Hematopoietic cell transplantation for pediatric myelodysplastic syndromes

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ABSTRACT

Myelodysplastic syndromes (MDS) are uncommon in children and present distinct features compared to adults. Allogeneic hematopoietic cell transplantation (HCT) is considered the standard curative treatment for many children with MDS, including all patients with MDS with excess of blasts and those with refractory cytopenia of childhood associated with unfavorable karyotype, severe neutropenia or transfusion dependence. In this article, we reviewed the indications of HCT in pediatric MDS.

Keywords: Myelodysplastic Syndromes. Hematopoietic Stem Cell Transplantation. Child.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a clonal hematologic neoplasm characterized by peripheral blood cytopenia, ineffective hematopoiesis, and a high risk of progression to acute myeloid leukemia (AML). With incidence of one to 1,000,000 patients between 0 to 14 years old, it is a rare disease in childhood[1–5].

Since 2003, with the identification of distinct characteristics of the disease observed in adults, a first classification for the pediatric population was proposed. Hasle *et al.*[1] proposed the entities refractory cytopenia of childhood (RCC), refractory anemia with excess blasts (RAEB), and refractory anemia with excess blasts in transformation (RAEB-t). RAEB is also recognized as advanced MDS because of increased blasts and aggressive disease without treatment. Recently, the classification of hematologic neoplasms was revised, but the diagnostic criteria remained similar. The World Health Organization (WHO) and the International Consensus Classification (ICC) kept pediatric MDS as a distinct entity, despite of using different nomenclatures. The WHO adopted pediatric myelodysplastic neoplasia with increased blasts or with low blasts, and the ICC kept RCC and MDS with excess blasts[6,7].

In recent years, several observations strongly supported the role of hereditary predisposition in the development of childhood primary MDS, other than those characterizing the setting of MDS related to

inherited bone marrow failure syndromes. This increased awareness of non-syndromic familial MDS/AML predisposition syndromes, such as those caused by mutations in GATA2, ETV6, SRP72, SAMD9, and SAMD9L, and has led to these syndromes being considered as a separate category since the revised 2016 WHO classification of myeloid neoplasms[6–10].

For all children diagnosed with MDS, human leukocyte antigen (HLA) typing and the search for a compatible donor must be carried out immediately after diagnosis. Due to the risk of familial MDS, in the case of potential related donors, it is important to rule out the same genetic alterations present in the patient, in addition to hematological evaluation of the donor with complete blood count, myelogram, bone marrow biopsy, and karyotype, to rule out incipient MDS[11].

REFRACTORY CYTOPENIA OF CHILDHOOD

RCC is the most common subtype of MDS in the pediatric population[2–4]. Patients without an unfavorable karyotype can keep the disease stable for a long time. Thus, in the absence of transfusion dependence or severe neutropenia, a careful observation strategy without treatment is recommended[2–5,12]. The indications for allogeneic hematopoietic cell transplantation (allo-HCT) with the best available donor are demonstrated in Table 1.

Table 1. Indications for allogeneic hematopoietic cell transplantation in refractory cytopenia of childhood.

Indications
Presence of monosomy of chromosome 7 or deletion of the long arm of chromosome 7, due to the high risk of progression to more advanced forms of the disease and acute myeloid leukemia[2,5,13]
Complex karyotype (three or more chromosomal aberrations, at least one structural), despite the unfavorable prognosis even with hematopoietic stem cell transplantation[2,5,14]
Sustained neutropenia (< 1,000/mm^3) or need for transfusion[2–5]

Source: Elaborated by the authors.

