Allogeneic Hematopoietic Stem Cell Transplantation for Children and Adolescents with Acute Myeloid Leukemia in Brazil: A Multicentric Retrospective Study

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Abstract
The survival rates of children with high-risk acute myeloid leukemia (AML) treated with hematopoietic stem cell transplant (HSCT) range from 60% to 70% in high-income countries. The corresponding rate for Brazilian children with AML who undergo HSCT is unknown. We conducted a retrospective analysis of 114 children with AML who underwent HSCT between

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2008 and 2012 at institutions participating in the Brazilian Pediatric Bone Marrow Transplant Working Group. At transplant, 38% of the children were in first complete remission (CR1), 37% were in CR2, and 25% were in CR3+ or had persistent disease. The donors included 49 matched-related, 59 matched-unrelated, and six haploidentical donors. The most frequent source of cells was bone marrow (69%), followed by the umbilical cord (19%) and peripheral blood (12%). The 4-year overall survival was 47% (95% confidence interval [CI] 30%–57%), and the 4-year progression-free survival was 40% (95% CI 30%–49%). Relapse occurred in 49 patients, at a median of 122 days after HSCT. There were 65 deaths: 40 related to AML, 19 to infection, and six to graft versus host disease. In conclusion, our study suggests that HSCT outcomes for children with AML in CR1 or CR2 are acceptable and that this should be considered in the overall treatment planning for children with AML in Brazil. Therapeutic standardization through the adoption of multicentric protocols and appropriate supportive care treatment will have a significant impact on the results of HSCT for AML in Brazil and possibly in other countries with limited resources.

Keywords
pediatric AML, HSCT, Brazil

Introduction
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 40% of children with AML die of refractory/relapsed disease or treatment-related toxicity5. Recently, event-free survival (EFS) and overall survival (OS) rates greater than 60% and 70% in 5 years, respectively, have been reported in high-income countries (including transplant patients and those who did not need a transplant). The best therapeutic results are achieved by integrating intensive chemotherapy, optimal supportive care, and hematopoietic stem cell transplant (HSCT) adapted to each individual patient’s risk of relapse6–9.

Patients with low-risk or intermediate-risk AML are typically not candidates for HSCT in first remission (CR1), whereas patients with high-risk disease or poor response to induction therapy are referred for HSCT in CR1. Allogeneic HSCT offers the best chance of long-term cure for children with relapsed AML4,10–12.

In countries classified by the World Health Organization as middle-income countries, such as Brazil, HSCT has been implemented at several centers, particularly in wealthier regions. Sociocultural and economical limitations pose great challenges to diagnosing AML in these patients and treating them with chemotherapy and HSCT. Many patients do not undergo a proper cytogenetic and molecular evaluation and classification of their disease at diagnosis, and they may not be treated using standardized treatment protocols. In these countries, there is a limited number of hospital beds available for chemotherapy or transplantation, and optimal supportive care and management of comorbidities may not be available, compromising cure rates and increasing the risks associated with these complex and expensive procedures13–18.

Pediatric AML has an estimated incidence of 400 cases per year in Brazil19. In a recent Brazilian cohort, 5-year OS was reported to be less than 40%18. Results for HSCT have been reported for adult patients in Brazil, but the survival rates for children, adolescents, and young adults are unknown20. The objective of this study was to describe the outcomes of children with AML treated with chemotherapy followed by HSCT.

Materials and Methods

Patient Data
This was a multicenter retrospective study using datasets (demographic, disease, and transplant-related characteristics from coded patients) provided by the Brazilian Pediatric HSCT Working Group (BPHWG). The participating institutions reported to the BPHWG all consecutive allogeneic HSCTs performed between 2008 and 2012 to treat AML in patients younger than 21 years at the time of transplant (except those with Down syndrome or promyelocytic leukemia).

Ethics Statement
The protocol was approved by the Ethics Committee of the coordinating institution (Hospital Pequeno Príncipe, Curitiba) (code CAAE: 53705016.7.1001.0097). Informed consent was waived because we used coded datasets provided by the BPHWG.

