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ACUTE MYELOID LEUKEMIA IN CHILDREN AND ADOLESCENTS IN BRAZILIAN INSTITUTIONS: REALITY AND CHALLENGES

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ABSTRACT

Objective: To describe the outcome of acute myeloid leukemia (AML) among children treated in Brazilian institutions. Methods: A structured online questionnaire was sent to pediatric oncologists affiliated to the Brazilian Society of Pediatric Oncology. The physicians and institutions were unidentified. Results: One hundred and four pediatric oncologists in all Brazilian regions answered the questionnaire. The treatment-related mortality rate was reported to be higher than 30% by 29.8% of the participants. Difficulty in accessing the intensive care unit (ICU) was reported by 54.8%. About 85% had access to cytogenetics, 78% to molecular testing, 94% to the measurement of residual disease by flow cytometry. About 90% of participants reported access to HSCT, but 86% of them had difficulties in providing HSCT timely. About 95% of the participants indicated the need to create a national treatment protocol, and 89.4% are willing to collaborate with a national study group. Conclusion: Our study demonstrated large gaps in the treatment of pediatric AML. To improve outcome, a national protocol will have to consider the regional differences and adapt the management according to the local resources.

Keywords: Pediatric AML. HSCT. Brazil

INTRODUCTION

Myeloid neoplasms represent a heterogeneous group of hematological disorders that originate from the myeloid, monocytic, erythroid and megakaryocytic precursors. Among them, acute myeloid leukemia (AML) is the most frequent in pediatric and adolescent age group, representing between 15-20% of all acute leukemias 1. When treated with conventional chemotherapy regimens, about 80-90% of these patients attain complete remission (CR). The 5-year event-free survival (DFS) and overall survival (OS) rates approach 60% and 70%, respectively, in high-income countries [2, 3].

Eradication of the leukemia cells and restoration of the bone marrow function are the main treatment goals in AML. The use of intensive chemothera-

py regimens to obtain rapid myelosupression is standard practice. The combination of cytarabine, daunorubicin and etoposide form the basis of most remission induction treatment protocols [4, 6]. With two courses of intensive chemotherapy, the complete remission (CR) rates are above 90%. Refractory or resistant disease rates are approximately 5% [2, 7]. Other strategies aimed to optimize the treatment include reducing the interval between the initial cycles of chemotherapy ("intensive timing") 8 and replacing daunorubicin with idarubicin 4 or mitoxantrone 6. Several international study groups (BFM, CCG, NOPHO, LAME, MRC) have observed that the intensification of induction along with optimal supportive care increases the CR but not the EFS rates [5, 9].

Post-remission strategies also did not improve EFS, because of failure to significantly reduce the relapse. The improvement of OS rates observed over the past 25 years is due to improvements in salvage therapies, including hematopoietic stem cell transplantation (HSCT). The better outcome of pediatric AML after 1999 coincided with the broader utilization of HSCT. Without HSCT, the EFS and likely OS will not surpass 50%, irrespective of the frontline chemotherapy employed [10].

The intensity of the treatment utilized to attain and maintain remission, including HSCT in first or subsequent remission have raised concerns about acute and long-term side effects. It is estimated that over 30-40% of children with AML die from refractory disease/relapse or treatment-related toxicity 11. Recent studies have shown that the use of low-intensity induction schemes can result in long-term remissions with less treatment-related toxicity, but with relapses associated with the selection of treatment-resistant clones [12, 13].

Central nervous system (CNS) therapy is a critical component in many therapeutic protocols because CNS relapse is relatively common in pediatric AML 14. Intrathecal chemotherapy without cranial radiotherapy has been used 5-7. Systemic minimal-myelossuppressive maintenance therapy was routinely used in several protocols but because of the lack of benefits, most modern treatment protocols do not prescribe maintenance regimens [7, 11].

