13TH EDITION

JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY

JBMTCT

MAY/2023;V4N2

ISSN 2675-374X
DOI: 10.46765/2675-374X.2023v4n2

SBTMO

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JBMTCT

SBTMO
SOCIEDADE BRASILEIRA DE TERAPIA CELULAR E TRANSPLANTE DE MEDULA ÓSSEA

JBMTCT
2023;V4N2

JBMTCT - Journal of Bone Marrow Transplantation and Cellular Therapy

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The JBMTCT, Journal of Bone Marrow Transplantation and Cellular Therapy, is an official publication of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO).

Journal of Bone Marrow Transplantation and Cellular Therapy – JBMTCT

Rio de Janeiro; Brazilian Society of Bone Marrow Transplantation, v. 4, n. 2, May, 2023.

87 p.: il. color.

ISSN: 2675-374X

1. Bone Marrow Transplantation. 2. Cellular Therapy. I. Title.

CDD: 610.73072

Dear transplant colleagues

In 2019 we celebrated the 40th anniversary of the first bone marrow transplant (BMT) in our country, with the pioneering spirit of Professor Ricardo Pasquini, Eurípides Ferreira and his team, a fact that was undoubtedly a milestone and the driving force for us to arrive where we are. Today, we are 84 BMT-enabled centers in Brazil and we have seen the great success of these teams, demonstrating a process of maturation of our transplant recipients.

Our company was founded in 1996 by a group of specialists and within this same premise. Today we are prominent in the worldwide transplanting community, having entered into several partnerships with international entities, such as ASCT, LABMT, CIBMTR, FACT, among others.

We have a research group at GEDECO (Grupo de Estudo Doença Enxerto Contra o hospedeiro e complicações tardias) ,coordinated by our dear Dr. Mary Flowers and Dr Afonso Celso Vigorito. This started small as a group of studies on graft disease and because of its quality and empathy, it has now become the gateway to cooperative studies on various topics in our society. SBTMO also maintains a Pediatrics Group, a flow cytometry group, a multidisciplinary group and one of data managers. Every two years, a consensus of indications and complications of transplants is performed, which serves as a guide for the guidance of specialists and public policies.

Faced with this scenario, in a natural way, arose the need to have a journal that could disseminate the work of this scientific community, doctors and multidisciplinary professionals, thus strengthening our interaction with transplantation professionals from various countries.

It is with this spirit of joy and hope that we launched this volume of JBMCT, Journal of Bone Marrow Transplantation and Cellular Therapy, which will certainly be a periodical to publicize the work of all those who believe that science , research and caring for patients, is the best way to improve our walking.

Fernando Barroso Duarte *Nelson Hamerschlak*

Summary

"LIFE IS AWESOME"
MERULA STEAGALL

Nelson Hamerschlak[1], Fernando Tricta[2]

1 Hospital Israelita Albert Einstein (Brazil)
2 Head of Innovation Strategy, Chiese Global Rare Diseases (Canada)

Merula Anargyrou Steagall, an extraordinary social entrepreneur, businesswoman, wife and mother of three, passed away on November 12, 2022 at the age of 56 from complications of thalassemia major.

Merula was 3 years old when her parents were told that she had thalassemia major and that they shouldn't get too attached to her as she wouldn't live past the age of 5. Taking advantage of the continuous advances in medicine, their life expectancy was progressively increasing. Awareness of a short lifespan gave her an unusual sense of urgency and practicality. By her late teens, she was a successful businesswoman in the travel and commerce industry. At the age of 33, she was elected president of the Associação Brasileira de Thalassemia (Abrasta), a small organization for patients in difficulty. One of her first actions in this capacity was to map all patients with thalassemia in Brazil and the health care professionals and institutions that assisted them. She then organized a large international conference on thalassemia for all, initiating a national update on the care of patients with this condition. Abrasta soon became a reference center for patients and health professionals as a source of information and assistance so that all patients had access to care in accordance with the latest medical recommendations.

When her eldest son, Daniel, at the age of 5 years, was diagnosed with cancer, Merula realized that despite all the scientific advances, patients and healthcare professionals still faced numerous difficulties in ensuring access to optimal treatment for all patients. Merula's gratitude for all the care she and her son had received, including blood from donors she never met, and for the life she lived with her husband and children, made her more open to devoting her efforts to helping others. Inspired by Abrasta's achievements in improving care for patients with thalassemia, Merula and a group of cancer patients and their families created the Associação Brasileira de Leukemia e Linfoma – Abrale, with the slogan "100% effort where there is 1% of chance". In 2006, it organized the Alianza Latina Network, currently made up of 120 social health organizations, to encourage the exchange of good practices and the professionalization of health entities. In 2014 she was invited to participate in the World Economic Forum in Davos, Switzerland. In the same year, he orchestrated the formation of the movement "All Together Against Cancer", calling actors from all segments of

the country related to cancer to a joint effort to improve the national policy for cancer prevention and control. The following year, they created the Oncology Observatory, which consolidates public data on cancer treatment in Brazil and provides information that helps support demands made by the Ministry of Health or other public bodies.