Endpoints and Definitions
High-risk cytogenetics at this study include t(6;11)(q27;q23)/MLLT4-KMT2A, t(10;11)(p12;q23)/MLLT10-KMT2A, t(10;11)(p12;q23)/ABI1-KMT2A, t(6;9)(p23;q34)/DEK-NUP214, t(8;16)(p11;p13)/KAT6A-CREBBP, t(16;21)(q24;q22)/RUNX1-CBFA2T3, t(5;15)(p15.5;q35)/NUP98-NSD1, inv(16)(p13.3q24.3)/CBFA2T3-GLIS2, t(11;15)(p15;q35)/NUP98-KDM5A, t(3;5)(q25;q34)/NPM1-MLF1, FLT3-ITD, and monosomy 76. The primary endpoint was OS. Secondary endpoints were hematopoietic recovery, relapse, progression-free survival (PFS), non-relapse mortality (NRM) rates, and acute Graft versus host disease (aGVHD) and chronic GVHD (cGVHD). OS was defined as the time from
HSCT to death from any cause. Surviving patients had their survival times censored at the last follow-up. Relapse was defined as the presence of morphologic or cytogenetic evidence of disease in the peripheral blood, marrow, or extramedullary sites. PFS was defined as the time from HSCT until relapse, progression, or death without evidence of disease. Treatment-related mortality was defined as mortality unrelated to disease progression or relapse. Neutrophil engraftment time was defined as the interval between the transplant and the first of three consecutive days with an absolute neutrophil count of \(\geq 0.5 \times 10^9/L\). Platelet engraftment time was defined as the interval between transplant and the last of seven consecutive days with a platelet count of \(\geq 20 \times 10^9/L\) without platelet transfusion support. Primary graft failure was defined as the failure to achieve an absolute neutrophil count of \(\geq 0.5 \times 10^9/L\) for three consecutive days or donor chimerism of <5%. Secondary graft failure was defined as initial donor engraftment followed by graft loss, as evidenced by a persistent decline in the absolute neutrophil count to \(\geq 0.5 \times 10^9/L\) and/or donor chimerism of <5%. aGVHD and cGVHD were classified according to the criteria of Glucksberg et al.²¹ and the NIH 2014 criteria²². Donor human leukocyte antigen (HLA) matching was defined as the use of HLA-matched sibling or alternative donors, including HLA-matched or mismatched unrelated donors and mismatched family members (haploidentical donors). Matched sibling donors were HLA-A, HLA-B, or HLA-DR/DRB1 typed. Unrelated bone marrow matching was evaluated at a minimum of eight HLA alleles and unrelated umbilical cord blood matching at a minimum of six HLA alleles. Patients were labeled as myeloablative conditioning (MAC) recipients if they received a total body irradiation (TBI) of \(\geq 8\) Gy fractionated or a busulfan dose of >8 mg/kg. Reduced-intensity conditioning (RIC) regimens differ from MAC conditioning because the dose of alkylating agents or TBI is reduced by at least 30%. Most often, these RIC regimens combine fludarabine with an alkylating agent, melphalan, busulfan, thiotepa in reduced doses, or fludarabine with reduced dose TBI²³.

**Statistical Analysis**

Statistical analyses were performed using the R statistical software, version 3.6.0 (www.r-project.org). A two-sided \(P\)-value of <0.05 was considered to indicate statistical significance. Descriptive analyses were reported as absolute and relative values. Continuous data were expressed as the median and standard deviation. Comparisons were performed using the chi-square test or Fisher’s exact test, as appropriate, for categorical variables and the Wilcoxon or Kruskal–Wallis test for continuous variables.

The analysis of the incidence of transplant-related mortality considered relapse as a competitive event. The analyses of the incidence of graft failure, neutrophil recovery, and platelet recovery considered death as a competitive event. For PFS analyses, relapse or death were considered events. The incidences of aGVHD and cGVHD were estimated with death and primary graft failure considered as competitive events. Incidence curves were compared using Gray’s test.

The Cox proportional hazards regression model (random effects) was used to assess the impact of potential risk factors on mortality in multivariable analyses, providing hazard ratios (HRs) with their 95% confidence intervals (CIs). Variables were added sequentially to the model and kept if \(P\) was less than 0.05. We then included potential confounders in the model and reassessed the results. The proportional hazard assumption was checked by analyzing the Schoenfeld residuals.

OS and disease-free survival were estimated using the Kaplan–Meier method.

**Results**

**Patients**

A total of 114 patients younger than 21 years with AML underwent allogeneic HSCT at 10 Brazilian institutions between January 2008 and January 2012. The median age at the time of transplant was 10 years (range 0.8–20 years), 60% of the patients were male, and 80% were white.