High rates of toxicity and death have been observed in the induction of AML in Brazil with the use of conventional international protocols. Strategies to reduce the intensity of the regimens used in induction to decrease early treatment-related mortality might be an option for countries with limited resources. A study group, within the Brazilian Society of Pediatric Oncology (SOBOPE), denominated Childhood Acute Myeloid Leukemia Study Group (GELMAI), aims to start a dialog among pediatric oncologists of Brazilian institutions treating children and adolescents with AML and elaborate a uniform treatment protocol adapted to the local resources. The strategy is to administer a minimally myelosuppressive regimen for the first induction remission and risk-adapted therapy for the subsequent courses. The main goal is to avoid early treatment-related mortality. To initiate this effort, we developed a questionnaire directed to pediatric oncologists treating children and adolescents in institutions in different Brazilian regions. In this study, we report an analysis of surveyed data provided by treating physicians on pediatric AML in Brazil.

METHODS

Study design

This is a transversal quantitative and descriptive study conducted in Brazil between 1st and 30th of May 2020 with pediatric oncologists associated with SOBOPE (Brazilian Society of Pediatric Oncology), based on the individual perception of the participants, without identifying the respective institutions. A multiple-choice online questionnaire developed by the GELMAI group containing 21 questions was sent by the google forms application to all pediatric oncologists registered with SOBOPE.

Variables included

The variables analysed included information regarding the number of medical doctors and multidisciplinary staff in each team, the number of available beds, the accessibility to exams, the treatment availability including chemotherapy, antibiotics, antifungals, transplantation of hematopoietic stem cells (HSCT), the access to intensive care and other items related to therapy and patient support. Using a dichotomous question, the interest of the medical doctors in participating in the protocol and national study group was consulted.

Statistical analysis

All answers were tabulated in excel format. Descriptive statistical analyzes were used to calculate the absolute and relative values of each variable and graphic analyzes were included. All analysis were performed using Microsoft Excel 2016.

Ethical approval

This study was previously approved by the Ethics Committee (code CAAE: 53705016.7.1001.0097) and the ethical principles were in accordance with Declaration of Helsinki on human subject research.

RESULTS

The Brazilian Society of Pediatric Oncology (SOBOPE) have 272 registered medical doctors who received the questionnaire. From this cohort, 104 (38.2%) agreed to participate in this research. All regions of Brazil were represented, and the majority of participants (37.5%) were from the southeast region (figure 1).

When questioned about AML pediatric treatment in Brazil, 97 (93.3%) believe that there is a need for a Brazilian treatment protocol for pediatric AML, and 93 (89.4%) expressed interest in participating in the construction/elaboration of new protocols with SOBOPE. The quantification of all answers related to opinions regarding the institution is described in table 1. Institutions conditions are concerned especially related to the absence of HEPA filter in 46 (44.2) cases and the impairment of care by the lack of a multi-professional team in 15 (14.4%) and lack of nursing staff in 18 (17.3%) of participating institutions.

Table 2 describes the quantification of answers about treatment access and quality in pediatric AML care. Service quality is concerned in some of the aspects of patient treatment and care, especially regarding lack of access to blood transfusion for 14 (13.5%) of the participants, delay or absence of blood products during critical periods like holidays in 35 (33.6%) of the cases, rare access to prophylactic antifungals in 15 (14.4%) of the cases and absence of HSCT for 7 (6.7%) of the participating institutions.

Figure 2 represents the exams access for AML diagnosis and disease control and management during treatment regardless of whether they are performed in the service or not (considering access of exams and results in a timely manner as not to compromise patient's treatment). Despite being a developing country, almost half of the participants (47.1%) have access to the necessary exams for appropriated disease management.

Figure 3 depicts the drugs available in the surveyed institutions. Among prophylactic antifungals, the most frequent used was micafungin. The chemotherapic agents most frequently used was idarubicin and between other classes such as cardioprotector was the cardioxane.

Regarding the estimatives of number of AML pediatric patients per year, mortality rate and the treatment expectations (Table 3), it's possible to observe that most participants manifested interest in participating in a cooperative protocol. Furthermore, the estimated number of patients was less than five in 42 (40.4%) of participating institutions and between 6-10 n 39 (37.5%). Finally, the estimated mortality rate due to treatment complications was between 11-30% in 43 (41.3%) of the participating institutions.

DISCUSSION

Brazil is a developing country with about 209 million inhabitants; 56,4% of them residing in the southeast and south, the richest regions of the country. The median family income in Brazil is only up to US$ 330 per month, depending on the region of the country 15. Only 30% of the population have private medical insurance 16 while the remaining individuals depend on governmental resources and structure, and cannot pay for medical care. There is substantial inequality in Brazil and due to informal economic networks, it is hard to generalize information and generates precise outcome data in each area.