Patients with hypocellular bone marrow and without an unfavorable karyotype can benefit from a reduced intensity conditioning (RIC) regimen. For the others, a myeloablative conditioning (MAC) regimen is indicated[15–17]. The European Working Group of Myelodysplastic Syndromes in children (EWOG-MDS) recommends a conditioning regimen with treosulfan and fludarabine for patients with hypocellular RCC without unfavorable karyotypic abnormalities and a regimen with thiotepa/treosulfan/fludarabine for those with normo-/hypercellular bone marrow and unfavorable chromosomal aberrations[18]. Due to the difficulty of using thiotepa and treosulfan in Brazil, especially in the public health system, the Brazilian Cooperative Study Group for Pediatric Myelodysplastic Syndrome (GCB-SMD-PED) has used busulfan (BU) and fludarabine (FLU)[19] for patients with hypocellular bone marrow without unfavorable karyotype, and busulfan/fludarabine/melphalan (MEL)[20] for the others (Tables 2 and 3).

Table 2. Conditioning regimens for refractory cytopenia of childhood currently recommended by the Brazilian Cooperative Study Group for Pediatric Myelodysplastic Syndrome.

Patients with hypocellular bone marrow without unfavorable karyotype	Busulfan (dose according to body weight* or adjustment based on pharmacokinetic studies#, if available): D-7 to D-4 Fludarabine 30 mg/m^2/day: D-7 to D-3
Patients with normo-/hypercellular bone marrow and unfavorable chromosomal aberrations	Busulfan (dose according to body weight* or adjustment based on pharmacokinetic studies#, if available): D-7 to D-4 Fludarabine 30 mg/m^2/day: D-7 to D-3 Melphalan 140 mg/m^2/day: D-2

*IV daily dose = < 9 kg: 4 mg/kg; 9 to < 16 kg: 4.8 mg/kg; 16–23 kg: 4.4 mg/kg; > 23 to 34 kg: 3.8 mg/kg; > 34 kg: 3.2 mg/kg; #target AUC 4,000–5,000 µMol•min. Source: Elaborated by the authors.

Table 3. Graft-*versus*-host disease prophylaxis for refractory cytopenia of childhood currently recommended by the Brazilian Cooperative Study Group for Pediatric Myelodysplastic Syndrome.

Matched sibling donor	Cyclosporine as a single agent for patients with normo-/hypercellular bone marrow and unfavorable chromosomal aberrations. Cyclosporine combined with short methotrexate (D +1, +3 and +6) for patients with hypocellular bone marrow without unfavorable karyotype.
Matched unrelated donor*	Calcineurin inhibitors (cyclosporine or tacrolimus) combined with short methotrexate (D +1, +3 and +6).
Unrelated cord blood*	Calcineurin inhibitors (cyclosporine or tacrolimus) combined with mycophenolate mofetil

*Anti-thymocyte globulin (ATG) during conditioning regimen for *in-vivo* T-cell depletion/modulation. Source: Elaborated by the authors.

Results of unrelated cord blood (UCB) transplantation in pediatric patients with MDS (including RCC) have been reported to be inferior to results when using either bone marrow or peripheral blood as a source for stem cells. Thus, this type of allograft can be recommended only for those patients who lack a matched related or unrelated donor[2,21].

In recent years, several studies using haploidentical HCT reported promising long-term survival for acute leukemia in adults and children. Thus, for pediatric MDS patients with no matched sibling donor (MSD) or matched unrelated donor (MUD), haploidentical transplant could be a valuable option. However, so far, there are only a few reports on using HCT from a haploidentical donor for the treatment of pediatric MDS[22,23].

In the absence of a suitable donor, immunosuppressive treatment with anti-thymocyte globulin (ATG) and cyclosporine may be an option for patients with hypocellular bone marrow, without a bad prognosis karyotype. However, these patients remain at risk of relapse and clonal evolution and need careful surveillance[24,25].

PRIMARY MYELODYSPLASTIC SYNDROMES WITH EXCESS BLASTS

The treatment of children diagnosed with MDS with excess blasts remains a major challenge. Allo-HCT is the only curative treatment, although the data published in the literature generally include a small number of patients, heterogeneously transplanted[2,14,20]. The presence of a complex karyotype is strongly associated with a poor prognosis[26].

