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ORIGINAL ARTICLE

Allogeneic bone marrow transplantation in children: initial experience of the Santa Casa de Misericórdia Hospital in Belo Horizonte

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Bone Marrow Transplantation,
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Abstract

Objective: To report the clinical experience of a tertiary care hospital with allogeneic hematopoietic stem cell transplantation in children. **Methods:** Data analysis of medical charts of the first 6 pediatric patients transplanted between April 2018 and December 2018. **Results:** 6 patients (4 boys and 2 girls) with leukemia (5 ALL e 1 CML) received allogeneic transplants. The median age was 8 years. Donor sources were bone marrow (4 cases) and peripheral-blood stem cells (2 cases). All patients survived the first 100 days after transplantation and had a median clinical follow-up of 168 days. One patient developed acute GVHD and all patients developed at least one infection. Catheter-related bloodstream infections occurred in 66% of patients. Fever and mucositis were observed in all kids. The average length of stay at the hospital after transplantation was 38 days, 83% of the patients were admitted again due to infection or relapse. **Conclusion:** The obtained results are similar to others reported and make possible to know better all the factors that can influence the transplant success and survival in children and adolescents. However, Brazilian studies are still scarce. More studies should be encouraged, in order to increase the survive rate of our children.

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INTRODUCTION

Bone marrow transplantation (BMT) is today a therapeutic option for a wide variety of malignant and non-malignant diseases in pediatric patients. The transplant consists of the intravenous infusion of hematopoietic stem cells with the aim of reestablishing spinal function in patients with damaged or defective bone marrow[1]. However, less than half of the patients with indication for transplant have a compatible related donor, making it necessary the search for alternative donors.[1] Despite donor number growth, the chances of finding a fully compatible donor for Brazilian patients is still not great, and transplants performed with unmatching persons are associated with higher rates of complications, especially graft versus host disease (GvHD) and rejection[2].

There are between 50,000 and 60,000 bone marrow transplants performed worldwide each year[3]. Of the 6,742 Brazilian hospitals that serviced the Public Healthcare System (SUS) in 2014-2016, only 39 (0.58% of the total) underwent bone marrow transplantation. Our hospital ranks 11th in this group.[4] Our first bone marrow transplant was performed in November 2012 on a 56-year-old patient with acute leukemia. The hospital continued to perform bone marrow transplants, but the service did not include the pediatric population. Since 2017, there was an expectation to start a pediatric bone marrow transplant unit, but it was only in April 2018 that the first transplant was performed on a child. After starting the service, in the first six months that followed, six transplants were performed, all in children with some type of leukemia.

Aiming to assist in understanding, improving and choosing the best treatment options for children undergoing a bone marrow transplant, this study aims to evaluate the first results of HSCT performed on children and adolescents after the opening of this service in a tertiary hospital in Minas Gerais .

OBJECTIVE

To report the initial clinical experience of a tertiary hospital with allogeneic bone marrow transplantation in children, providing for comparison with established services and further studies that show the progress in our service.

METHODS

The study was carried out inside a tertiary hospital servicing the SUS exclusively. Data from the medical records of the first six pediatric transplant patients were analyzed from the opening of the service in April 2018 to the end of the same year (December 31, 2018).

Service features

From 2014 to 2017 the hospital performed 662 transplants. In the first quarter of 2017 alone, 23 bone marrow transplants were performed (42% of the total performed in the entire year of 2016). The transplant unit now has 39 beds intended for hospitalization, and since 2016 the Transplant Center has had day hospital and outpatient care. The unit has full capacity to carry out an average of 350 monthly consultations and a day hospital service to service clinical complications - thus reducing the need for hospitalization. On April 27, 2018, the first bone marrow transplant was performed on a child in the service. By the end of the year, five more children had been transplanted.

Patient characteristics

All six patients, under the age of 19, who underwent HSCT from April 2018 (when the first transplant was performed) until the end of the same year (12/31/2018) were included in the study. All patients had leukemia as the underlying disease, with ages varying from three to twelve years, with a median of 8 years. Two patients were females and four patients were males. Table 1 describes the other patients' characteristics.

All transplants performed were allogeneic, with one patient undergoing a haploidentical related transplant and five were submitted to unrelated transplants. Two patients received peripheral stem cells (PSC) and four received bone marrow (BM).