**Clinical Characteristics**

Cytogenetic data were available for 81 patients, and 31 presented alterations that classified them as high risk⁷ (Table 1). Positive cerebrospinal fluid cytology at diagnosis was reported for 13 of 105 patients (12%); data were unavailable for the remaining nine patients. The French–American–British (FAB) classification subtype was reported for 100 patients, and the most frequent FAB subtype was M5 (reported for 23% of cases).

**HSCT Indications**

The main indications for HSCT were relapse in 48 patients (42%), persistent disease after induction in 16 (14%), and refractory disease in 13 (11.9%). For those patients who experienced remission, the indications for HSCT included cytogenetics in 12 (11%), secondary AML in 10 (9%), M7 FAB subtype in eight (7.3%), and positive matched-related donors (MRDs) after induction in two (1.8%). Data on the indication for HSCT were unavailable for five patients.

**Remission Status Before Transplant**

Twenty-three patients (20%) had not reached morphologic remission before undergoing HSCT (i.e., they had active disease). At the time of HSCT, 43 patients (37.7%) were in CR1, 42 (36.8%) were in CR2, and 29 (25.4%) had advanced disease or relapse (23 had active disease and six were in CR3+).
Myeloablative conditioning was used in 104 patients (91%) and a reduced-intensity regimen in 10 (8.7%). Sixty patients (53%) received busulfan in combination with cyclophosphamide, five (4.4%) received busulfan in combination with fludarabine, and seven (6%) received busulfan in combination with melphalan. TBI combined with cyclophosphamide was used in 11 patients (10%) and TBI combined with fludarabine in 17 (15%). Fourteen patients (10%) received other conditioning regimens.

Supportive Care and Infection Prophylaxis

Antibiotic prophylaxis was used in 92% of the patients, with levofloxacin or ciprofloxacin being used for most of them (66.6% of 114 patients). Antifungal prophylaxis, mostly with fluconazole (in 86.8% of cases), was administrated to 111 patients. The main transplant characteristics are shown in Table 2.

Donors and Stem Cell Source

There were 49 MRDs, six haploidentical donors, and 59 matched-unrelated donors (MUDs), 22 of whom had 6/6 or 8/8 compatibility. The most frequent source of cells was bone marrow (69%), followed by the umbilical cord (19%) and peripheral blood (12%).

Engraftment

After undergoing HSCT, six patients (5.3%) were not evaluable for engraftment. One hundred and one patients (88.6%)
showed engraftment at a median of 19 days for neutrophil recovery (12–162 days) and at a median of 22 days (9–156 days) for platelet recovery. Primary rejection was observed in eight patients (7%), four of whom (50%) received a second HSCT.

### GVHD

GVHD prophylaxis included a calcineurin inhibitor (cyclosporine or tacrolimus) in 90% of the patients; this was combined with methotrexate in 50% of these cases.

Of 101 evaluable patients, 49 had aGVHD. The median time to occurrence of aGVHD was 27 days (range 10–99 days), and the main site was skin (in 29 patients [59.2%]). The incidence of grade I or II aGVHD was 43% (95% CI 33%–52%), being significantly higher \( (P = 0.038) \) in patients who received transplants from unrelated donors (52%; 95% CI 38%–63%) than in patients who received transplants from related donors (31%; 95% CI 17%–43%). For grade III or IV aGVHD, the incidence was 18% (95% CI 10%–24%), and there was no significant difference \( (P = 0.083) \) between recipients of transplants from unrelated donors (23%; 95% CI 12%–33%) and recipients of transplants from related donors (10%; 95% CI 13%–18%).

The incidence of cGVHD was 23% (95% CI 15%–30%), with severe disease being observed in six patients. The median time to onset of cGVHD was 195 days (range 52–406 days). There was no significant difference between recipients of transplants from related donors (31%; 95% CI 17%–43%) and recipients of transplants from unrelated donors (17%; 95% CI 7.2%–26%; \( P = 0.076 \)).

### Fungal and Viral Infection

Fungal infection was observed in 19 patients (17%), with 11 of these cases (58%) being caused by candida spp. Viral infections occurred in 67 of the patients (59%), with 36 of these infections (54%) being caused by cytomegalovirus (CMV). In addition to CMV, the other viral infections reported were Epstein–Barr virus, adenovirus, herpes simplex virus 1 and 2, herpes virus type 6, varicella-zoster virus, polyomavirus, parainfluenza, influenza A, H1N1 influenza, metapneumovirus, and respiratory syncytial virus (Table 3).