In 2016, Abrale expanded its education program for physicians and health professionals with the creation of the Onco Teaching platform, offering free specialization courses in oncology to approximately 200 public hospitals in the country. In 2021, to minimize the negative impact that the COVID-19 pandemic brought to the provision of healthcare, Abrale implemented a telemedicine service, providing patients with virtual medical appointments. Abrale also implemented Onco-Tele Interconsult, to facilitate interaction between oncologists and hemo-oncologists from anywhere in Brazil to discuss difficult clinical management decisions.

In 2013 Merula received the Social Entrepreneur Award from the Schwab Foundation, a non-profit organization based in Geneva, Switzerland, whose mission is to provide a global platform to disseminate innovative and sustainable socio-environmental models. In 2021 Abrale was recognized as the best NGO in the health sector in Brazil.

Merula was a visionary entrepreneur with an amazing ability to gather around her the people and institutions that could guarantee the success of her social projects. She sets the example that having a serious condition that requires blood transfusions every 2-4 weeks, medication for 8 to 12 hours every day, are not impediments to a productive life. Her legacy lives on through the many people who were privileged to have known her.

We had the privilege of being friends with and doctors of this remarkable woman. We became close to her family and whenever we could, we helped Merula with her never ending projects. She always had new ones and used to make everyone around her to work for her always worthy causes.

After she passed, her son Daniel Steagall, on behalf of his family, paid tribute to her and listed the

Good job Merula!

10 GREAT LESSONS THAT MERULA TAUGHT US. THEY ARE HER LEGACY. HERE THEY ARE:

1. Life is 10% what happens to us and 90% how we react to it

2. Have faith, God is in charge

3. Don't leave for tomorrow what you can start right now

4. Willpower can overcome any obstacle

5. It's better to help than to need help, to help a privilege

6. Those who love their work will never have a job

7. Take care of your health and control your treatment choices

8. As painful as our challenges are, they could always be worse

9. The more we envision good things, the more they are attracted to us

10. Always thank and celebrate each achievement

DOI: 10.46765/2675-374X.2023V4N2P187

ANTIEMETICS IN HEMATOPOIETIC CELL TRANSPLANTATION: AN OVERVIEW OF RANDOMIZED TRIALS

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Received: 12 Jul 2022 • Revised: 11 Apr 2023 • Accepted: 12 May 2023.

ABSTRACT

Antiemetics play a key role in hematopoietic cell transplantation (HCT). High-dose chemotherapy and total body irradiation (TBI) have a high emetogenic potential, and vomiting and nausea during conditioning regimen and thereafter impair oral intake, which can lead to weight loss, hyperglycemia due to parenteral nutrition, infectious disease, and increased transplant-related mortality. We searched for randomized trials on antiemetics in HCT. Triplet prophylaxis with a 5-HT antagonist, an NK-1 antagonist, and dexamethasone is a common practice in hematopoietic cell transplantation. Prophylaxis is usually given during the conditioning regimen and sometimes up to a few days later. NK-1 antagonist usage is supported by randomized trials. Olanzapine reduces nauseas, based on a randomized trial. Although recommended by the ASCO guideline, the use of dexamethasone should be considered controversial given the higher incidence of adverse events with this medication in a randomized study and given a possible higher risk of infections, and therefore dexamethasone should be used with caution as an antiemetic in hematopoietic cell transplantation. Metoclopramide, diphenhydramine, and lorazepam are other drugs that also have antiemetic activity, have been used in HCT, and can be used in selected cases.

INTRODUCTION

Antiemetics play a key role in hematopoietic cell transplantation (HCT). High-dose chemotherapy and total body irradiation (TBI) have a high emetogenic potential[1] antiemetics, and antiemetic regimens and to provide recommendations on the use of dexamethasone as a prophylactic antiemetic in patients receiving checkpoint inhibitors (CPIs, and vomiting and nausea during conditioning regimen and thereafter impair oral intake, which can lead to weight loss, hyperglycemia due to parenteral nutrition, infectious disease, and increased transplant-related mortality[2].

With the novel antiemetics, namely serotoninergic (5-HT) antagonists and neurokinin-1 (NK-1) antagonists, acute chemotherapy-induced nausea and vomiting (CINV) can be adequately controlled while control of delayed CINV is somewhat poorer[3]. The objective of this study is to review the randomized studies of antiemetics in HCT.

METHODS

We searched PubMed for (antiemetic*[Title] OR nausea[Title] OR vomit*[Title]) AND (transplant*[Title] OR (high[Title] NEXT dose[Title])) AND (randomized[Title/Abstract] OR randomised[Title/Abstract]) from 2000 and for (metoclopramide[Title] OR diphenhydramine[Title] OR promethazine[Title]) transplant*[Title] without any time limit.

RESULTS

The search yielded 19 studies. We found a total of 11 randomized trials, which are outlined below. Another study was added because of its historical importance.