Regarding the underlying disease, we transplanted five patients with acute lymphoblastic leukemia (ALL) and one with chronic myeloid leukemia (CML).

Conditioning Regimen and GvHD prophylaxis

The conditioning scheme was chosen considering mainly the underlying disease and donor type. The choice of

Table 1. Characteristics of the entire patient group.

	Total no.of patients	%
Patient age		
<10 years	4	66
≥10 years	2	33
Sex		
Females	2	33
Males	4	66
Baseline disease		
ALL	5	83
CML	1	16
Donor type		
Kin	1	16
No kin	5	83
Source of hematopoietic stem cells		
Bone marrow	4	66
Umbilical cord blood	0	0
Peripheral stem cells	2	33
TOTAL	**6**	**100**

Source: study data.

the prophylaxis regime for graft against the host disease also took into account the factors mentioned above, sometimes being influenced by the clinical conditions of each patient's progress.

The conditioning regimen used in all patients with ALL was cyclophosphamide (Cy), total body irradiation (TBI) and antithymocytic globulin (ATG), except in the patient who received BM from a related donor, who was conditioned with fludarabine associated with melfan (FluMel) and TBI. The conditioning regimen chosen for the patient with CML was Cy, busulfan (BU) and ATG table 2.

For GvHD prophylaxis, the choice for all patients receiving unrelated transplantation was cyclosporine (CSA) and methotrexate (MTX) and, for the patient receiving related transplantation, it was cyclophosphamide, cyclosporine and mycophenolate (MMF).

The neutrophilic take was defined as a neutrophil count above 500 for two consecutive days, the first day being considered the take day. Platelet take was defined by platelets above 20,000 after three days without transfusion. Patients who had partial or complete graft harvest were considered evaluatable for the occurrence of acute or chronic GvHD.

RESULTS

All patients included in the study are alive, with the mortality rate before D+100 (one of the parameters used to assess procedure toxicity) so far. The median follow-up after transplantation for the patients included in the study is 168 days (112 to 248 days).

As all patients survived more than 30 days after HSCT, all were assessed for graft take. None of the patients had primary take failure. The grafting time varied from 10 to 29 days for neutrophilic take (median of 11 days) and from 10 to 33 days for platelet take (median of 17.5 days). After merrow take, all children were evaluated for GvHD, with only one case identified, acute, in grade 2 skin, which responded to corticosteroids, in a patient who received peripheral stem cells.

The length of stay at the time of the transplant ranged from 27 days to 46 days, with an average length of stay of 38 days. Only one patient (16%) required admission to the intensive care unit at the time of the transplant. Table 3 depicts the main immediate clinical complications related to HSCT.

All the patients had fever. Febrile neutropenia was the main complication in the first hospitalization after BMT, occurring in five of the six transplant patients (83%). We used Cefepime and Vancomycin in all the patients with febrile neutropenia. Teicoplamine, polymyxin E, meropenem, amikacin and amphotericin B were the other drugs associated with the scheme according to the clinical evolution of each patient.

Of the patients who had an infection, four (66%) had catheter-related infection, three (50%) had acute sinus disease (all confirmed with CT of the sinuses), two (33%) pneumonia, one of them progressing to septic shock with acute respiratory failure, one (16%) had urinary tract infection and one (16%) fungal sepsis.

Of the four patients who presented catheter-related infection, cultures were positive in the catheter reflux, but in none of them the paired blood culture was also positive. Among the germs isolated in the reflux, Staphylococcus (hominis, epidermidis and lugdunenesis) stood out, isolated in reflux from three different patients (75% of patients with catheter-related infection). The other germs isolated were Pseudomonas sp, and Acinetobacter lwoffii. Only one catheter tip culture was positive with Candida parapsilosis.

The patient treated for urinary tract infection, had clinical and urine culture with more than 100,000 colonies of Pseudomonas aeruginosa.

Only one patient had positive blood culture without the presence of another evident infection, Fusarium sp and Candida guliermondii were isolated at a later date, and then treatment for fungal sepsis was started with liposomal amphotericin B. Only one patient had all negative cultures during hospitalization.

Mucositis was the complication related to BMT toxicity found in 100% of patients. Only one patient had grade 3 mucositis, and all others (83%) were classified as grades 1 or 2. Drug-related renal and hepatic toxicity for GvHD prophylaxis occurred simultaneously in only one patient, and resulted in non-dialythic acute kidney failure (AKI) with transient increase in transaminases. Toxicity was reversed after discontinuing cyclosporine and methotrexate, and it was then decided to start, for GvHD prophylaxis, after 1 mg/kg methylprednisolone.

