Hematopoietic stem cell transplantation for pediatric acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia (AML) accounts for 15% to 20% of pediatric acute leukemia cases. Treatment failure is influenced by both genetic risk and response to therapy[1,2,3,4]. 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]. Improved survival outcomes are associated with comprehensive strategies that combine intensive chemotherapy, effective supportive care, and hematopoietic stem cell transplantation (HCT), adjusted to the relapse risk profile of each patient[6-10]. 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. This is the 2025 update of the previously guideline[11].

Keywords: Stem Cell Transplantation. Leukemia. Myeloid. Acute. Child. Guideline.

INTRODUCTION

Acute myeloid leukemia (AML) accounts for 15 to 20% of pediatric acute leukemia cases. Treatment failure is influenced by both 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]. Improved survival outcomes are associated with comprehensive strategies that combine intensive chemotherapy, effective supportive care, and hematopoietic stem cell transplantation (HCT), adjusted to the relapse risk profile of each patient[6–10].

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 HCT for childhood AML, and to establish evidence-based recommendations for the optimal management of this disease. This is the 2025 update of the previously guideline[11].

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FIRST REMISSION

Patients classified as high risk, either for genetic/molecular factors or for persistent disease after induction therapies, should be referred for HCT in first clinical remission (CR1)[6]. Currently, HCT is not recommended for patients CR1 when they are classified as low or intermediate risk.

In AML, relapses occur predominantly during the early post-diagnosis period, with the majority emerging within the first six months. When allogeneic HCT (allo-HCT) is not performed during this critical timeframe, the relapse risk increases substantially. This temporal pattern may potentially negate the benefit of proceeding with transplantation CR1 when significantly delayed. For cases in which allo-HCT cannot be performed within this optimal window, we recommend comprehensive case review and multidisciplinary discussion to reassess transplant indications.

MOLECULAR AND GENETIC EVALUATION

With the evolution of methods for detecting genetic/molecular alterations, novel genetic alterations have been correlated with different clinical and prognostic characteristics[6,12]. Table 1 shows the abnormalities with a more consolidated prognostic impact.

Table 1. Molecular genetic abnormalities with prognostic impact in pediatric acute myeloid leukemia.

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*
Unfavorable

Continued...

Continuation.

-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**
t(11;15)(p15;q35)/*NUP98-KDM5A*
Complex karyotype (≥ three changes)
FLT3/ITD
FAB MO, M6 e M7 without t(1;22) or without *GATA-1*
Secondary AML (Myelodysplastic Syndrome or previous treatment)

*Mast KJ, Taub JW, Alonzo TA, Gamis AS, Mosse CA, Mathew P, Berman JN, Wang YC, Jones HM, Campana D, Coustan-Smith E, Raimondi SC, Hirsch B, Hitzler JK, Head DR. 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;144(4):466–72. https://doi.org/10.5858/arpa.2018-0526-OA; **Gruber TA, Larson Gedman A, Zhang J, Koss CS, Marada S, Ta HQ, Chen SC, Su X, Ogden SK, Dang J, Wu G, Gupta V, Andersson AK, Pounds S, Shi L, Easton J, Barbato MI, Mulder HL, Manne J, Wang J, Rusch M, Ranade S, Ganti R, Parker M, Ma J, Radtke I, Ding L, Cazzaniga G, Biondi A, Kornblau SM, Ravandi F, Kantarjian H, Nimer SD, Döhner K, Döhner H, Ley TJ, Ballerini P, Shurtleff S, Tomizawa D, Adachi S, Hayashi Y, Tawa A, Shih LY, Liang DC, Rubnitz JE, Pui CH, Mardis ER, Wilson RK, Downing JR. An Inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia. Cancer Cell. 2012;22(5):683–97. https://doi.org/10.1016/j.ccr.2012.10.007. Source: Elaborated by the authors.

MINIMAL RESIDUAL DISEASE

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

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.

Given the challenge, patients previously categorized as low or intermediate risk—referred for HCT exclusively due to detectable levels of residual disease after the induction phase—have the flow archive reviewed by the MRD group of the SBTMO, for further definition of the HCT indication by its Pediatric Group[5].

The risk classification is outlined in Table 2.

Table 2. Risk classification based on diagnostic characteristics associated with measurable residual disease (MRD).