Serotoninergic Receptor Antagonists

Okamoto et al[4] have compared granisetron with prophylaxis based on metoclopramide and found that granisetron was superior to metoclopramide in preventing CINV in HCT ($p < 0.001$). The use of 5-HT antagonists is now standard in HCT. Constipation and headaches are the main adverse effects of 5-HT antagonists.

Different serotoninergic antagonists

Fox-Geiman et al[5] compared three regimens: oral granisetron 1 mg twice daily, oral ondansetron 24 mg/day, and intravenous bolus ondansetron 32 mg/day until 1 day after the completion of the chemotherapy, all with dexamethasone 10 mg/day. All three regimens demonstrated similar efficacy.

Bubalo et al[6] compared granisetron (2-3 mg/day) or ondansetron (up to 32 mg/day), with dolasetron (1.8 mg/kg, capped at 100 mg, which could be increased to 200 mg/day for refractory patients), combined with dexamethasone, with or without lorazepam and prochlorperazine, during chemotherapy or TBI. Dolasetron-treated patients had fewer days free from emetic episodes ($p < 0.005$). Major or complete responses were also lower with dolasetron.

Slaby et al[7]granisetron, tropisetron and ondansetron, during conditioning for autologous stem cell transplantation (ASCT compared ondansetron 8 mg twice daily, granisetron 3 mg/day, and tropisetron 5 mg/day for 7 days. Dexamethasone was given only in case of failure. Emesis control with ondansetron 8 mg twice daily was significantly poorer than the other two regimens.

Neurokinin-1 receptor antagonists

Bubalo et al[8] et al tested the addition of aprepitant 125 mg followed by 80 mg daily until D+4 to ondansetron 8 mg (twice daily, and 4 times daily in patients receiving busulfan 4 times daily) and dexamethasone (before TBI or cyclophosphamide). Conditioning regimens were BuCy or CyTBI. Complete and major responses were higher in the aprepitant group (85% vs 45%, $p = 0.02$).

Svanberg & Gunnar[9] also tested the addition of aprepitant until 7 days after the end of the chemotherapy. The standard prophylaxis included tropisetron 5 mg/day and betamethasone (6 mg/day). There was a significantly lower number of vomiting episodes in the aprepitant group ($p = 0.001$).

Schmitt et al[10], in patients with multiple myeloma, added aprepitant 125 mg on day 1 and 80 mg/day on days 2 to 4 to granisetron 2 mg D1-4 and dexamethasone 4 mg on D1 and 2 mg on D2-3. Melphalan 100 mg/m2 was given on days 1 and 2. Complete response was achieved more frequently in the group that received aprepitant (58% vs 41%, $p = 0.004$).

Stiff et al[11] added aprepitant 125 mg on day 1 and 80 mg/day for 4 days to ondansetron 8 mg three times daily and dexamethasone 7.5-10 mg/day until the following day of chemotherapy completion. Complete response rates were higher in the aprepitant arm (82% vs 66%, $p < 0.001$).

In summary, these studies demonstrate that the addition of aprepitant is effective and safe in preventing nausea and vomiting in the context of high-dose therapy and hematopoietic cell transplantation and should be offered to all patients.

Dexamethasone

Matsuoka et al[12] tested the addition of dexamethasone to granisetron in patients receiving high-dose chemotherapy with or without total body irradiation (TBI). Patients received 40 mcg/kg with or without 4 mg dexamethasone 30 minutes before each dose of chemo or radiotherapy and repeated 12 hours after the first dose. Granisetron and dexamethasone were given no more than twice daily. Although complete emesis control was higher with dexamethasone (100% vs 63%, $p = 0.02$), adverse reactions were more frequent in the dexamethasone group (68% vs 5%), even though the authors have not specified the rates of infectious complications. The use of corticoids has been associated with higher rates of invasive fungal infections[13] and, in patients with acute myeloid leukemia (AML), with higher infectious death rate even with a low median number of days of corticosteroid administration[14]. In the haploidentical setting, the use of corticosteroid as premedication before graft infusion has been linked to higher CMV reactivation[15].

Olanzapine

Clemmons et al[16] tested the addition of olanzapine 10 mg/day to an antiemetic scheme that included ondansetron 8-16 mg/day, dexamethasone 8-20 mg/day, and fosaprepitant 150 mg/day, given until 3 days after the chemo/radiotherapy. Complete protection (no emesis, rescue antiemetic, or significant nausea) was seen in 55% of the patients who received olanzapine, against 26% ($p = 0.003$) in the control group. The main side effect of olanzapine is sedation.

Dopaminergic receptor antagonists

Gilbert et al[17] cyclophosphamide, and carmustine with autologous bone marrow support were randomized to receive one of four double-blinded antiemetic regimens: 4-day continuous infusion prochlorperazine (6 mg/m2 intravenous [i.v.] loading dose followed by 1.5 mg/m2/hour compared metoclopramide 20 mg/m2.hour with prochlorperazine 1.5 mg/m2.hour, both in combination with diphenhydramine 25 mg 4 times daily and lorazepam 1 mg/m2 every 4 hours, with either dronabinol 5 mg/m2 or placebo. Both metoclopramide and prochlorperazine in combination with lorazepam and diphenhydramine offered similar control of nausea and vomiting, although dose reductions due to toxicity were frequent. The addition of dronabinol did not improve the results.