### Relapse

Forty-nine patients (48.5%) experienced a relapse. The median time from HSCT to relapse was 122 days (range 17–2424 days). After relapse, 12 patients received a second HSCT, and four received donor lymphocyte infusions (DLI). Of the patients who experienced relapse, only six (12.2%) survived (at a median follow-up of 6 years).

### Survival

The median follow-up time for surviving patients was 4.4 years. Sixty-five patients died, at a median of 159 days after HSCT (range 10–2660 days). The major causes of death were related to relapse \( (n = 40) \), infection \( (n = 19) \), and GVHD \( (n = 6) \).

The 1-year NRM was 19% overall, 10% for recipients of transplants from related donors, and 25% for recipients of transplants from unrelated donors \( (P = 0.097) \).

The 4-year OS was 47% (95% CI 30%–57%), and the 4-year PFS was 40% (95% CI 30%–49%) (Fig. 1). There was no significant difference in survival between recipients of transplants from related donors and recipients of transplants from unrelated donors.

In univariable analysis, 4-year OS was significantly associated with the disease status before transplant \( (P = 0.001) \), fungal infection \( (P = 0.012) \), and FAB subtype \( (P = 0.017) \) of which M7 AML had the lowest survival. The following variables were assessed in the model: age, disease status before transplant, stem cell source, donor type (matched related or alternative), and conditioning regimen (myeloablative or reduced intensity). In the multivariable analysis, only disease status before the transplant was independently associated with 4-year OS and PFS (Tables 4 and 5). There was a significant association \( (P < 0.0001) \) between 4-year OS and pretransplant disease status of CR3+ (HR 5.63; 95% CI 2.02–15.67) and between 4-year OS and active disease (HR 3.69; 95% CI 1.83–7.43). A similarly significant association \( (P < 0.0001) \) was observed for 4-year PFS, with worse outcomes being recorded for patients in CR3+ (HR 6.71;
Discussion

In this study, we sought to evaluate the impact of HSCT on the outcomes of children with AML in Brazil. We analyzed data on 114 children with AML who underwent HSCT consecutively at 10 Brazilian institutions. Primary rejection (failure to achieve an absolute neutrophil count of ≥0.5 × 10⁹/L for three consecutive days or donor chimerism of <5%) was observed in eight patients (7%). Acknowledging that some patient also received RIC in this study, 7% is still quite high compared with the current literature (retrospective studies have estimated the overall incidence of graft failure around 5.5%)²⁴–²⁶. The 4-year OS of children with AML who received transplants between 2008 and 2012 was slightly more than 40%. Patients in CR1 or CR2 had significantly higher survival than those in CR3+ or those with persistent disease at the time of HSCT.

In our study, the outcomes of HSCT in children with AML appeared 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 conditioning²⁷. Data from the British MRC10 and MRC12 trials showed a 5-year OS of 68% in children who received transplants of marrow from matched sibling donors²⁸. The Nordic Society of Paediatric Haematology and Oncology (NOPHO) reported a 3-year EFS of 61% in children who underwent the transplant in CR1.⁵ Locatelli et al. analyzed the outcome 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
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.

Improving the outcomes of HSCT for children with AML in Brazil and other countries with limited resources requires overcoming several barriers. The first of these is the lack of HSCT units and dedicated beds to meet the increasing demand for cellular therapies, including HSCT. The CIBMTR has shown that the number of transplants performed worldwide has increased substantially during the past two decades. However, most of these transplants have been performed in North America, Western Europe, Japan, or Australia. Far fewer transplants have been performed in lower-income countries in South America, Africa, the Middle East, and East Asia. The ratio of inhabitants to transplants performed in Brazil is unbalanced, and many patients do not have access to HSCT even when donors are available. Data from the Brazilian Transplant Registry indicate that uninsured patients may have to wait for an organ transplant for more than a year after donor identification. Because most of the Brazilian HSCT centers are located in the Southern or Southeast regions, expenses associated with travel and housing can be prohibitive for many families. The ability of families to care for children after transplant might also be undermined by sociocultural factors such as poor living conditions and a lack of understanding of the complexity of the medical care required.