All patients required transfusion of some blood component after transplantation. The number of platelet transfusions received ranged from one to ten, with an average of 4.1. A

Table 2. Conditioning of all the patients and of the subgroup of patients per disease and by donor type.

	Total no patients %	ALL %	CML %	Kin donor %	Non-kin donor %
Conditioning					
Cy+TBI+ATG	4 (66)	4 (80)	0 (0)	0 (0)	4 (80)
BU+Cy+ATG	1 (16)	0 (0)	1 (100)	0 (0)	1 (20)
FluMel + TBI	1 (16)	1 (20)	0 (0)	1 (100)	0 (0)
TOTAL	**6 (100)**	**5 (100)**	**1 (100)**	**1 (100)**	**5 (100)**

Fonte: Dados da pesquisa.

Table 3. Complications after HSCT of the entire group of patients and the subgroup per disease.

Complications	Total no. of patients (%)	ALL (%)	CML (%)
Acute HvGD	1 (16)	1 (20)	0 (0)
Febrile neutropenia	5 (83)	4 (80)	1 (100)
Mucositis	6 (100)	5 (100)	1 (100)
Grade I-II	5 (83)	4 (80)	1 (100)
Grade ≥III	1 (16)	1 (20)	0 (0)
Catheter-related infection			
Others			
Acute sinusitis	3 (50)	3 (60)	0 (0)
Seizures	1 (16)	1 (20)	0 (0)
SAH	2 (33)	2 (33)	0 (0)
Septic shock	1 (16)	1 (20)	0 (0)
UTI	1 (16)	0 (0)	1 (100

Source: study data.

single patient did not receive red blood cell concentrate, with the other five receiving it one to four times, with an average of two transfusions per patient.

After the first hospital discharge, considering an average follow-up of 180 days for all patients, five of the six patients (83%) had at least one new hospitalization. Abdominal pain with diarrhea and/or vomiting were the main causes identified, being the reason for hospitalization of three of the five patients (60%) readmitted. The other two causes of hospitalization were meningeal and pulmonary tuberculosis, in one patient, and disease recurrence in another patient, who was then admitted for chemotherapy table 4.

The time elapsed between the date of transplantation and the occurrence of a new hospitalization ranged from 19 to 192 days, with a median of 51 days. The duration of these hospitalizations ranged from 2 to 57 days, with an average of 21 days.

The patient with earlier readmission was also the patient readmitted more often. This was the only CML patient in the group, having faced four hospitalizations for complications after transplantation, against one hospitalization in all the other four patients who were hospitalized again. The longest readmission occurred with the hospitalized patient due to disease recurrence in the transplant, when chemotherapy was started.

Of the readmitted patients, two (40%) evolved with catheter infection, and Staphylococcus epidermidis was in the cultures from both patients.

Among the two inpatients with diarrhea, only 1 tested positive for clostridium in the stool examination. The patient in question was hospitalized three times with diarrhea with positive clostridium, progressing to pseudomembranous colitis in one of the admissions.

DISCUSSION

Results from studies around the world show that increasingly more children have survived bone marrow transplantation, most of them free from their disease[5]. However, publications on the results are still scarce.

Some studies in Brazil have proposed to present results with bone marrow transplantation in children. In 1996, Odone Filho, V. published the preliminary experience of the Instituto da Criança Pedro de Alcântara, from the University of São Paulo Medical School Hospital, with bone marrow transplantation in 20 cancer patients. After such study, the Sírio Libanês Hospital, the pediatric oncology service of the Hospital de Clínicas of Porto Alegre, the bone marrow transplant service of the University Hospital of the Federal University of Paraná and the Amaral Carvalho Hospital also published reports of their experiences, with patient samples ranging from seven to 208. More recently, Seber A. published a review of the current landscape concerning HSCT in children, based on a paper presented at the 12th SBTMO Congress in 2008, in which twenty Brazilian institutions reported the results of 1,149 transplants performed on patients under 19 years old, between March/1985 and December/2007. The importance of this type of study is clear when the comparison between them enables us to reach some conclusions.