CONCLUSION

Triplet prophylaxis with a 5-HT antagonist, an NK-1 antagonist, and dexamethasone is a common practice in hematopoietic cell transplantation. Prophylaxis is usually given during the conditioning regimen and sometimes up to a few days later. NK-1 antagonist usage is supported by randomized trials. Olanzapine reduces nauseas, based on a randomized trial. Although recommended by the ASCO guideline[1] antiemetics, and antiemetic regimens and to provide recommendations on the use of dexamethasone as a prophylactic antiemetic in patients receiving checkpoint inhibitors (CPIs, the use of dexamethasone should be considered controversial given the higher incidence of adverse events with this medication in a randomized study and given a possible higher risk of infections, and therefore dexamethasone should be used with caution as an antiemetic in hematopoietic cell transplantation. Metoclopramide, diphenhydramine, and lorazepam are other drugs that also have antiemetic activity, have been used in HCT, and can be used in selected cases.

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DOI: 10.46765/2675-374X.2023V4N2P186

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IS AN EFFECTIVE TREATMENT OPTION IN EARLY RELAPSED AND PRIMARY REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA IN THE BRITISH HOSPITAL TRANSPLANT UNIT

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Received: 06 Dec 2022 • Revised: 16 May 2023 • Accepted: 18 May 2023.

ABSTRACT

Introduction: Around 10-15% of diffuse large B-cell lymphomas (DLBCL) patients fail to achieve complete response (CR) after R-CHOP, and are considered primary refractory. There is limited transplant data in this population. **Objetive:** to evaluate the outcomes of primary refractory DLBCL patients transplanted at our center. **Results:** we evaluated 34 R/R patients treated with R-CHOP as first line. After second line, 30.4% of primary refractory/early relapse achieved CR, and 88.2% did so after ASCT. Median follow-up: 56.1 months, median OS was not reached; the estimated 5-year OS was 61.7%. Median OS of late relapse (Group 1) was not reached, and was 52 months for primary refractory/early relapse (Group 2) (p=0.023). The 5-year OS was 87.5% in Group 1 vs 49% in Group 2 (p=0.023). **Conclusions:** Primary refractory and early relapsed DLBCL undergoing second-line therapy and ASCT have worse OS compared to late relapse. However, 49% of primary refractory patients who proceeded to ASCT had prolonged survival, which supports the role of ASCT in this population.

Keywords: Hematopoietic stem cell transplantation. Autologous transplantation. B cell lymphomas. Diffuse large cell lymphoma. Primary Refractory.

INTRODUCTION

Around 10-15% of patients with diffuse large B-cell lymphomas (DLBCL) do not achieve complete response (CR) after first line chemoimmunotherapy with R-CHOP, and are considered primary refractory.[1]

In addition, a subgroup of those achieving initial CR will relapse 3-6 months after the end of treatment. In this situation, the standard of care for fit patients is Rituximab associated with second-line chemotherapy followed by consolidation with autologous stem cell transplantation (ASCT) in chemosensitive patients. Overall, 40-50% of these patients can be cured with this approach.[2-5]

This strategy is based on the results of the PARMA study, which enrolled 215 patients with relapsed Non-Hodgkin Lymphoma (NHL); 109 responded after two cycles of salvage therapy with DHAP (dexamethasone, cisplatin, and cytarabine) and were randomized to either conventional therapy (four additional cycles of DHAP) or ASCT. The 5-year OS was

53% for the patients undergoing transplantation vs 32% for those receiving conventional therapy.[2]

Primary refractory patients are scarcely represented in the medical literature.

In the pre-rituximab era, the Memorial Sloan Kettering Cancer Center group presented a series of 85 patients primary refractory to CHOP, who received second-line ICE protocol and consolidation with ASCT. The 3-year event free survival (EFS) was 25% and the 3-year overall survival (OS) was 22%.[6]

In the rituximab era, the British Columbia Cancer Agency (BCCA) published their series of 45 patients younger than 70 years with primary refractory DLBCL who were fit for ASCT; 12 were chemosensitive to two lines: 27% in the intention to treat analysis. The 5 years OS was 8%.[7]

The study of Vardhana *et al* from Memorial Sloan Kettering Cancer Center (MSKCC) is the largest series published in this field. They presented 82 patients with less than a partial response after R-CHOP who received second line chemotherapy. The 3-year OS was 38% and the PFS was 29% for the global cohort. In the 33 patients that proceeded to ASCT, 3-year OS was 65% and 3-year PFS was 60%.[8]

There is limited data on primary refractory DLBCL in the rituximab era. We evaluated the outcomes of primary refractory DLBCL transplants at our center, analyzing CR and OS rates. We compared these outcomes with those of patients transplanted for DLBCL relapsing beyond 6 months after the end of therapy.

