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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Chronic myeloid leukemia (CML) accounts for approximately 2 to 3% of all pediatric leukemias. Compared to adults, children tend to present with more aggressive features, such as higher leukocyte counts and massive splenomegaly, and are more likely to be diagnosed with advanced stage disease. Before the advent of tyrosine kinase inhibitors, a couple of decades ago, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was the mainstay of treatment for this disease. This, however, was associated with considerable treatment-related morbidity and mortality. Even so, despite its secondary and somewhat limited indication today, allo-HSCT remains an important alternative and the only curative treatment for CML. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO) convened a task force to provide evidence-based guidance on the use of allo-HSCT for the appropriate management of childhood CML, the results of which are presented here.

Keywords: Hematopoietic Stem Cell Transplantation, Tyrosine Kinase Inhibitors, Chronic Myeloid Leukemia, Childhood, Pediatric, Consensus Guidelines.

Chronic myeloid leukemia (CML) accounts for approximately 2 to 3% of all childhood and adolescent (under 15 years old) leukemias[1]. These patients tend to present with more aggressive features, such as higher leukocyte counts and massive splenomegaly, and are more likely to be diagnosed with advanced stage disease[1]. Pediatric CML presents the same morphologic, cytogenetic and molecular features observed in adult CML. As such, it is characterized by the presence of the Philadelphia chromosome (Ph+), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22 [t (9;22) (q34; q11)], which leads to the BCR-ABL fusion gene. This rearrangement encodes a new protein, with uncontrolled tyrosine kinase activity[2].

Despite their acknowledged applicability in the adult population, adult risk scores for CML cannot be applied to children, with the exception of the one defined by the European Treatment and Outcome Study, which is able to predict progression and long-term event free survival (EFS), but not overall survival (OS)[1,3,4]. Therefore, risk scores are not commonly used to guide treatment in pediatric patients with this disease.

Ever since the introduction of tyrosine kinase inhibitors (TKIs) in pediatric Ph+ CML, as in adults, notable changes have been observed in EFS and progression, as well as in the indication for hematopoietic stem cell transplantation (HSCT)4-6. Before the advent of TKIs, a couple of decades ago, allogeneic HSCT was the mainstay of treatment for this disease; even so, despite its secondary and somewhat limited indication today, it remains an important alternative and the only curative treatment for pediatric CML.

One of the major caveats of TKI-based therapy is that it should be used continuously, maybe lifelong, although this is still an unsolved issue. Moreover, TKIs are associated with a number of side effects, some of which are well known, such as growth delay and endocrine disorders, among others, not to mention potential long-term events[7,8]. Besides, the most appropriate approach to assessing treatment response remains unclear, and prospective studies are needed to better define the optimal timing for treatment discontinuation[1,5,6,9,10]. Allogeneic HSCT may thus help circumvent the long-term effects of indefinite TKI therapy in this population. One should, however, ponder the trade-off between its curative potential and its myriad acute and late toxicities when considering this treatment strategy.

Overall, outcomes of allogeneic HSCT tend to be superior in childhood CML as compared to those of adults with this disease, with an OS rate between 45 and 87%11-14. Some of the most favorable results may be explained by the improvement in supportive care measures and the use of reduced intensity conditioning regimens (RIC), adopted with a view to reducing the mortality risk associated with these procedures.

The choice of graft source might alter the results of HSCT for CML. A retrospective analysis of the Center for International Blood and Marrow Transplant (CIBMTR) showed worst EFS rates when peripheral blood stem cells (PBSC) were used when compared to bone marrow (BM) in children. Although the incidence of acute graft-versus-host disease (GVHD) was similar between children and adults, chronic GVHD rates were also higher in the group that used PBSC as stem cell source[15].

INDICATIONS FOR HSCT IN CML

In a study published in Leukemia in 2016, including 669 patients (among whom only 14 were younger than 20 years of age), 427 were eligible for transplant and randomized between drug therapy and HSCT, depending on related donor availability. The OS of the patients who underwent HSCT was 76% against 69% in the drug therapy arm. Additionally, superior rates of molecular remission were noted in the HSCT group (56% vs. 39%), and 56% of the HSCT patients were no longer in need of drug treatment, as compared to only 6% of those in the non-transplant group[16].

There are no robust studies to date in the pediatric population comparing TKIs and HSCT in the treatment of CML. As a rule, treatment is similar to the one applied in adults, where HSCT is indicated after failure of a second generation TKI or in advanced stage (accelerated and blast phase) disease17. In specific cases, HSCT may be indicated after failure of a first line TKI (imatinib mesylate), or when there is a T315I mutation[17]. As for third line TKIs (ponatinib), further studies are needed to better define their efficacy and safety in this population. As previously mentioned, the possibility of adverse events and of poor adherence to the long-term use of TKI, coupled with the potential for curing the disease with HSCT, should be carefully weighed and conditioned upon shared decision-making with the patient and his/her family, on a case-by-case basis, when choosing the best treatment approach for this population18-22.