In the largest cohort of children with advanced MDS reported to date, the EWOG-MDS demonstrated a five-year overall survival (OS) of 63% in 97 patients undergoing allo-HCT with the same MAC regimen—BU/cyclophosphamide (CY)/MEL. Age older than 12 at HCT, interval between diagnosis and HCT longer than four months, and occurrence of acute or chronic extensive graft-*versus*-host disease (GVHD) were associated with increased transplant-related mortality (TRM), whereas the risk of relapse increased with more advanced diseases[14]. A more recent update of the EWOG-MDS data, with the same conditioning regimen mentioned above, showed a decrease in TRM, particularly in the adolescent subgroup, after the intensification of GVHD prophylaxis for patients ≥ 12 years old[18]. The update also showed that the outcome for patients who received a transplant from either an HLA MSD or MUD was similar[2].

Recently, authors from Arizona, United States of America, reported a 10-year experience of allogeneic hematopoietic stem cell transplantation (HSCT) in pediatric and young adult patients with myeloid malignancies, including MDS, conditioned with myeloablative targeted dose-BU, FLU, and MEL. Twenty-three patients underwent MSD, MUD, UCB or haploidentical HSCT post-BU/FLU/MEL. With a median follow-up of 41.6 months, the relapse rate is only 4.5% with an OS of 100%, progression-free survival of 95.5%, and graft-*versus*-host-free-relapse-free survival of 67.8%. Of caution, the unacceptably high acute and chronic GVHD seen in patients receiving MSD and MUD peripheral blood stem cell transplants with methotrexate + cyclosporine GVHD prophylaxis[20].

Although the EWOG-MDS 2016 consensus recommendation is to use the conditioning regimen consisting of BU/CY/MEL for all patients with MDS with excess blasts receiving MSD, MUD, and UCB transplant, regardless

of the patient's age, due to the high toxicity of this regimen in older patients, the GCB-SMD-PED has recommended the regimen with BU/FLU/MEL for patients over 6 years old, as also indicated by the current Brazilian protocol of the Study Group on Acute Myeloid Leukemia (Table 4).

Table 4. Conditioning regimens recommendations in pediatric myelodysplastic syndromes with excess blasts receiving matched sibling donor, matched unrelated donor, and unrelated cord blood transplant.

Patients < 6 years old busulfan + cyclophosphamide + melphalan	Busulfan (dose according to body weight* or adjustment based on pharmacokinetic studies#, if available): D-8 to D-5 Cyclophosphamide 60 mg/kg/day + Mesna (150% of cyclophosphamide dose): D-4 and D-3 (starting 24 h after busulfan) Melphalan 140 mg/m^2/day: D-2
Patients ≥ 6 years old busulfan + fludarabine + melphalan	Busulfan (dose according to body weight* or adjustment based on pharmacokinetic studies#, if available): D-7 to D-4 Fludarabine 30 mg/m^2/day: D-7 to D-3 Melphalan 140 mg/m^2/day: D-2

*IV daily dose = < 9 kg: 4 mg/kg; 9 to < 16 kg: 4.8 mg/kg; 16–23 kg: 4.4 mg/kg; > 23 to 34 kg: 3.8 mg/kg; > 34 kg: 3.2 mg/kg; #target AUC 4,000–5,000 µMol•min. Source: Elaborated by the authors.

Even though there are few reports on haploidentical HCT with post-transplant cyclophosphamide (PTCy) in children with advanced MDS, the conditioning regimen with BU/FLU/MEL appears to be a good option in this scenario as well[20]. Furthermore, exciting results with haploidentical HSCT with PTCy using this regimen and prophylactic donor lymphocyte infusion (DLI) were published by Jaiswal *et al*.[27] in patients with refractory/relapsed acute myeloid leukemia (Table 5).

Table 5. Conditioning regimen recommendation in pediatric myelodysplastic syndromes with excess blasts receiving haploidentical transplant.