METHODS

This is a retrospective single-center cohort study that evaluates the outcomes of second-line therapy and OS in primary refractory DLBCL and compares them with the outcomes of patients transplanted in late relapse.

Population:

All patients with DLBCL transplanted at the British Hospital´s hematopoietic stem-cell Transplant Unit from 2000 to 2020 were included.

Inclusion criteria were adult patients (>18 years) with relapsed and/or refractory histologically confirmed DLBCL or transformed low-grade lymphoma undergoing ASCT as second line consolidation. Exclusion criteria: rituximab-free first-line therapy, ASCT at first CR after R-CHOP, patients on the same protocol as first and second line, and CNS primary DLBCL.

Early relapse was defined as the relapse occurring within 6 months after completion of the first line treatment. Primary refractoriness was defined as not achieving CR at a maximum of 6 cycles of R-CHOP. Late relapse was defined as a relapse occurring beyond 6 months from the end of frontline therapy.

For this analysis, Group 1 included patients with late relapses, whereas Group 2 included primary refractory and early relapsed patients.

Response criteria were defined according to the Report of the International Workshop to standardize response criteria for non-Hodgkin's lymphomas and, since PET-CT became available, by the Lugano Response Criteria for Non-Hodgkin Lymphoma.[9,10]

Second-line therapies and the timing for ASCT were defined by the treating physician. The protocols used are shown in table 1.

Transplantation procedures:

After 5 days of stimulation with granulocyte colony-stimulating factor (G-CSF) with 10 mg/kg/d, repeated leukaphereses were performed to obtain a minimum of 2 x 10^6/kg recipient´s body weight of CD34+ cells. Peripheral blood stem cells (PBSC) were frozen using a controlled-rate method and stored in liquid nitrogen at -196 °C. The standard conditioning regimen was BEAM (Carmustine, Etoposide, Cytarabine and Melphalan). In 5 patients, due to a shortage in Carmustine, NEAM (Mitoxantrone, Etoposide, Cytarabine and Melphalan) protocol was used. Harvested stem cells were infused 24 hours after the end of chemotherapy, and patients received G-CSF 5 mg/kg/d subcutaneously from day +5 until leukocyte recovery after ASCT.

Response evaluation was performed around day 100 post-transplant and included routine analysis and imaging (PET-CT or CT) as judged by the treating physician.

Statistical Analysis:

OS was defined from the date of transplant until death from any cause, and patients who did not die during the study period were censored at the date of last follow-up. EFS was defined from the date of transplant until treatment failure, relapse or death, whichever came first, and patients who did not experience any of these events were censored at the date of last follow-up.

The data was analyzed using descriptive statistical methods, and statistical significance for differences between groups was calculated using t- test for non-categorical variables and chi-square or Fisher's exact test for categorical variables. Survival was determined with the Kaplan Meier curve. Significance was established with logrank test at $P < 0.05$.

Ethics:

All the procedures were in accordance with the Helsinki Declaration of 1975, revised in 2008 and with the acceptance of the Hospital Britanico's Ethics Committee.

RESULTS:

Between 2000 and 2020, 66 ASCT were performed in 66 patients with DLBCL at our institution. Of them, 34 fulfilled the inclusion criteria and are our study cohort. (Figure 1).

Patients´ characteristics:

Median age was 56 years (29-71) and 26.4% were older than 60 years; 50% were males.

Ann Arbor stage at diagnosis was I-II in 29.4%, and III-IV in 70.6%. B symptoms were present in 53%. R-IPI was intermediate or high in 76.4%. Patients' characteristics are shown in Table 1. The evaluation of response after R-CHOP was done with PET-CT in 22 patients (64.7%). A biopsy to confirm refractory/relapse disease was decided by the treating hematologist and it was done in 17 (50%) of the study cohort.

Salvage therapy:

Eleven patients had late relapses (Group 1), while 23 patients were primary refractory or early relapsed (Group 2). Table 2 shows the characteristics of group 1 and 2. These groups are balanced regarding age and response to second line therapy.

DHAP was the most used second-line therapy (44.1%), followed by ICE (29.4%) and GDP (11.8%). Rituximab was used in 10 patients, 7 from Group 1, and 3 from Group 2, p=0.003. Responses to second line therapy before ASCT were 29.4% CR (10), 55.9% PR (19) and 14.7% progression (5). This response was evaluated by CT in 25 patients (73.5%) and by PET-CT in 9 (26.5%).

Outcomes after transplant:

Response rates: at day-100 after ASCT, 88.2% achieved CR (76.7% assessed by PET and 23.3% by CT) and 11.8% progressed (50% assessed by PET and 50% by CT). (Figure 2)

Overall survival: with a median follow-up of 56.1 months (1.8-177.4), the median OS was not reached in the whole cohort; the estimated 5-year OS was 61.7%. (Figure 3) Median follow-up in the primary refractory and early relapse group (Group 2) was 42.5 months (1.8-141.2) compared to 97 months (38.5-177.4) for the late relapse group (Group 1). (Figure 4).

