HEMATOPOIETIC CELL TRANSPLANTATION FOR JUVENILE MYELOMONOCYTIC LEUKEMIA AND OTHER MYELOPROLIFERATIVE NEOPLASMS

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ABSTRACT

Juvenile myelomonocytic leukemia (JMML) is a rare and distinctive hematologic neoplasm affecting infants and younger children. Hyperactivation of the RAS signaling pathway is a central initiating event in JMML, which also delineates its various genetic and clinical subtypes. While a small percentage of children may achieve spontaneous clinical remission, allogeneic hematopoietic cell transplantation (HCT) remains the only possible cure for most JMML patients. In this article, we reviewed the indications of HCT in JMML. Other myeloproliferative diseases, such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis, are extremely rare in pediatrics and are briefly discussed.

Keywords: Leukemia, Myelomonocytic, Juvenile. Hematopoietic Stem Cell Transplantation. Polycythemia Vera. Thrombocythemia, Essential. Primary Myelofibrosis. Child.

INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare hematologic neoplasm of infants and younger children. Characterized by the proliferation of granulocytes and monocytes associated with dyspoiesis, JMML is responsible for 3% of all childhood leukemias[1–3]. Mutations in genes of the *RAS-MAPK* pathway (*NRAS*, *KRAS*, *PTPN11*, *NF1*, and *CBL*) are involved in the pathogenesis of almost all patients with JMML, with a well-defined phenotype-genotype association[4–8]. The identification of the mutated gene is currently necessary not only for diagnosis, but also for prognostic definition and therapeutic strategy, since it identifies subgroups of patients with variable clinical characteristics and evolution[8,9].

Allogeneic hematopoietic cell transplantation (HCT) represents the only possible cure for the vast majority of patients with JMML, in contrast to a smaller percentage of children who survive long-term without HCT and eventually experience spontaneous clinical remissions[6–10].

No randomized clinical trials have compared pre-HCT therapy *versus* proceeding directly to transplant. While several chemotherapeutic approaches have been evaluated for reducing disease burden prior HCT, to date, no conventional chemotherapy regimen has demonstrated reduced post-HCT relapse incidence[2,6,8,11,12]. Another approach to upfront treatment involves hypomethylating agents. In the last years, several case series describing hematological and molecular responses to azacitidine and decitabine treatment in pediatric patients with JMML have been published[13–17]. The recent phase 2 study of the European Working Group of Myelodysplastic Syndromes in children (EWOG-MDS) demonstrated that azacitidine provides valuable clinical benefit to JMML patients prior to HCT[18].

HEMATOPOIETIC CELL TRANSPLANTATION INDICATIONS IN JUVENILE MYELOMONOCYTIC LEUKEMIA

Patients harboring somatic PTPN11 mutation generally have the highest risk of rapid progression and early death without HCT. Similarly, JMML is also fatal in the absence of HCT in patients with neurofibromatosi type 1 (NF1). Children with somatic KRAS mutation generally exhibit highly aggressive disease manifestations, requiring prompt treatment. However, they respond particularly well to low-dose azacitidine, often achieving sustained clinical and molecular remissions and possibly cure without HCT in those patients with a low-risk profile.

JMML associated with somatic NRAS mutation displays considerable clinical heterogeneity: some patients experience spontaneous disease regression without HCT, while others have an aggressive disease, with a high rate of relapse after HCT (usually older children, with high-fetal hemoglobin levels). Most children with CBL germline mutation present with a self-resolving disease, and observation without therapy is generally recommended, but recent studies reported acquired somatic CBL mutations in some patients showing more aggressive disease and heterogeneous disease course even among patients with germline CBL mutations. For patients presenting with a JMML phenotype but no detectable RAS pathway mutation, HCT is recommended. However, it is essential to exclude other rare myeloproliferative disorders, acute leukemias and non-malignant diseases[6–10,19–22]. HCT indications according to driver mutation are described in Table 1.

Table 1. Indications for hematopoietic cell transplantation (HCT) in juvenile myelomonocytic leukemia.

Ras pathway mutation	Allogeneic HCT indication
Somatic PTPN11	Swift HCT
Germline NF1	Swift HCT
Somatic KRAS	Azacitidine and/or HCT
Somatic NRAS	HCT for many, careful selection of candidates for watch-and-wait.
Germline CBL	Watch-and-wait. HCT if disease progression.
All negative	Most patients require HCT

Source: Mayerhofer *et al.*, 2021.

DONOR SELECTION, CONDITIONING REGIMEN, AND GRAFT-*VERSUS*-HOST DISEASE PROPHYLAXIS

In more recent years, using a human leukocyte antigen (HLA) matched/1-antigen-disparate unrelated donor (MUD) offers minimal or no significant disadvantage compared with a matched sibling donor (MSD) for HCT in JMML[23–25]. Available data also indicate that umbilical cord blood (UCB) transplantation is a suitable option for children with JMML lacking an HLA-compatible relative[26]. Although there are only a few reports available to date regarding haploidentical HCT for JMML, it can be considered for those patients who lack an HLA-matched donor or need an urgent allograft[27–29].

The EWOG-MDS and the European Society for Blood and Marrow Transplantation (EBMT) recommend busulfan (BU) + cyclophosphamide (CY) + melphalan (MEL) as the standard conditioning regimen for patients with JMML, resulting in a four-year overall survival (OS), event-free survival (EFS), relapse, and transplant-related mortality (TRM) rates of 64, 52, 35, and 13%, respectively[23].