The characteristics of our group of patients confirm much of what the other studies show. Until the end of this study, 100% of the transplanted patients had leukemia, the seventh scheduled transplant would be the first in a child with marrow aplasia. This data follows the trend of other studies, in which hematological malignancies lead the indications for BMT. Acute leukemias are the most frequent diagnoses among transplanted children[3].

Table 4. Medical complications after hospital discharge with the need for readmission.

Complication	No of readmissions	Day of readmission
Diarrhea	4	D34 D51 D70 D85
Vomits	1	D41
Tuberculosis	1	D192
UTI	1	D19
Disease recurrence	1	D118

Source: study data.

Males predominated in the studies that divide their samples by sex, as in ours. The age group of eight years was the most reported median.

In Brazil, the main bone marrow donors are brothers with HLA identical to that of the patient[3]. Studies reinforce this trend, which has not yet been confirmed in our service, where up to now 83% of donors have been unrelated, a situation in which the mortality is usually double that seen in transplants with compatible HLA siblings.[3] Our predominance of unrelated transplants may reflect the increase in the number of voluntary donors registered with national and international banks, which increases the chances of finding a donor every day with proper compatibility. Regarding mortality, the "high resolution" HLA typing, based on molecular methods, already enables a better selection of unrelated donors, leading to a progressive improvement in transplant results, which in large centers are already comparable to those obtained with transplants between compatible HLA brothers[3].

Despite the increasing use of cord blood as a source of stem cells in allogeneic pediatric transplants, bone marrow is the main source, since the use of peripheral stem cells (PSC) is associated with higher mortality rates[3]. The risk The developing chronic GvHD, especially difficult to manage, is also associated with the use of PSC[6]. In our study, the only case of GvHD was in a patient who received PSC, but the reaction was acute and not chronic.

Disease relapse, GvHD, infections and toxicity of the preparatory regimen are the main causes of transplant failure[3]. Despite the toxicity associated with our procedure being low (since all patients survived the first 100 days after transplant), all of them faced at least one of these complications that increased the chances of failure. In our study, fever and mucositis were found in 100% of patients, which is repeated in other published studies. It is very important that the attending physicians are aware of this, since the occurrence of mucositis is related to food refusal, and adequate nutrition is fundamental in the recovery of these patients. The use of a single dose of prophylactic fluconazole has already proved to be an alternative for reducing mucositis severity[7].

Liver toxicity, characterized by a temporary and reversible elevation of transaminases in our and other studies, was associated with the drugs used in the conditioning regime. Acute renal failure occurred in a patient with septic shock, which was also reported in other services, as well as the occurrence of systemic arterial hypertension. Both manifestations can also be associated with the use of nephrotoxic medications. Liver veno-occlusive disease, has not stood out as a common complication.

Odone Filho, V. also reported the initial experience of his service, reporting a predominance of Staphylococcus epidermidis and Pseudomonas aeruginosa among the infectious agents identified in the transplanted patients. Other studies that did not identify the agents highlighted the positivity of blood cultures for gram negative and gram positive agents.[6] Such results are extremely important and help guide the choice of antimicrobials for these patients, placing the association of vancomycin with cefepime (used in our service and also mentioned as a choice by Odone Filho, V.) as a good alternative.

Post-hospital discharge complications are rarely described in the literature, but they are extremely important for understanding the clinical outcomes of these patients and for analyzing mortality. Late deaths (after D100) related to allogeneic BMT are more rare and are generally associated with disease recurrence. In our analysis, infections stood out among the causes of rehospitalization, with the longest hospital stay being the only one related to disease recurrence, even when compared to patients with severe infections, such as meningeal tuberculosis.

Finally, it is worth mentioning that this study has the limitations of a being retrospective and with a small sample of patients. However, considering the service's operating time, the number of transplants is promising, close to the average of other well-established services, if this pace is maintained. In our initial series of patients, the low toxicity resulting from the procedure stands out, with all the first six patients surviving the first 100 days after transplantation, an encouraging result for a newly installed service.

CONCLUSION

The evaluation of results obtained with HSCT in children, from studies like this, enables us to better understand the main factors that affect the results of transplants performed for children and adolescents in Brazil. Such a measure is of great value for the pediatricians, hematologists and oncologists involved, directly influencing the chances of curing our children. Brazilian studies are still scarce and should be encouraged.

As BMT stands out as a therapeutic option for a series of severe diseases, with a simultaneous increase in the number of donors, the importance of expanding marrow transplant services becomes clear, as it happened in our service.

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