In summary, the main indications for HSCT in children with CML are17:

1) Accelerated phase (AP) or blast phase (BP) at the time of diagnosis;

2) Progression to AP or BP. T315I mutation is associated with poor prognosis; children with this mutation may rapidly progress to BP; treatment failure with 1st (imatinib) and 2nd generation (dasatinib, nilotinib) TKI; benefits of the use of 3rd generation TKI are not well known in this population;

3) Poor adherence to TKI treatment (upon discussion of the possible benefit of HSCT in this situation);

4) Severe toxicities related to the use of TKIs.

CONDITIONING REGIMEN

A recent prospective, non-randomized study from a Japanese group compared results between RIC HSCT plus imatinib vs. imatinib alone in the treatment of young adults (including children) with CML in early (<12 months) chronic phase (CP) or late (≥12 months) CP, with a median age of 34 (11-49) years23. In this study, patients undergoing HSCT were conditioned with fludarabine 30mg/m2/day from D-10 to D-5, oral busulfan 4mg/kg/day or intravenous busulfan 3.2mg/kg/day from D-6 to D-5, and Thymoglobulin® – rabbit anti-thymocyte globulin (Fresenius®) 5mg/kg/day from D-4 to D-1. GVHD prophylaxis consisted of cyclosporine, mycophenolate mofetil (MMF), and methotrexate. In this group, imatinib was also used at a dose of 400mg/day, three to 12 months before HSCT, and, as a prophylactic drug, at a dose of 300mg to 400mg/day, from D+100 until 1 year after transplant. Prolonged treatment with a higher dose of imatinib was used for patients with

persistent residual disease or hematologic or cytogenetic relapse. In these cases, the drug was only discontinued 12 months after complete cytogenetic remission. Patients in the imatinib-only group took the usual 400mg/day dosage, with adjustments according to toxicity and response. The estimated 10-year OS and EFS were comparable between the groups. In the late CP CML group, although both treatments resulted in similar survival, a worse 10-year EFS was noted in the imatinib-alone group as compared to the HSCT + TKI group (40.8 vs. 66.7%, p = 0.047, respectively). Of note, HSCT patients with higher European Group for Blood and Marrow Transplantation (EBMT) risk scores had a worse OS than those with lower scores (69.2 vs. 92.9%, p = 0.04). The authors concluded that HSCT in combination with imatinib seems more cost-effective than imatinib alone and should be considered as an appropriate option, particularly for patients with low EBMT risk scores and for whom cure of CML is the ultimate goal.

Regarding haploidentical HSCT for pediatric CML, there are only a few studies available to date, all of which are limited to retrospective analyses of a small number of cases. Hence, further studies are needed to better define the role of this transplant modality in this population[24,25].

RECOMMENDATIONS:

1. Related donor HSCT: fludarabine + busulfan (RIC)23 or busulfan + cyclophosphamide (myeloablative)12. GVHD prophylaxis: cyclosporine + methotrexate.
2. Unrelated donor HSCT: fludarabine + busulfan + anti-thymocyte globulin (RIC)23 or busulfan + cyclophosphamide + anti-thymocyte globulin (myeloablative)12. GVHD prophylaxis: cyclosporine + methotrexate.

USE OF TYROSINE KINASE INHIBITORS AFTER HSCT

In the study by Zhao Y et al., 2017, imatinib was used prophylactically at a dose of 300mg to 400mg/day from D+100 until 1 year after HSCT. In patients with persistent residual disease, or with hematologic or cytogenetic relapse, a higher dose of imatinib (600mg/day) was used for at least 1 year after achieving complete cytogenetic remission[23].

In case of disease progression while using imatinib prior to transplant, one should switch to another generation TKI (dasatinib, nilotinib, or other), according to one's clinical history and mutational status.

STRATEGIES TO AVOID DISEASE RELAPSE

A few strategies can be used to avoid disease relapse after HSCT, as presented in the ASH Educational Program published in Hematology in 2018[17]:

1. Minimize pre-transplant disease burden;
2. Optimize conditioning regimen;
3. Optimize the graft-versus-leukemia (GVL) effect: minimize post-transplant immunosuppression and use prophylactic donor lymphocyte infusion (DLI).

Importantly, disease status should be regularly monitored in children with CML, with molecular and cytogenetic studies, following the National Comprehensive Cancer Network (NCCN), European Leukemia Net (ELN), or European Society of Medical Oncology (ESMO) guidelines, both pre- and post-transplant, since this will allow for appropriate and timely interventions according to optimal treatment response assessments[5].

Chronic myeloid leukemia	Allogeneic HSCT	Autologous HSCT
Chronic phase	Yes (standard of care, clinical evidence)	No
1st chronic phase refractory to TKIs	Yes (standard of care, clinical evidence)	No
1st chronic phase intolerant to TKIs	Yes (standard of care, clinical evidence)	No
Accelerated phase	Yes (standard of care, clinical evidence)	No
Blast phase	Yes (standard of care, clinical evidence)	No

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