Classification	Diagnostic characteristics + MRD
Low risk	Favorable genetic alterations and MRD < 0.1% after second induction
Intermediate risk	Patients who do not have criteria for low or high risk
High risk	Unfavorable genetic alterations or MRD ≥ 0.1% after second induction

Source: Elaborated by the authors.

RELAPSED ACUTE MYELOID LEUKEMIA

In relapses, the second remission is achieved in about two-thirds of patients with AML, but, with only chemotherapy regimens, lasting remissions in these cases are rare. Thus, in relapsed disease, allogeneic transplantation constitutes an absolute indication and ought to be performed without delay upon confirmation of renewed remission[10,13].

ACUTE PROMYELOCYTIC LEUKEMIA

For patients with acute promyelocytic leukemia in second complete remission (CR2) following first relapse who achieve complete molecular remission (undetectable PML-RARA in bone marrow), autologous transplantation represents the preferred approach, demonstrating lower morbidity and mortality compared to allogeneic transplantation. Conversely, for cases with persistent molecular or flow cytometry-detectable disease, as well as those in third or subsequent remissions (CR3+), allogeneic transplantation is indicated due to its superior cure rates in these high-risk scenarios[14,15].

DOWN SYNDROME

In pediatric patients with AML and Down syndrome, HCT should be considered in specific scenarios, such as high-risk genetic abnormalities, or relapsed/refractory disease. These individuals exhibit heightened sensitivity to chemotherapy, but also an increased risk of treatment-related toxicity, necessitating a careful risk-benefit assessment, tailored to their unique biological and clinical characteristics[16].

GRANULOCYTIC SARCOMA

In children and adolescents with granulocytic sarcoma, also referred as myeloid sarcoma, HCT should be considered in cases of relapse following initial treatment, refractory disease, or when granulocytic sarcoma presents as a manifestation of AML with high-risk features, such as poor-risk cytogenetics or persistent MRD[17,18].

AUTOLOGOUS TRANSPLANT

To date, the benefit of autologous transplantation has not been proven when compared to isolated intensive chemotherapy and/or to allogeneic transplantation for non-promyelocytic AML in CR1[19,20]. Thus, autologous transplantation as remission consolidation should only be performed in research protocols.

BRIDGING THE GAP: HEMATOPOIETIC STEM CELL TRANSPLANTATION OUTCOMES FOR ACUTE MYELOID LEUKEMIA IN BRAZIL *VERSUS* INTERNATIONAL BENCHMARKS

A study reviewing the outcomes of 1,940 pediatric AML patients treated with the BFM protocol from 1987 to 2012 demonstrated that although event-free survival has remained similar since the 1990s, improvements in supportive care and HCT have made patients who become in CR2 potentially redeemable, and this resulted in an increase of approximately 20% in overall survival in the last 30 years[9].

In a study with Brazilian HCT centers for children, adolescents, and young adults, overall and event-free survival in four years were 47 and 40%, respectively[10]. Brazilian outcomes of HCT in children with AML are inferior to those reported in the United States of America and Europe[7,8,20–22]. *ACUTE MYELOID LEUKEMIA* SCT-BFM study aimed at standardizing pediatric HCT for AML across centers in Germany and Austria reported four-year event-free survival and overall survival of 61 and 70%, respectively[23]. When assessing the survival advantage of HCT, the increased transplant-related mortality rate in our setting should be taken into account.

The main prognostic factor for the success of HCT in patients with AML remains the stage of the disease. Center for International Blood and Marrow Transplant Research data show three-year overall survival of 70, 65, and 31%, respectively, for patients under 18 years old undergoing related HCT in early (CR1), intermediate (CR2), and advanced stages (active disease or ≥ CR3) of Acute Myeloid Leukemia[20]. Patients with treatment-refractory AML or with more than one relapse still have a dismal prognosis[24].

The current indications for transplantation are summarized in Table 3.

Table 3. Hematopoietic stem cell transplantation indications for pediatric patients: Brazilian Bone Marrow Transplantation Society Consensus recommendations for acute myeloid leukemia.

Disease	Allogeneic				Autologous
	Familiar		Unrelated		
	MSD	HAPLO	MUD	MMUD	
AML 1 CR high risk	Yes	Yes	Yes	Yes	No
2 CR	Yes	Yes	Yes	Yes	No
3 CR	Yes	Yes	Yes	Yes	No
Refractory	Yes	Yes	Yes	Yes	No
APL CR2 CMR	No	No	No	No	Yes
APL CR2 non CMR	Yes	Yes	Yes	Yes	No

AML: acute myeloid leukemia; CR: complete remission; APL: acute promyelocytic leukemia; CMR: complete molecular remission; MSD: matched sibling donor; HAPLO: familiar haploidentical donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor. Source: Elaborated by the authors.