NRM due to infectious complications and GVHD were higher in our study than in most recently published international series. In our study, the rate of death not associated with AML was 19%. Zaucha-Prazmo et al. reported an NRM
rate of 11% in 82 children with AML in Poland. In a study by Svenberg et al. of 201 children who underwent HSCT consecutively at the Karolinska University Hospital, Sweden, between January 2003 and December 2013, the NRM rates were 12% and 14% at 1 and 5 years, respectively. In a study by Nemecek et al. of 58 children with AML who underwent HSCT between January 1990 and December 1999, children in CR2 (n = 12), those in untreated first relapse (n = 11), and those with refractory disease (n = 35) had estimated NRMs of 0%, 27% (range 0%–54%), and 17% (range 5%–30%), respectively.

Factors related to the evaluation and treatment of patients with AML before referral to transplant centers might also influence the outcomes after transplant. Centers that manage pediatric AML usually lack access to comprehensive relapse-risk assessment before or after induction remission, and not all cases of AML undergo genetic characterization before treatment is initiated. This precludes accurate stratification of children who might be considered for HSCT soon after remission is attained. Post-remission chemotherapy for such patients would increase the morbidity because of the infectious, cardiac, and renal complications associated with the treatment, in addition to delaying HSCT. A lack of effective methods to measure residual disease after remission induction chemotherapy at many institutions also contributes to inadequate patient selection for HSCT and referral. Even though multiparametric flow cytometry laboratories are available at most Brazilian leukemia treatment centers, multiparametric flow cytometry processes must be standardized for MRD investigations in order to provide reliable and reproducible results that ensure quality in the clinical application of the method.

Finally, since the 1980s, several interventions have been implemented to reduce NRM and improve outcomes after HSCT. More effective approaches to preventing GVHD, fungal infection, and CMV disease and to HLA typing and matching have been introduced. Pharmacokinetics-based targeting of busulfan dosing has been adopted. For patients receiving transplants, enhancements have been made in the last decades. At the same time, relevant advances have occurred in related fields, including critical care medicine, nephrology, and transfusion medicine. Prophylaxis for bacterial, fungal, and viral infections was not uniformly performed for the patients in our study. It is possible that the mortality associated with infection would be decreased by applying uniform guidelines for infection prophylaxis.

A critical point to be evaluated in the Brazilian healthcare context, in which beds for HSCT are still insufficient, is whether HSCT should be offered to children with AML who are expected to have a dismal prognosis after HSCT. In our study, patients with persistent disease after relapse had extremely poor outcomes. Similarly, only one of 10 patients with megakaryoblastic leukemia survived after undergoing the transplant. Finally, patients with secondary AML also had very poor prognoses.

The outcomes of HSCT can be improved by establishing communication between transplant centers and pediatric oncology units that are the point of the first contact with children newly diagnosed with AML, identifying the children with AML who would require HSCT early in the treatment course, and implementing uniform guidelines for infection prophylaxis before and during HSCT. It is also critical to involve community support groups to facilitate transport and to provide food, housing, and psychosocial and educational support for patients and families.

Our study has several limitations because of the differences in practices among transplantation centers, including differences in patient selection for HSCT, the choice of stem cells, conditioning regimens, prophylaxis for GVHD and infection, and general supportive care measures. Once resources in this setting are a significant variable, time from eligibility to transplant could be of particular importance. Unfortunately, as this study is a retrospective work from a database, this information was not available. Also, during the study period, according to the Brazilian National Transplant System, a public organization, 312 individuals younger than 21 years with AML underwent HSCT, but 114 (36.5%) were included in this study. Because, pediatric transplant services have different eligibility criteria for age, many patients with AML were transplanted in adult HSCT units during the study period, and we did not have access to data on patients treated on adult HSCT services.

**Conclusion**

In conclusion, the results of our study, with patients transplanted from 2008 to 2012, suggest that the outcomes of HSCT for children with AML in first and second complete remission are acceptable, and this should be considered in the overall treatment planning for children with AML in Brazil.

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**Author Contributions**

Conceptualization: ALMR, CB, AS, RCR, BCF; formal analysis: ALMR, CB, AS, LA, GLP, RCR, BCF; funding acquisition: BCF; investigation: ALMR, CB, AS, VARC, VGZ, SN, LED, JFF, AKV, LGDJ, AAG, LA, RCR, BCF; methodology: ALMR, CB, AS, LA, RCR, BCF; resources: BCF; supervision: CB, AS, RCR, BCF; writing—original draft: ALMR, CB, AS, LL, RCR, BCF; writing—review and editing: ALMR, CB, AS, LL, RCR, BCF.