A recent prospective clinical study from the Japan Pediatric Leukemia/Lymphoma Study Group demonstrated that the BU + fludarabine (FLU) + MEL regimen may provide similar survival outcomes as BU + CY + MEL, resulting in a three-year OS, EFS, relapse, and TRM rates of 63, 52, 18, and 21%, respectively[24]. In an attempt to reduce toxicity, a prospective randomized trial from the Children's Oncology Group study compared BU/CY/MEL with BU/FLU alone, but terminated early due to the excessive disease recurrence in the latter arm[30]. HCT conditioning regimens recommendations for JMML are described in Table 2.

Table 2. Conditioning regimens recommendations in juvenile myelomonocytic leukemia.

Standard: 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
Alternative: 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.

The most frequently employed protocols for graft-*versus*-host disease (GVHD) prophylaxis in HCT for JMML consist of cyclosporine in MSD HCT and calcineurin inhibitors combined with methotrexate and anti-thymocyte globulin (ATG) in MUD HCT[23,31]. Although incorporating ATG into GVHD prophylaxis sparked concerns about potentially reducing the graft-*versus*-leukemia (GVL) effect, its administration did not lead to higher relapse rates in children with JMML undergoing MUD transplantation[23,26]. However, studies have shown a lower incidence of disease recurrence after HCT associated with the presence of GVHD in children with JMML, suggesting the existence of a GVL effect directed against JMML cells with subsequent protection against relapse[25,26,32]. In view of these considerations, the EWOG-MDS recommends keeping immunosuppressive therapy with cyclosporine A at low levels and tapering early. Children carrying K-RAS mutations can be an exception to this recommendation, as in their experience, they have a lower relapse rate than children with other molecular abnormalities[2,6]. General GVHD prophylaxis recommendations for JMML patients are described in Table 3.

Table 3. Graft-*versus*-host disease prophylaxis recommendations in juvenile myelomonocytic leukemia.

Matched sibling donor	Cyclosporine as a single agent
Unrelated donor*	Calcineurin inhibitors (cyclosporine or tacrolimus) combined with short methotrexate (D +1, +3 and +6).
Umbilical 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.

PREVENTION AND MANAGEMENT OF POST-HEMATOPOIETIC CELL TRANSPLANTATION DISEASE RELAPSE

Relapse remains the leading cause of treatment failure following HCT in JMML, occurring in 30–50% of patients. It generally occurs within the first two years after HCT, with a peak at a median time of two–six months[23,33–35]. Rigorous and regular post-HCT monitoring of donor-recipient chimerism serves as a valuable tool for identifying JMML patients at risk of a forthcoming relapse. In such cases, prompt withdrawal of immunosuppression can prevent disease progression[36,37].

Age at diagnosis ≥ 2 years old, NF1 or somatic PTPN11 mutation, and high DNA methylation define a patient group whose risk of JMML recurrence after HCT is even higher than 50%, bringing up the question of post-transplant prophylaxis. In these cases, some authors suggest considering the use of azacitidine + donor lymphocyte infusions, although emphasizing that there are no systematic data for this approach in JMML[8,9].

For children with JMML who have overt leukemia relapse after HCT, a second allograft with a low-intensity GVHD prophylaxis can be an effective salvage therapy for at least one-third of patients[2,23,33,34]. Targeted therapies are currently under investigation for patients with relapsed/refractory JMML[38].

MYELOPROLIFERATIVE NEOPLASMS

Beyond chronic myeloid leukemia BCR-ABL1+, classic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). These conditions exhibit extremely low occurrence rates in pediatric population, with about 0.82 cases for every 100 thousand patients, about 100 times less than in adults. Consequently, understanding of clinical manifestations, molecular profiles, disease outcomes, and optimal therapeutic approaches remains limited for pediatric cases[39–41].

Pediatric patients typically exhibit a reduced frequency of mutations commonly found in adults, thrombotic events, and transformation to secondary myelofibrosis and acute leukemia[39–41]. Furthermore, well-defined prognostic criteria and corresponding treatment guidelines, including specific indications for allogeneic HCT, remain limited for pediatric patients[41–43].

Most pediatric patients with PV and ET are treated with supportive care and sometimes cytoreductive therapies[44,45]. In adults, PMF and post-ET/PV myelofibrosis are BCR-ABL1-negative MPNs with the worst survival rates, but allogeneic HCT offers curative potential for many patients. Among children and adolescents, myelofibrosis (MF) is the rarest type of MPNs, and data regarding HCT outcomes in this group remain limited.

Recently, a retrospective study of the EBMT evaluated 35 children with MF, including 33 with primary myelofibrosis and two with secondary myelofibrosis transplanted from MSD, MUD, or UCB. Conditioning was usually chemotherapy-based (busulfan-based in 68.6%) and myeloablative. Six-year non-relapse mortality (NRM) was 18%, relapse incidence was 15.9%, progression-free survival (PFS) was 66.1%, and OS was 71.1%. Six-year PFS and OS were significantly higher after bone marrow transplantation compared to HCT from other sources, whereas NRM was significantly lower. This pioneering multicentric study examining allogeneic HCT outcomes in children with myelofibrosis demonstrated both the feasibility and curative potential of this procedure, while highlighting the need for further investigation[46].

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, Ferreira RS, Zamperlini G, Bassani ACF, Michalowski MB and Lee MLM. **Conception and design:** Villela NC and Oliveira AF. **Manuscript writing:** Villela NC, Oliveira AF, Ferreira RS, Zamperlini G, Bassani ACF, Michalowski MB and Lee MLM. **Final approval:** Villela NC and Oliveira AF.

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