DONOR AND STEM CELL SOURCE

The results of transplants using related, unrelated (matched or partially matched, with a greater than 8/10 HLA-match), and haploidentical donors are very similar in AML, with no significant difference between type of donor, whether in overall survival and incidence of acute or chronic graft-*versus*-host disease (GVHD)[10,25].

In children, bone marrow is preferable in comparison to peripheral blood as stem-cell source, given the higher extensive chronic GVHD and transplant-related mortality with the use of peripheral blood stem cells[26,27]. 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[28].

In haploidentical hematopoietic cell transplantation, maternal donors are associated with an elevated risk of chronic GVHD, reduced overall survival, and inferior graft-*versus*-host relapse-free survival. Consequently, maternal donors should be avoided when alternative options exist. If maternal donation is utilized, preferential use of bone marrow over peripheral blood as the stem cell source is recommended, to mitigate additional chronic GVHD risk[29].

An important consideration is that haploidentical transplantation is widely performed in Brazil. In such cases, meticulous attention must be paid to the presence of anti-HLA antibodies against the donor, along with their clinical implications and management strategies. This complex discussion should be guided by HLA specialists.

CONDITIONING REGIMENS

For patients scheduled for autologous HCT, the standard conditioning regimen comprises busulfan and melphalan[14,15,19].

As for conditioning in allogeneic transplants, there are better results (toxicity *versus* relapse) with the use of myeloablative protocols based on busulfan AUC 4,000–5,000 µMol•min or based on total body irradiation (TBI)[23,30–36].

Although transplantation for active disease (≥ 5% blasts in the bone marrow) is controversial, in cases with adequate performance benefit from the adapted FLAMSA conditioning scheme has been reported, curing at least 20% of these children with refractory disease[37,38].

A contemporary Brazilian single-center study, initially encompassing eight patients and subsequently expanded to 13 pediatric cases of refractory AML treated with a modified FLAMSA regimen, reported 46% overall survival. Mortality analysis revealed relapse as the predominant cause of death (43%), followed by infectious complications (29%)[39].

Due to important differences in the transplant-related mortality rate (TRM) regarding age and conditioning regimen, according to the risk/benefit and rates of event-free survival and overall survival for patients in

pre-HCT remission, we propose different conditioning for children over or under 6 years old undergoing either matched sibling donor (MSD) or unrelated donor (MUD)[40–42]. The preparatory regimen will consist of busulfan, cyclophosphamide, and melphalan in those patients who are 6 years old or younger (TRM was considerably higher in older children, especially those aged 12 and over). The rationale for implementing a triple-alkylating agent conditioning regimen derived from multiple lines of clinical evidence, associated with a better event-free survival and a lower incidence of relapse[40–42]. For patients aged above 6, the conditioning regimen will comprise busulfan, fludarabine, and melphalan.

The recent advent of haploidentical transplantation has made the search for a more agile donor and, consequently, has allowed transplants to be carried out for a larger number of patients. According to the exciting results presented by Jaiswal et al.[43], for transplants with haploidentical donors, the suggested scheme is an adaptation of the therapeutic strategy of those studies.

Young children (under 10 years old) may develop GVHD up to eight times more frequently than adults when receiving post-transplant cyclophosphamide. For these patients, the use of donor lymphocyte infusion post-transplantation requires careful consideration to avoid potential harm[44].

Depending on the experience of each transplant unit, there is the possibility of adopting other conditioning protocols.

An overview of the proposed conditioning schemes is provided in Table 4. The weight-adjusted Busulfan doses are detailed in Table 5.

Table 4. Suggested conditioning regimen.