Low-income countries such as Brazil will present limitations regarding treatment options and laboratory tests for diagnosis and disease follow-up. For instance, Brazil's public health system (SUS, created in 1988), which attends the majority of Brazilian patients, has a considerable difficulty in sponsoring genetic AML characterization of the diagnosis. Due to the high costs, access to diagnostic tests is limited to conventional karyotype. A few centers have access to a basic panel of molecular tests [17, 18].

The high treatment intensity can partially explain the low rates of long-term survival among pediatric AML in Brazil patients. A study group with participants of different regions utilizing a uniform treatment protocol with predetermined adaptations for each institution has the potential to improve the overall outcome. Understanding the real situation of the treatment of pediatric AML in Brazil will make possible to unify treatment approaches creating chemotherapy and supportive care guidelines, and a forum for ongoing discussion would allow for improved outcome. Mortality rates during induction remission remain high in developing countries but can be reduced by improved supportive care and adapted initial chemotherapy. It is expected that by discussing the case in group and adapting uniform treatment in real time, the early mortality will decrease. A Brazilian study, that involved 1472 children and adolescents, treated for acute lymphoid leukemia, showed an increase in survival among those treated on protocols when compared with those not enrolled on protocols [19].

Another important point is linked to treatment-related cardiotoxicity, which significantly influences over-

all survival and event-free survival, as demonstrated by the Children's Oncology Group in AAML0531 trial 20. Events may be acute during treatment, or late. Cardioprotection measures to mitigate and prevent this expected and unwanted adverse effect, in a socially and economically diverse country such as Brazil, requires a broad strategy that includes a detailed initial assessment of cardiac function, combined with cardioprotective use and continuous cardiac monitoring during and after treatment, in a rational and cost-effective manner [21].

The benefit of allogeneic HSCT as post-remission consolidation treatment in pediatric AML is well-documented in specific risk groups [22]. Pediatric AML in first CR and favorable karyotype may not be benefited from allogeneic HSCT. The indications of allogeneic HSCT in first remission must take into consideration the benefit and toxicity for those patients with an indeterminate prognosis; the objective is to decrease the rate of toxic death by avoiding HSCT in this group because the morbidity and mortality related to the procedure. In cases of definitive poor prognosis, the intention is to perform the HSCT in first remission. Because of the lack of laboratory support and other limitations related to the availability of transplantation in our country, we may not have opportunity to increase the number of HSCT in CR1 as recommended. In the meantime, patients who relapse should be considered for HSCT [23].

Improvements in genetic molecular classification, efforts aiming to improve salvage therapy and increasing access to HSCT will provide a better outcome for all these patients.

CONCLUSION

Our study reveals the challenges of managing pediatric AML in a country with limited resources and wide regional economic and cultural disparity. The understanding of the needs of each of the regions can be addressed by the implementation of uniform guidelines adapted to the current resources of each of the regions. A study group networking collaboratively with pediatric oncologists and hematologists from the diverse regions may bring changes that improve to outcome of Brazilian children with AML.

DECLARATION 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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TABLE 1 – Quantification of pediatric oncologists opinions regarding institution infrastructure for pediatric AML care