Busulfan + fludarabine + melphalan	Busulfan (dose according to body weight* or adjustment based on pharmacokinetic studies#, if available): D-6 to D-4 Fludarabine 30 mg/m^2/day: D-7 to D-3 Melphalan 140 mg/m^2/day: D-2

*IV daily dose = < 9 kg: 4 mg/kg; 9 to < 16 kg: 4.8 mg/kg; 16–23 kg: 4.4 mg/kg; > 23 to 34 kg: 3.8 mg/kg; > 34 kg: 3.2 mg/kg; #target AUC 4,000–5,000 µMol•min. Source: Elaborated by the authors.

GVHD prophylaxis recommendations in pediatric MDS with excess blasts are described in Table 6.

Table 6. Graft-*versus*-host disease prophylaxis recommendations in pediatric myelodysplastic syndromes with excess blasts.

Matched sibling donor	Cyclosporine as a single agent
Matched unrelated donor*	Calcineurin inhibitors (cyclosporine or tacrolimus) combined with short methotrexate (D +1, +3 and +6).
Unrelated cord blood*	Calcineurin inhibitors (cyclosporine or tacrolimus) combined with mycophenolate mofetil
Haploidentical donor	Cyclophosphamide (D +3 and D +4) combined with mycophenolate mofetil and cyclosporine

*Anti-thymocyte globulin (ATG) during conditioning regimen for *in-vivo* T-cell depletion/modulation. Source: Elaborated by the authors.

Pre-HCT treatment remains a controversial issue, and there is currently no consensus on the use of cytoreductive therapy[28,29]. AML-like chemotherapy and hypomethylating agents have been used to reduce disease burden, without real improve in survival; new alternatives, with less toxicity, like *BCL2* inhibitor, have been incorporated recently[30–33].

PREVENTION OF POST-HEMATOPOIETIC CELL TRANSPLANTATION RELAPSE IN PEDIATRIC MYELODYSPLASTIC SYNDROMES

For patients with unfavorable karyotype RCC and MDS with excess blasts, it is important to closely monitor chimerism and clonal evolution. Disease status should be regularly monitored, with bone

marrow evaluation being generally recommended on days +30, +60, +90, +180 and +365. If the patient develops mixed chimerism or has molecular or cytogenetic relapse, strategies such as early withdrawal of immunosuppression can prevent rapid disease progression. As in adult patients, DLI with or without azacitidine can be considered[34–36]. A few reports of prophylactic azacitidine and DLI in pediatric patients with high-risk disease have also been published[37,38].

THERAPY-RELATED MYELOID NEOPLASMS

According to the 5th edition of the WHO classification, this category, currently called "myeloid neoplasms post cytotoxic therapy," includes AML, MDS, and MDS/MPN (myelodysplastic/myeloproliferative neoplasms) arising in patients exposed to cytotoxic (DNA-damaging) therapy for an unrelated condition[7].

Therapy-related myeloid neoplasms (tMNs) are a challenging late complication of cancer therapy. Allo-HCT is the only treatment that offers the possibility of long-term cure. However, even with HCT, the overall survival remains dismal, and outcomes data for pediatric patients are limited[39–41].

A recent multi-center retrospective study with 401 pediatric patients who underwent HCT demonstrated that a diagnosis of therapy-related MDS, as compared to therapy-related AML, was associated with worse EFS and a higher risk of relapse. They also compared MAC and RIC regimen before HCT. Although no significant difference in long-term survival or relapse related to conditioning intensity was found, survival fell precipitously in the RIC cohort during years 2–5 after the transplant. Disappointingly, the cumulative incidence of TRM was comparable in the RIC and the MAC cohorts. Exposure to total body irradiation (TBI) and developing grade III/IV acute GVHD were associated with worse OS. These data suggest that reduced-toxicity (but not reduced-intensity) regimens might help to decrease relapse while limiting mortality associated with TBI-based HCT conditioning in pediatric patients with tMNs[41].

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Villela NC, Oliveira AF, Gouveia RV, Caleff MF, Landi GGF and Lee MLM. **Conception and design:** Villela NC and Oliveira AF. **Manuscript writing:** Villela NC, Oliveira AF, Gouveia RV, Caleff MF, Landi GGF and Lee MLM. **Final approval:** Villela NC and Oliveira AF.

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