HCT	Conditioning
Autologous (BuMel)	BU (AUC 4,000–5,000 µMol•min) D-7 to D-4 + MEL (140 mg/m^2) D-2
Haploidentical (Jaiswal adapted BuFluMel regimen)	BU (AUC 4,000–5,000 µMol•min) D-6 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + MEL (140 mg/m^2) D-2 + PTCY (100 mg/kg) D+3 and D+4 + Mesna (1.4 × dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + DLI: D+21 (1×10^6/kg of CD3$^+$ cells), D+35 (5×10^6/kg of CD3$^+$ cells), D+60 (5×10^6/kg of CD3$^+$ cells)
For children with active disease (FLAMSA adapted regimen)	Intrathecal chemotherapy D-14 + VP16 (600 mg/kg) D-13 to D-10 + FLU (120 mg/m^2) D-13 to D-10 + ARA-C (8,000 mg/m^2) D-13 to D-10 (4 h after FLU) + CY (120 mg/kg) D-3 and D-2 + Mesna (1.4 × dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + BU (9.6 mg/kg) D-6 and D-5 + DLI: D+21 (1×10^6/kg of CD3$^+$ cells), D+35 (5×10^6/kg of CD3$^+$ cells), D+60 (5×10^6/kg of CD3$^+$ cells) + AZA (160 mg/m^2), divided in five consecutive days, with one, two, three, four, and five months after transplantation (total of five cycles).
For children < 6 years old MSD (BuCyMel)	BU (AUC 4,000–5,000 µMol•min) D-8 to D-5 + CY (120 mg/kg) D-4 and D-3 (start 24 h after BU) + Mesna (1.4 × dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) +MEL (140 mg/m^2) D-2
For children < 6 years old MUD (BuCyMel)	BU (AUC 4,000–5,000 µMol•min) D-8 to D-5 + CY (120 mg/kg) D-4 and D-3 (start 24 h after BU) + Mesna (1.4 × dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) +MEL (140 mg/m^2) D-2 + ATG (0.5 mg/kg/day) D-8, ATG (2.5 mg/kg/day) D-5 to D-6
For children > 6 years old MSD (BuFluMel)	BU (AUC 4,000–5,000 µMol•min) D-7 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + MEL (140 mg/m^2) D-2
For children > 6 years MUD (BuFluMel)	BU (AUC 4,000–5,000 µMol•min) D-7 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + MEL (140 mg/m^2) D-2 + ATG (0.5 mg/kg/day) D-8, ATG (2.5 mg/kg/day) D-5 to D-6

MSD: matched sibling donor; MUD: matched unrelated donor; Cy: cyclophosphamide; FLU: fludarabine; BU: busulfan; ATG: thymoglobulin; VP16: etoposide; MEL: melphalan; ARA-C: cytarabine; DLI: donor lymphocyte infusion; total doses (shown in parentheses) should be appropriately fractionated for each chemotherapy administration. Start DLI regardless of hematological engraftment, and suspend it in case of graft-*versus*-host disease. Depending on patient tolerance, the dose of AZA may be escalated incrementally with each cycle, up to a maximum of 75 mg m^2/day. If available AUC for busulfan, 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. In patients with relevant central nervous system involvement, total body irradiation (TBI) + CY may be considered as a conditioning regimen option. In patients scheduled for FLAMSA who fail to achieve remission after the first chemotherapy phase (etoposide, fludarabine, and cytarabine), but remain in good clinical condition, substituting busulfan with 1,200 centigray TBI (maintain cyclophosphamide) may improve therapeutic efficacy. Source: Elaborated by the authors.

Table 5. Busulfan dosage.

Weight in kg	Busulfan dose (mg/kg/day)	Cumulative dose of busulfan (mg/kg)
≤9	4	16
>9–≤16	4.8	19.2
>16–≤23	4.4	17.6
>23–≤34	3.8	14.2
>34	3.2	12.8

Source: European Society for Blood and Marrow Transplantation (EBMT) guidelines for hematopoietic stem cell transplantation.

GRAFT-*VERSUS*-HOST DISEASE PROPHYLAXIS REGIMEN

Immunosuppressive protocol selection in pediatric HCT is intrinsically linked to donor type and compatibility.

For MSD transplants, calcineurin inhibitors-either cyclosporine (CSP) or tacrolimus-are administered as monotherapy[45–47]. In contrast, MUD HCT typically employs a combined prophylactic approach, incorporating short-course methotrexate (MTX) alongside a calcineurin inhibitor[45–47].

Post-transplant cyclophosphamide has gained recognition as a promising therapeutic approach for both MUD and haploidentical HCT, although further studies are awaited to define the optimal regimen regarding long-term outcomes for these patients[48–50].

The therapeutic utility of anti-thymocyte globulin in MUD transplantation remains a subject of ongoing debate, primarily owing to heterogeneity in both preparation methods and dosage regimens[51].

For umbilical cord blood transplantation, the immunosuppressive regimen usually comprises the combination of a calcineurin inhibitor with mycophenolate mofetil. 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[47].