Regarding the number of medical professionals directly involved in leukemia treatments, in your service you consider that:	**N (%)**
The team is adequate for the number of patients	64 (61.5)
The number is reduced, impairing the quality of care (care for children, considering the number of visits)	6 (5.8)
The number is reduced, generating overwork, but without compromising the quality of care	34 (32.7)
Regarding the number of beds for patient care in your ward:	**N (%)**
Care is compromised due to lack of beds in some periods	14 (13.5)
The number of beds is adequate for the demand	49 (38.5)
The number of beds is generally adequate for the demand with periods of higher occupation, without seriously compromising the assistance	41 (39.4)
The AML patient	**N (%)**
Shared bed with HEPA filter	7 (6.7)
Shared bed without HEPA filter	39 (37.5)
It is in an isolated bed with HEPA filter	12 (11.5)
It is in an isolated bed without HEPA filter	46 (44.2)
Regarding access to the ICU	**N (%)**
Eventually there is some difficulty of vacancies, but patients are able to be served more than 90% of the time without clinical damage	46 (44.2)
There is difficulty in access with clinical impairment in up to 25% of the time	7 (6.7)
There is difficulty in access with clinical impairment in more than 50% of the times	2 (1.9)
There is difficulty in access with clinical impairment between 25% and 50% of the time	2 (1.9)
Whenever necessary, we have a place in the ICU	47 (45.2)
Regarding the nursing team	**N (%)**
The nursing team is adequate at the Hospital	40 (38.5)
Eventually there is a lack of professionals, but without serious damage to assistance	44 (42.3)
The nursing staff is deficient in relation to the number of patients frequently, impairing care	18 (17.3)
I prefer not to comment	2 (1.9)
Multiprofessional Team (except nursing)	**N (%)**
The multidisciplinary team is adequate at the Hospital	44 (42.3)
The team at the Hospital is not complete, but the support institution helps us, maintaining adequate care	24 (23.1)
Eventually there is a lack of professionals, but without serious damage to assistance	21 (20.2)
Professionals are often lacking, impairing care	15 (14.4)
Support house (suitable or not)	**N (%)**
The house sometimes lacks beds	19 (18.3)
The house often lacks beds	5 (4.8)
The house has beds available with ease	66 (63.5)
We don't have or have a lot of difficulty with support house beds	9 (8.6)
I prefer not to comment	5 (4.8)

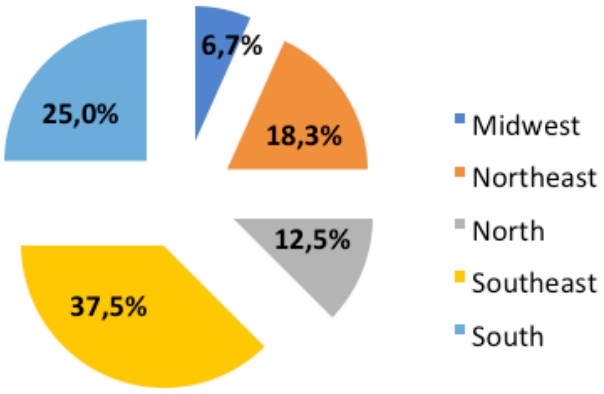
TABLE 2 - Quantification of answers about treatment access and quality in pediatric AML care in Brazil

Regarding venous access, you consider that in your service	**N (%)**
Most or almost all patients who need catheter access are able to place it in a timely manner	73 (70.2)
Some patients are able to place the catheter at the correct time, but others cannot	26 (25.0)
My patients have difficulty placing a catheter	5 (4.8)
Regarding the procedures (collection of CSF / Intrathecal / Myelogram)	**N (%)**
Most procedures are performed at the time and under the conditions that I consider appropriate	34 (32.7)
I can do them in the time and under the conditions I consider appropriate	70 (67.3)
Regarding blood transfusion	**N (%)**
I do not have access to irradiated and leukocyte-depleted blood components if necessary	14 (13.5)
I prefer not to comment	1 (1.0)
I have access to irradiated and leukocyte-depleted blood components if necessary	61 (58.6)
I have partial access to irradiated and leukocyte-depleted blood components if necessary	28 (26.9)
Your blood bank or transfusion agency	**N (%)**
Meets needs almost always with rare delays or missing components	64 (61.5)
Delays frequently or we lack blood components frequently up to 50% of the time	5 (4.8)
Has occasional delays or absences, particularly during critical periods such as extended holidays	35 (33.6)
Do you think you have access to the prophylactic antifungals that you would like to use to treat AML	**N (%)**
Eventually, but the administration or Infection Control Service makes it difficult to use	8 (7.7)
I prefer not to comment	5 (4.8)
Rarely	15 (14.4)
Yes	45 (43.3)
Yes, but the Infection Control service or administration makes it difficult to use	31 (29.8)
Regarding Bone Marrow Transplantation	**N (%)**
More than 50% of patients are affected by delays	4 (3.8)
We don't have access	7 (6.7)
I prefer not to comment	4 (3.8)
We have access at the Hospital or partner hospital and the same is done with delays affecting between 25% and 50% of patients in the queue	11 (10.6)
We have access at the Hospital or partner hospital and the same is done with delays affecting at least 25% of patients in the queue	24 (23.1)
We have access at the Hospital or partner hospital and the same is done with small delays	40 (38.5)
We have access at the Hospital or partner hospital and the same is done without delays	14 (13.5)