The median OS of Group 1 was not reached, and it was 52 months for group 2, log rank p=0.023. The 3-year OS was 100% in Group 1 vs 60% in Group 2, and the 5-year OS was 87.5% versus 49%, p=0,023.

No difference in OS between transplanted patients in CR or PR after second line therapy was observed (p = 0.44); 26.5% were evaluated by PET/CT before ASCT. There was no statistically significant difference in OS among patients within Group 2 (primary refractory, progressive disease or early relapse). The 5-year event free survival (EFS) was 87.5% in Group 1 and 51.4% in Group 2, p=0.075. (Figure 5).

DISCUSSION

Overall, DLBCL can be cured in 50-70% of the cases.[11]

The standard treatment in fit patients who achieve less than CR after frontline R-CHOP therapy is a second line of therapy followed by ASCT. The same approach is recommended for those who relapse, early or late after the end of frontline treatment. Primary refractory patients have been defined in various ways, in some studies they are those who achieve PR or less with R-CHOP, in others only those who achieve less than PR with R-CHOP.[8,12] These patients have been underrepresented in studies that evaluate the role of ASCT in DLBCL.

One of the main factors that impact the outcomes of refractory/relapsed DLBCL is response to second line treatment. The complete response rate to second line chemotherapy in our series was 27.3% and 34.8% in patients with late relapse and primary refractory disease, respectively. Noteworthy, only 29.4% received Rituximab associated with second line treatment. This is due to regulatory issues in our country, where Rituximab is approved for second-line use in patients with late relapses only.

In our series, 1/3 of the patients had their response evaluated with PET at this stage while the others were evaluated with CT.

Novel imaging techniques like PET/CT provide additional sensitivity and specificity compared to CT. However, non malignant pathologies may yield false positives. The evaluation of response to therapy has been varied in recent studies, some including only CT and others with PET/CT. The CORAL study showed a CR rate of 24% for R-ICE and 28% for R-DHAP, in a cohort where 53% were late relapses, with a median time to relapse of 89 months overall. The response was evaluated by CT.[4] Responses to second line in a French retrospective study with 104 patients were CR 23%, with 77% patients receiving Rituximab in salvage regimens.[13] The NCIC-CTG LY.12 study showed a CR of 13.8% for GDP and 14.6% for

DHAP in a population with 71% primary refractory or relapsed within 1 year. In this study, the response was also evaluated by CT.[5]

Compared to these results, our patients achieved slightly higher rates of response to second line treatment. In the CORAL study more than half of the patients had late relapses whereas in the NCIC-CTG LY.12 the most frequent were primary refractory or early relapses. In addition, the evaluation of response in these trials did not include the use of PET/CT, which may interfere with the interpretation of differences, as 1/3 in our study were evaluated with this technique.

In our series, at the time of ASCT, 29.4% were in CR, mostly assessed by CT (73.5%) After ASCT, CR rates increased to 88.2%, supporting the role of high-dose chemotherapy in this context. However, 4 (11.8%) patients progressed after ASCT (50% assessed by PET). Of them, 2 were in PR and 2 in progression at ASCT according to PET in 3 and CT in 1. It is important to notice that 3 of the 5 patients transplanted in progression achieved a CR after transplant. Of them, 2 are alive and in CR and 1 relapsed 21 months after transplant and died 28 months after ASCT due to progressive disease. This is a real world series, and even though transplant is indicated in chemosensitive DLBCL, 5 of our patients were transplanted in progression (3 confirmed by PET). Although the numbers are small some of them achieved long-term survival after ASCT.

The results of our series show an estimated median OS at 5 years of 61.7%. There are few published studies with a large number of patients in this setting, particularly in the real world.

A study published in 2017 from MSKCC reported the outcomes of 33 patients after second line and ASCT: 27% were in CR, and the estimated 3-year OS and PFS were 65% and 60% respectively.[8]

The Danish registry identified 90 refractory or relapsed patients who proceeded to ASCT. The 5-year OS from the time of infusion was 46% (95% CI: 37%–59%), and the median survival was 1,172 days. In this cohort, there was no difference in OS in the refractory or relapsed population.[14]

The CIBMTR report is the largest addressing this topic, including primary refractory DLBCL patients who received an ASCT between 2003 and 2018. Primary refractory disease was defined as either stable disease (SD) or progressive disease (PD) after rituximab and anthracycline-containing frontline chemoimmunotherapy. One hundred and sixty-nine adult patients with primary refractory DLBCL were included. The majority had PD (N=124; 73%) and the remaining had SD (N=45; 27%) after completion of frontline chemoimmunotherapy. All patients showed chemosensitivity to salvage therapy before ASCT. PFS or OS did not differ significantly at any time points between the two groups. Regarding the status of remission before ASCT, the 4-year PFS was 39% for the CR group versus 43% for the PR group (p=0.69). At 4 years, OS is comparable at 50% in the CR vs 49% in the PR groups, respectively (P=0.8).[12]