A comprehensive breakdown of regimen-specific protocols is delineated in Table 6.

Table 6. Graft-*versus*-host disease (GVHD) prophylaxis regimen in childhood acute myeloid leukemia.

Matched sibling donor	CSP 2 mg/kg or TAC 0.05 mg/kg in two divided IV doses—started on D-1 (SL CSP: 100–200 mcg/L or TAC: 5–15 ng/mL)
Matched unrelated donor	Short-term MTX (D+1, D+3, D+6)* + CSP or TAC
Haploidentical	PTCy 50 mg/kg (D+3 and D+4)** + CSP or TAC + MMF 15 mg/kg/dose q8h; maximum 2 g/day—started on D+5
Umbilical cord blood	Combination of CSP or TAC + MMF 15 mg/kg/dose q8h; maximum 2 g/day

CSP: cyclosporin; TAC: tacrolimus; SL: serum levels; MTX: methotrexate; PTCy: post-transplant cyclophosphamide; MMF: mycophenolate mofetil; UCB: umbilical cord blood; *MTX is used at doses of 10 mg/m^2; **coupled with mesna (140% of the Cy dose). Source: Elaborated by the authors.

BEST-TIME POINTS FOR MINIMAL RESIDUAL DISEASE ASSESSMENT

- Pre-HCT: MRD assessments should be made immediately before allo-HCT;
- Post-HCT: MRD assessments by multiparameter flow cytometry and/or reverse transcription quantitative polymerase chain reaction (RT-qPCR) are accurate in predicting relapse at days +30, +60, +90, +180, +270, and +365 post-HCT.

Any detectable MRD level post-HCT is highly predictive of relapse and poor survival[52]. When decisions that may change patient management are based on low levels of MRD, we would recommend that the SBTMO MRD Working Group review the flow cytometric data to increase accuracy of the results.

MANAGEMENT OF RELAPSE AND STRATEGIES TO MINIMIZE POST-TRANSPLANT RELAPSE

The persistently poor overall survival observed post-HCT, especially in high-risk and MRD-positive individuals, represents an unmet clinical need demanding novel relapse prevention strategies[53].

This consensus document features a comprehensive chapter dedicated to the management of leukemic relapse, incorporating: an extensive literature review, recommended therapeutic regimens for remission induction, and specialized strategies to minimize post-transplant relapse risk in AML, particularly for high-risk disease. Specific interventions discussed include early post-transplant intrathecal chemotherapy, incorporation of novel agents (venetoclax, azacitidine), and targeted therapies for actionable genetic markers (*e.g.*, FLT3-ITD mutations)[13,54,55]. The chapter additionally provides detailed protocols for disease monitoring, including recommended methods and frequency of reassessment.

FINAL CONSIDERATIONS

Despite the immunological effect of the grafted cells against leukemia, the toxicity and mortality related to the procedure remain an obstacle to be overcome. The heterogeneity of data related to patient selection and type of conditioning for HCT 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[10,22].

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 CR1 and CR2 are potentially redeemable with HCT, but from the second relapse and/or when the patient has a disease in progress, there is a drastic reduction in the chances of cure. Delay in HCT is harmful both due to the risk of losing remission and suffering a relapse, 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[10].

In the management of AML, it is advisable to consider 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 searching for a donor at the Brazilian Registry of Voluntary Bone Marrow Donors.

In the current context, many advances have been achieved, in particular through the connection between the SBTMO, the SOBOPE, and the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH), in the challenged goal of better treatment conditions for children and adolescents with AML, and greater knowledge of Brazilian data.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

The data will be available upon request.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Rodrigues ALM, Seber A, Ribeiro RC, Zecchin VG, Lee MLM, Daudt L, Souza L, Sousa AM, Zanette AA, Nolasco C, Climaco V, Ribeiro AC, Domingues L, Silva TCPM, Klinger P, Rocha C, Magalhães I. **Conception and design:** Rodrigues ALM, Seber A, Ribeiro RC. **Analysis and interpretation of data:** Rodrigues ALM, Seber A, Ribeiro RC. **Technical procedures:** Rodrigues ALM, Seber A, Ribeiro RC. **Statistics analysis:** Rodrigues ALM, Seber A, Ribeiro RC. **Manuscript writing:** Rodrigues ALM, Seber A, Ribeiro RC. **Final approval:** Rodrigues ALM.

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