated with MRD

Low Risk	Favorable genetic alterations and MRD ≤ 1% after the first cycle induction
Intermediate Risk	Patients who do not have criteria for low or high risk
High Risk	Unfavorable genetic alterations or MRD ≥ 0,1% after the second cycle of induction

In relapses, a second remission is attained in about two-thirds of patients with AML; however, lasting remissions in these cases are rare with chemotherapy regimens. Thus, in relapses, allogeneic bone marrow transplantation is always indicated, preferably soon after obtaining a new remission.[11,12]

A recent study reviewing the outcomes of 1940 pediatric AML patients treated with the BFM protocol, from 1987 to 2012, demonstrated that although EFS has remained similar since the 1990s, improvements in supportive care and HSCT have made patients who attained a second remission (CR2) potentially cured, and this resulted in an increase of approximately 20% in OS in the last 30 years.[11]

In a study with Brazilian HSCT centers for children, adolescents, and young adults, OS and EFS in 4 years were 47% and 40%, respectively.[12] Brazilian outcomes of HSCT in children with AML appear to be inferior to those reported in the United States and Europe. A report by Bitan et al. from the Center for International Blood and Marrow Transplant Research (CIBMTR) on 141 pediatric patients with AML who underwent the transplant in CR1 showed a 5-year PFS of 54% after myeloablative conditioning[13]. Data from the British MRC10 and MRC12 trials showed a 5-year OS of 68% in children who received marrow transplants from matched sibling donors[14]. The Nordic Society of Paediatric Haematology and Oncology (NOPHO) reported a 3-year EFS of 61% in children who underwent the transplant in CR[8]. Locatelli et al. analyzed the outcomes of 243 children with high-risk AML in CR1 who were enrolled in the AIEOP-2002/01 protocol and underwent either allogeneic (n =141) or autologous (n=102) HSCT. The 5-year probability of disease-free survival was 73%[15]. Finally, an AML SCT-BFM study aimed at standardizing pediatric HSCT for AML across centers in Germany and Austria reported 4-year EFS and OS of 61% and 70%, respectively[16].

The main prognostic factor for the success of HSCT in patients with AML remains the stage of the disease. CIBMTR data show 3-year OS of 70%, 65% and 31%, respectively, for patients under 18 years of age undergoing related HSCT in early (CR1), intermediate (CR2) and advanced stages (active disease or ≥ CR3) of LMA[17]. Patients with treatment-refractory AML or with more than one relapse still have a dismal prognosis[18].

The results of transplants using related, unrelated (matched or partially matched, with a greater than a 8/10 HLA-match) and haploidentical donors are very similar in AML, with no significant difference between type of donor, whether in overall survival, incidence of acute or chronic graft-versus-host disease (GVHD)[12,19]. In children, bone marrow is preferable in comparison to peripheral blood (PB) as stem-cell source, given the higher extensive chronic GVHD and transplant-related mortality with the use of peripheral blood stem cells[20,21]. The use of Umbilical Cord Blood is associated with higher transplant-related mortality in Brazil and should only be used by centers experienced with this stem cell source[22].

To date, the benefit of autologous marrow transplantation has not been proven when compared to isolated intensive chemotherapy and/or to allogeneic transplantation for non-promyelocytic AML in 1st CR. Thus, autologous transplantation as consolidation should be considered investigational. Conditioning with busulfan area under the curve (AUC) 4000-5000 µMol.min and melphalan total dose (TD) 140 mg/m2 is currently recommended[23-25].

As for conditioning in allogeneic transplants, there are better results (toxicity vs relapse) with the use of myeloablative protocols based on busulfan (BU) AUC 4000-5000 µMol.min or based on Total Body Irradiation (TBI) [16, 26-32].

Although transplantation for active disease (≥ 5% blasts in the bone marrow) is controversial, but in cases with adequate performance, benefit from the adapted FLAMSA conditioning scheme has been reported.[33-35]

FLAMSA regimen:

- Intrathecal chemotherapy D-14
- Etoposide: 150 mg/m2/day, D-13 to D-10
- Fludarabine: 30 mg/m^2/day, D-13 to D-10
- Cytarabine: 2000 mg/m2/day, D-13 to D-10 (4 h after fludarabine)
- Cyclophosphamide: 60 mg/kg/day, D-3 and D-2
- Mesna (1.4 x dose of cyclophosphamide, divided into 5 doses: 0, 3, 6, 9 and 12 hours of cyclophosphamide)
- Busulfan 4.8 mg/kg/day, D-6 and D-5
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave one day off the drug, to wait for the result and make necessary adjustments on the day after the break.
- Donor lymphocyte infusion (DLI): D+21 (106 CD3/kg), D+35 (5x106 CD3/kg), D+60 (5x106 CD3/kg), start DLI regardless of haematological engraftment, suspend in case of GVHD
- Azacitidine 75 mg/m2/day, for 5 consecutive days, with 1, 2, 3, 4 and 5 months after transplantation (total of 5 cycles)

Due to important differences in the transplant-related mortality rates (MRT) related to age and conditioning regimen, according to the risk/benefit and rates of Event-Free Survival (EFS) and Overall Survival (OS) for patients in pre-HSCT remission, investigators propose different conditioning for children over or under 6 years of age[36,37,38].