A Japanese study published in 2021 included 69 primary refractory patients after R-CHOP: 41 PR or early relapsed and 28 progressors under the first line. Of these, 17 proceeded to ASCT (13 partial responders and 4 primary progressors). The 3-year PFS and OS rates of the 17 patients treated with HDC-ASCT were 41% and 47%, respectively. Patients in the primary progressor group had a significantly poorer prognosis than those in the partial responders' group (3-year OS: 15% vs. 48%, respectively; $p < 0.001$).[15]

Nowadays, the use of bispecific antibodies and CART in DLBCL R/R are under development with promising results, but these strategies are yet unavailable in our country.[16,17]

It is noteworthy that ASCT after salvage chemotherapy provides the possibility of cure to a proportion of around 50% of RR DLBCL eligible patients, so it continues to be a useful and accessible strategy achieving good results. This study may have unintentional biases derived from its retrospective nature and the limited number of patients. In particular, there is a probable selection of fit, chemosensitive patients which makes broader generalizations difficult.

However, to the best of our knowledge, this is the first report from Latin America focusing on the outcomes of DLBCL patients transplanted for relapsed or refractory disease and it is one of the few international series approaching this issue.

CONCLUSIONS

Primary refractory and early relapsed patients with DLBCL undergoing second-line therapy and ASCT have worse OS compared to transplanted patients after late relapse. Chemoresistance is one of the most important factors affecting OS in DLBCL. However, 49% of primary refractory patients who proceeded to ASCT in this retrospective study had prolonged survival, which supports the role of ASCT in this population.

TABLE 1. Patients' characteristics.

N=34	Frequency (%)	
Median age (range)	56 (29-71)	
>60 years old	9 (26.4)	
Sex Female Male	 17 (50) 17 (50)	
Stage I-II III-IV	 10 (29.4) 24 (70.6)	
B symptoms	18 (53)	
HIV	1 (2.9)	
RIPI Low Intermediate High No data	 4 (11.8) 14 (41.4) 12 (35) 4 (11.8)	
Response after 1st line CR* PR+ Progressive	 16 (47) 13 (38.3) 5 (14.7)	 ByPET 10 (29.4) By PET 9 (26.5) By PET 3 (8.8)
Second-line therapy DHAP§ ICE** GDP++ MA § § Codox-M-IVAC*** ESHAP+++ R-CHOP § § §	 15 (44.1) 10 (29.4) 4 (11.8) 2 (5.9) 1 (2.9) 1 (2.9) 1 (2.9)	 +R: 5 (14.7) +R: 4 (11.8)
Pre ASCT response CR ≤ CR	 10 (29.4) 24 (70.6)	 By PET 9 (26.5)
Post ASCT response CR Progression	 30 (88.2) 4 (11.8)	
Indication for ASCT: Partial Response Progression Early relapse (<6 months) Late relapse (> 6 months)	 13 (38.2) 5 (14.7) 5 (14.7) 11 (32.4)	

*CR: Complete Response; +PR: Partial Response; §DHAP: Dexamethasone, Cisplatin, Cytarabine; **ICE: Ifosfamide, Carboplatin, Etoposide; ++GDP: Gemcitabine, Cisplatin, Dexamethasone; § §MA: Methotrexate, Cytarabine; ***Codox-M-IVAC: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Methotrexate, Ifosfamide, Cytarabine, etoposide; +++ESHAP: Etoposide, Cytarabine, Methylprednisolone, Cisplatin; §§§R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Prednisone.

TABLE 2. Characteristics of Groups 1 and 2

	Late relapse (Group 1) n (%)	Primary refractory and early relapse (Group 2) n (%)	p
N: 34	11	23	
Median age (rage)	50 (29-65)	57 (32-71)	0.093
Second line therapy DHAP* ICE+ GDP§ MA** Codox-M-IVAC++ ESHAP§§ R-CHOP***	 4 (36.4); +R 2 (18.2) 5 (45.5); +R 4 (36.4) 1 (9.1) 0 0 0 1 (9.1)	 11 (47.8); +R 3 (13) 5 (21.7) 3 (13) 2 (8.7) 1 (4.3) 1 (4.3) 0	NS
Rituximab in second line	7	3	0.003
Response at ASCT+++ CR§§§ ≤ CR	 3 (27.3) 8 (72.7)	 7 (30.4) 16 (69.6)	 0.84

*DHAP: Dexamethasone, Cisplatin, Cytarabine; +ICE: Ifosfamide, Carboplatin, Etoposide; §GDP: Gemcitabine, Cisplatin, Dexamethasone; **MA: Methotrexate, Cytarabine; ++Codox-M-IVAC: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Methotrexate, Ifosfamide, Cytarabine, etoposide; §§ESHAP: Etoposide, Cytarabine, Methylprednisolone, Cisplatin; ***R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Prednisone; +++ ASCT: Autologous Stem Cell Transplantation; §§§CR: Complete response.