**Ethical Approval**

This study was approved by the Ethics Committee of the coordinating institution of Hospital Pequeno Príncipe, Curitiba (code CAAE:
Statement of Human and animal Rights
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Statement of Informed Consent
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Declarations of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References
1. Estey E, Dohner H. Acute myeloid leukaemia. Lancet. 2006; 368(9550):1894–1907.
2. Lagunas-Rangel FA, Chávez-Valencia V, Gómez-Guijosa MA, Cortes-Penagos C. Acute myeloid leukemia-genetic alterations and their clinical prognosis. Int J Hematol Oncol Stem Cell Res. 2017;11(4):328–339.
3. Sadeghian MH, Rezaei Dezaki Z. Prognostic value of EVI1 expression in pediatric acute myeloid leukemia: a systematic review. Iran J Pathol. 2018;13(3):294–300.
4. Rubnitz JE. Current management of childhood acute myeloid leukemia. Paediatr Drugs. 2017;19(1):1–10.
5. Burke MJ, Wagner JE, Cao Q, Ustun C, Verneris MR. Allogeneic hematopoietic cell transplantation in first remission abrogates poor outcomes associated with high-risk pediatric acute myeloid leukemia. Biol Blood Marrow Transplant. 2013;19(7):1021–1025.
6. Rubnitz JE. How I treat pediatric acute myeloid leukemia. Blood. 2012;119(25):5980–5988.
7. Gibson BE, Webb DK, Howman AJ, De Graaf SS, Harrison CJ, Wheatley K. Results of a randomized trial in children with acute myeloid leukaemia: medical research council AML12 trial. Br J Haematol. 2011;155(3):366–376.
8. Abrahamsson J, Forestier E, Heldrup J, Jahnukainen K, Jonsson OG, Lausen B, Palje J, Zeller B, Hasle H. Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate. J Clin Oncol. 2011;29(3):310–315.
9. Rasche M, Zimmermann M, Borschel L, Bourquin JP, Dworzak M, Klingebiel T, Leinhbecher T, Creutzig U, Klussmann JH, Reinhardt D. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia. 2018;32(10):2167–2177.
10. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D, Gennero A, Kroger N, Lanza F. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. Bone Marrow Transplant. 2015;50(8):1037–1056.
11. Niewerth D, Creutzig U, Biering MB, Kaspers GJ. A review on allogeneic stem cell transplantation for newly diagnosed pediatric acute myeloid leukemia. Blood. 2010;116(13):2205–2214.
12. Meshinchi S. Hematopoietic cell transplantation in high-risk childhood acute myelogenous leukemia. Biol Blood Marrow Transplant. 2013;19(7):1002–1003.
13. Eid KAB, Miranda ECM, Vigorito AC, Aranha FJP, Oliveira GB, De Souza CA. The availability of full match sibling donors and feasibility of allogeneic bone marrow transplantation in Brazil. Braz J Med Biol Res. 2003;36(3):315–321.
14. Mendonça N. Leucemia mielóide aguda na criança: como andamos no Brasil? J Pediatr (Rio J). 2003;79(6):476–477.
15. Andrade FG, Noronha EP, Brisson GD, Dos Santos Vicente Bueno F, Cezar IS, Terra-Granado E, Thuler LCS, Lombo-de-Oliveira MS; Brazilian Study Group of Childhood Acute Myeloid Leukemia as c-a. Molecular characterization of pediatric acute myeloid leukemia: results of a multicentric study in Brazil. Arch Med Res. 2016;47(8):656–667.
16. Jaime-Perez JC, Padilla-Medina JR, Fernandez LT, Herrera-Garza JL, Gutierrez-Aguirre CH, Tarin-Arzaga L, Gomez-Almaguer D. Outcomes of adolescents and young adults with acute myeloid leukemia treated in a Single Latin American Center. Clin Lymphoma Myeloma Leuk. 2018; 18(4):286–292.
17. Felice MS, Rossi JG, Alonso CN, Gallego MS, Eberle SE, Alfaro EM, Guitter MR, Bernasconi AR, Rubio PL, Cocce MC, Zubizarreta PA. Experience with four consecutive BFM-based protocols for treatment of childhood non-promyelocytic acute myeloblastic leukemia in Argentina. Leuk Lymphoma. 2016;57(9):2090–2099.
18. Lins MM, Mello MIG, Ribeiro RC, De Camargo B, de Fatima Pessoa Militao de Albuquerque M, Thuler LCS. Survival and risk factors for mortality in pediatric patients with acute myeloid leukemia in a single reference center in low-middle-income country. Ann Hematol. 2019;98(6):1037–1056.
19. Pereira WV. Leucemia Mielocítica Aguda da infância e adolescência: fracassos e vitórias. Revista Brasileira de Hematologia e Hemoterapia. 2006;28(4):239–241.
20. Datoguia TS, Velloso E, Helman R, Musacchio JG, Salvino MA, Soares RA, Higashi M, Fadel AV, Silva RSAE, Hamerschlak N, de Souza Santos FP, et al. Overall survival of Brazilian acute myeloid leukemia patients according to the...
21. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18(4):295–304.

22. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21(3):389–401.e381.

23. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, Apperley J, Slavin S, Pasquini M, Sandmaier BM, Barrett J, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15(12):1628–1633.

24. Masouridi-Levrat S, Simonetta F, Chalandon Y. Immunological basis of bone marrow failure after allogeneic hematopoietic stem cell transplantation. Front Immunol. 2016;7:362.

25. Olsson R, Remberter M, Schaffer M, Berggren DM, Svahn BM, Mattsson J, Ringden O. Graft failure in the modern era of allogeneic hematopoietic SCT. Bone Marrow Transplant. 2013;48(4):537–543.

26. Alcazer V, Conrad A, Valour F, Bachy E, Salles G, Huynh A, de Latour RP, Labussiere-Wallet H, Ader F. Early-onset severe infections in allogeneic hematopoietic stem cell transplantation recipients with graft failure. Am J Hematol. 2019;94(4):E109–E111.

27. Bitan M, He W, Zhang MJ, Abdel-Azim H, Ayas MF, Bieilorai B, Carpenter PA, Cairo MS, Diaz MA, Horan JT, Jodele S, et al. Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. Blood. 2014;123(10):1615–1620.

28. Gibson BE, Wheatley K, Hann IM, Stevens RF, Webb D, Hills RK, De Graaff SS, Harrison CJ. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia. 2005;19(12):2130–2138.

29. Sauer MG, Lang PJ, Albert MH, Bader P, Creutzig U, Eyrich M, Greil J, Gruhn B, Holter W, Klingebiel T, Kremens B, et al. Hematopoietic stem cell transplantation for children with acute myeloid leukemia-results of the AML SCT-BFM 2007 trial. Leukemia. 2019;34(2):613–624.

30. Jaimovich G, Martinez Rolon J, Baldomero H, Rivas M, Hanesman I, Bouzas L, Bonfim C, Palma J, Kardus-Urueta A, Ubidia D, Bujan-Boza W, et al. Latin America: the next region for haematopoietic transplant progress. Bone Marrow Transplant. 2017;52(5):671–677.

31. Sabaio J, Hallak Neto J. Salário mínimo e distribuição de renda no Brasil a partir dos anos 2000*. Econ Soc. 2018;27(1):265–285.

32. Zaucha-Prazmo A, Gozdzik J, Debski R, Drabko K, Sadurska E, Kowalczyzk JR. Transplant-related mortality and survival in children with malignancies treated with allogeneic hematopoietic stem cell transplantation. A multicenter analysis. Pediatr Transplant. 2018;22(3):e13158.

33. Ikoma MR, Beltrame MP, Ferreira SI, Souto EX, Malvezzi M, Yamamoto M. Proposal for the standardization of flow cytometry protocols to detect minimal residual disease in acute lymphoblastic leukemia. Rev Bras Hematol Hemoter. 2015;37(6):406–413.

34. Short NJ, Ravandi F. How close are we to incorporating measurable residual disease into clinical practice for acute myeloid leukemia? Haematologica. 2019;104(8):1532–1541.

35. Ikoma MR, Beltrame MP, Ferreira SI, Souto EX, Malvezzi M, Yamamoto M. Proposal for the standardization of flow cytometry protocols to detect minimal residual disease in acute lymphoblastic leukemia. Rev Bras Hematol Hemoter. 2015;37(6):406–413.

36. Horan JT, Logan BR, Agovi-Johnson MA, Lazarus HM, Bacigalupo AA, Ballen KK, Brederon CN, Carabasi MH, Gupta V, Hale GA, Khoury HJ, et al. Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? J Clin Oncol 2011;29(7):805–813.