The preparatory regimen will consist of busulfan, cyclophosphamide and melphalan in those six years of age or older. The decision to adopt a preparative regimen containing a combination of three alkylating agents was based on several factors. First, the addition of a third alkylating agent was based on results of a preliminary study by Locatelli et al.[37], which demonstrated the safety of combining melphalan with busulfan in children, and in the fact that the analysis

A retrospective study of the EWOG-MDS group observed that a conditioning regimen containing a second alkylate was associated with a better EFS and a lower incidence of relapse when compared to regimens employing total body irradiation (TBI)[38]. Strahm published a TRM rate of 21% in a total cohort of children presenting a "BuCyMel" for advanced myelodysplastic syndromes[36]. Analyzing age groups separately, this MRT was considerably higher in those aged 12 years and over. With the increasing number of AML SCT-BFM 2007 recruitment, an identical MRT pattern has been reported for children and adolescents undergoing transplantation after "BuCyMel" for AML. An MRT of 32% in patients 12 years of age or older was considered unacceptable, while children under 12 have an excellent result after "BuCyMel," having an MRT rates below 10%. Therefore, we continue to recommend "BuCyMel" for younger children who are eligible for the treatment group.

Description of the "BuCyMel" scheme:

- Cyclophosphamide: 60 mg/kg/day, D-4 and D-3 (start 24 h after busulfan)
- Mesna (1.4 x dose of cyclophosphamide, divided into 5 doses: 0, 3, 6, 9 and 12 hours of cyclophosphamide)
- Melphalan 140 mg/m^2/day D-2
- Busulfan (per kg according to the table 3), D-8, D-7, D-6, D-5
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave a day without the drug, to wait for the result and make necessary adjustments the day after the break.

For children over 6 years old, the proposed scheme is the "BuFluMel":

- Fludarabine 30 mg/m2/day from D-7 to D-3
- Busulfan (per kg according to the table 3), D-7, D-6, D-5, D-4
- Melphalan 140 mg/m2/day D-2
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave a day without the drug, to wait for the result and make necessary adjustments the day after the break.

TABLE 3- Busulfan Dosage

Weight in kg	Busulfan dose (mg/kg/day)	Cumulative Dose of Busulfan (mg/kg)
≤9	4,0	16,0
> 9 - ≤16	4,8	19,2
>16 - ≤23	4,4	17,6
>23 - ≤34	3,8	14,2
> 34	3,2	12,8

The recent advent of haploidentical transplantation has made the search for a donor more agile, and as a consequence, has allowed transplants to be carried out for a larger number of patients. According to the exciting results presented by Jaiswal, for transplants with haploidentical donors, the suggested scheme is the one using busulfan AUC 4000-5000 µMol.min and melphalan (MEL) total dose (TD) 140 mg/m2, associated with fludarabine (FLU) TD 150 mg/m2. The infusion of donor lymphocytes on D+21, D+35 and D+60 had a positive impact on the outcome of patients with advanced disease/worse prognosis.

Depending on the experience of each Transplant Unit, there is the possibility of adopting other conditioning protocols.

About the Graft-versus-Host Disease (GVHD) prophylaxis regimen:

- In HLA-matched sibling donor (MSD) allo-HSCT, calcineurin inhibitors (Cyclosporine – CSP 2mg/kg or Tacrolimus – TAC 0.05mg/kg in two divided I.V. doses a day) as a single agent should be started on D-1, and switched to their corresponding P.O. formulations, with strict dose adjustment based on serum levels (100-200mcg/L for CSP and 5-15ng/ml for TAC), until 3 months after transplant, with subsequent tapering, in the absence of graft-versus-host disease (GVHD)[40-42].