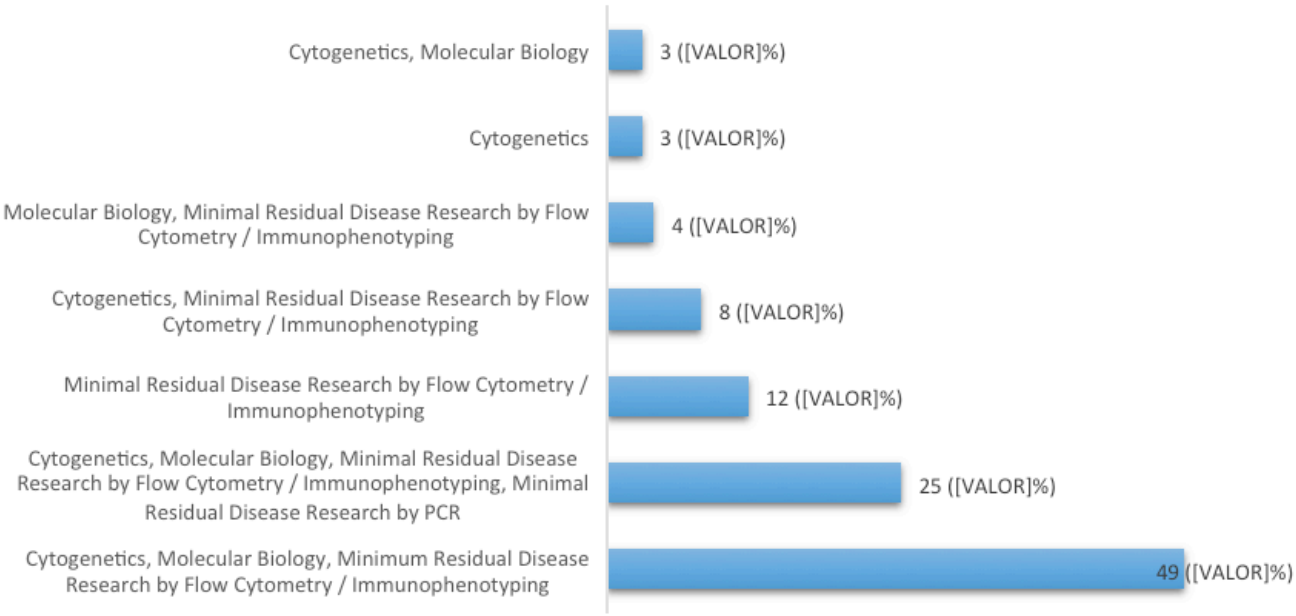
TABLE 3 – Estimatives and expectations of pediatric AML treatment protocol and outcomes for medical doctors of Brazilian institutions.

Regarding to the treatment of pediatric AML (except M3 and Down syndrome), you:	**N (%)**
Would you be willing to participate in a cooperative protocol	73 (70.2)
Will continue the local protocol or already participate in another group	1 (1.0)
Participate depending on the type of protocol proposed	29 (27.9)
Prefer to have only a treatment guide made	1 (1.0)
What number of pediatric AML patients does the service serve per year?	**N (%)**
16-20	7 (6.7)
More than 26	1 (1.0)
Less than 5	42 (40.4)
I don't know	3 (2.9)
11-15	12 (11.5)
6-10	39 (37.5)
In your experience, what has been the mortality rate due to treatment complications?	**N (%)**
11-20%	23 (22.1)
21-30%	20 (19.2)
31-40%	11 (10.6)
41-50%	11 (10.6)
5-10%	17 (16.3)
Above 51%	9 (8.6)
I don't know	13 (12.5)

GRAPHIC 1 – Institutions participating in the study according to the region of Brazil



GRAPHIC 2 – Number of Brazilian institutions that have access to the specialty tests regardless of whether they are performed locally.



GRAPHIC 3 - Treatment availability in the Brazilian surveyed institutions.