- In HLA-matched unrelated donor (MUD) HSCT, calcineurin inhibitors (Cyclosporine – CSP 2mg/kg or Tacrolimus – TAC 0.05mg/kg in two divided I.V. doses a day) as a single agent should be started on D-1, and switched to their corresponding P.O. formulations, with strict dose adjustment based on serum levels (100-200mcg/L for CSP and 5-15ng/ml for TAC), until 3 months after transplant, with subsequent tapering, in the absence of graft-versus-host disease (GVHD)[40,42].

  **The use of single-agent, post-transplant cyclophosphamide (PTCy) at a dose of 50mg/kg two days between D+3 and D+4 has shown similar results regarding GVHD control, although further studies are awaited in order to define the optimal regimen in terms of long-term outcome for these patients* [43-45].

- In unrelated allo-HSCT, CSP (at the same dose as that for related donor transplants) combined with methotrexate (MTX) for a short period of time (i..e, on days +1, +3, +6 and +11) is the standard prophylactic regimen. MTX is used at an initial dose of 15mg/m^2, followed by three doses of 10mg/m^2, TAC at a total daily dose of 0.05mg/kg can also be used, with similar results[40,42]. In contrast, the combination of mycophenolate mofetil (MMF) with CSP was shown to be less effective [43-45].

- Although the use of anti-thymocyte globulin (ATG), primarily for the prevention of GVHD, has been consolidated in unrelated donor HSCT in adults, there is limited evidence as to its benefit in the pediatric population, even though it is used in most protocols. In a randomized study comparing different dose regimens of ATG, use of ATG at lower doses (4,5 – 6 mg/kg) could reduce the rate of infection while maintaining similar acute and chronic GVHD rates, as well as relapse rates. The investigators concluded that low-dose ATG should be the standard serotherapy regimen for URD HCST in children with hematologic malignancies[46], even though it should be borne in mind that the different ATG formulations available have variable immune responses, which may hinder any definitive conclusions as to its real benefit in this regard.

- In haploidentical HSCT, cyclophosphamide is generally used at a dose of 50mg/kg/day, in a 2-hour infusion, on D+3 and D+4, coupled with mesna (100-160% of the cyclophosphamide dose), in combination with a calcineurin inhibitor (CSP or TAC) and MMF (15mg/kg/dose q8h; maximum dose 2g/day), both starting on D+5. Both these immunosuppressants are usually kept for 3 months post-transplant[47,48].

As for UCB transplantation, the immunosuppressive regimen usually comprises the combination of a calcineurin inhibitor with MMF. Studies on the association of CSP with low-dose MTX or with corticosteroids have yielded worse results, as well as a greater graft failure rate[42].

Best time points for MRD assessment:

Pre-HSCT: MRD assessments should be made immediately before allo-HSCT.

Post-HSCT: MRD assessments by multiparameter flow cytometry (MFC) and/or reverse transcription quantitative polymerase chain reaction (RT-qPCR) are accurate in predicting relapse at days +30, +60, +90, and +180 post-HSCT.

Any detectable MRD level on days +180 and +365 post-HSCT is highly predictive of relapse and poor survival[49]. When decisions that may change patient management are based on low levels of MRD, we would recommend that the SBTMO – MRD Working Group GBFLUX may review the flow cytometric data to increase accuracy of the results.

Despite the immunological effect of the grafted cells against leukemia, the toxicity and mortality related to the procedure remain large barriers. The heterogeneity of data related to patient selection, type of conditioning for HSCT and donors makes data interpretation difficult in the pediatric population, particularly in developing countries, but procedure-related mortality is estimated to be between 10-25% in our country[12].

Another key point for better results is carrying out the transplant without delay, which is hampered by the scarcity of beds for patients dependent on the public health system. Patients in first and second remissions are potentially curable with HSCT, but from the second relapse and/or when the patient has active disease, there is a drastic reduction in the chances of cure. Delaying the procedure is harmful both due to the risk of losing the remission status as well as exposure to the toxicity of a new cycle of chemotherapy, which can worsen the child's performance for transplantation, or even be fatal[12].

We recommend in the AML the HLA typing of the patient, parents and siblings at diagnosis. If no related donor is identified, collect the patient's anti-HLA antibody test and start search for a donor at REDOME.

Once the indication for transplantation is confirmed, the interaction between the pediatric oncologist and the transplant center is essential for the prompt donor search and planning of the procedure.

Currently, advances have been achieved, in particular through the connection between the Brazilian Societies of Bone Marrow Transplant – SBTMO, of the Pediatric Oncology Society – SOBOPE, theFlow Cytometry – GBFlux and the Brazilian Association of Hematology, Hemotherapy and Cell Therapy -ABHH, in the challenging goal of improving the treatment of children and adolescents with AML. These efforts will also contribute to agreater knowledge of Brazilian experience.

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