FIGURE 1. Flowchart of DLBCL transplanted patients

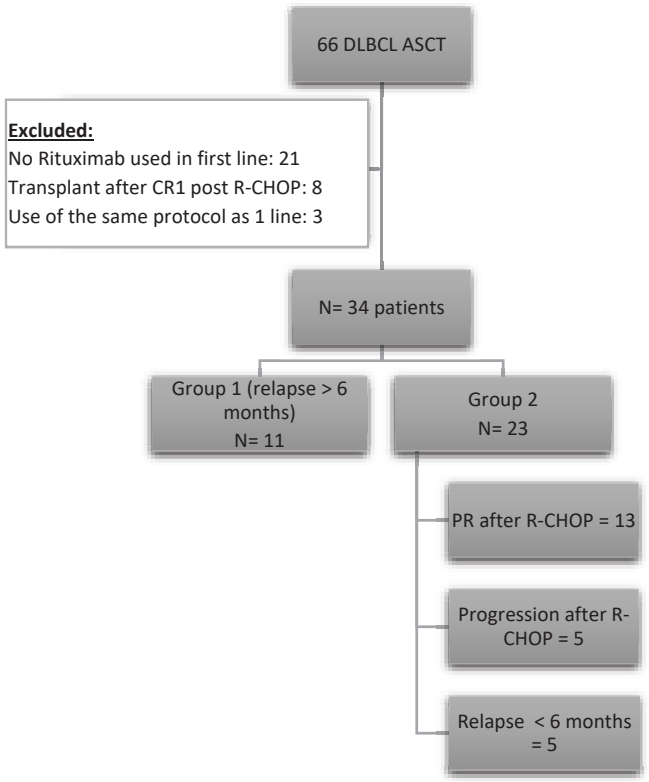


FIGURE 2. **Response before and after Autologous Stem Cell Transplantation.**

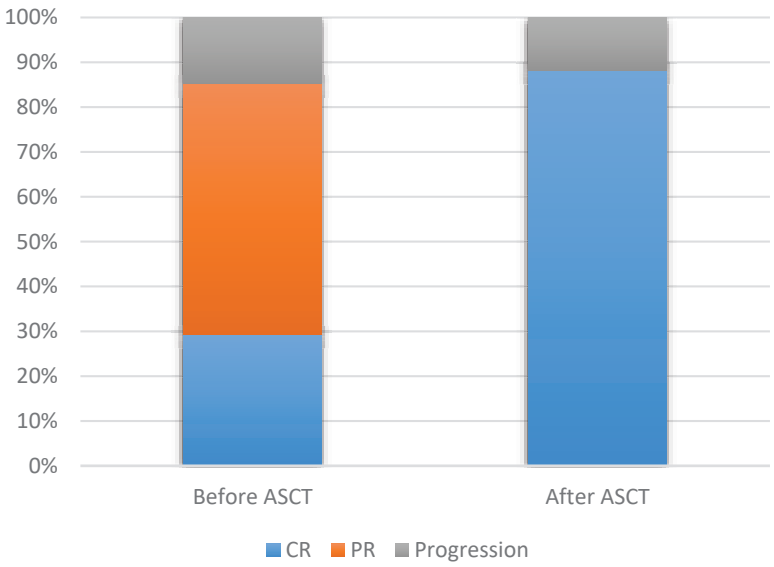


FIGURE 3. **Overall Survival in the entire cohort.**

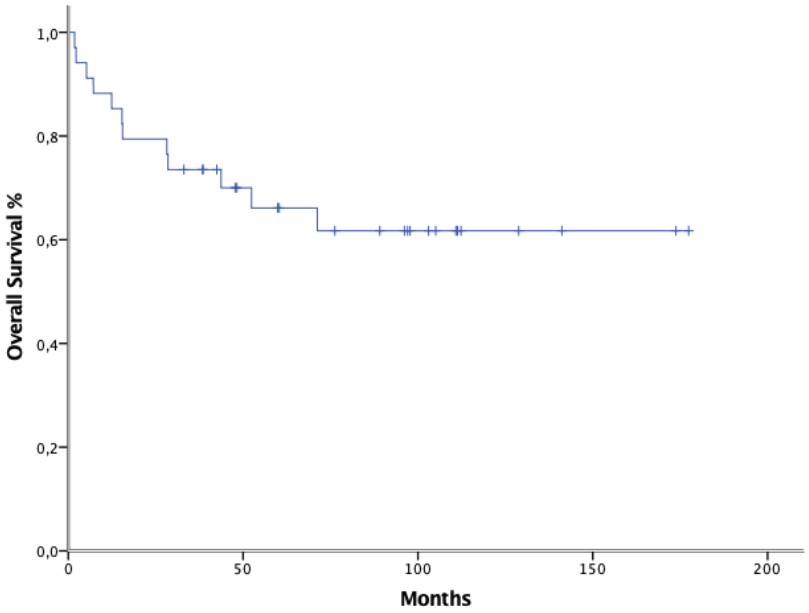


FIGURE 4. **Overall Survival according to time to relapse or primary refractory to R-CHOP.**

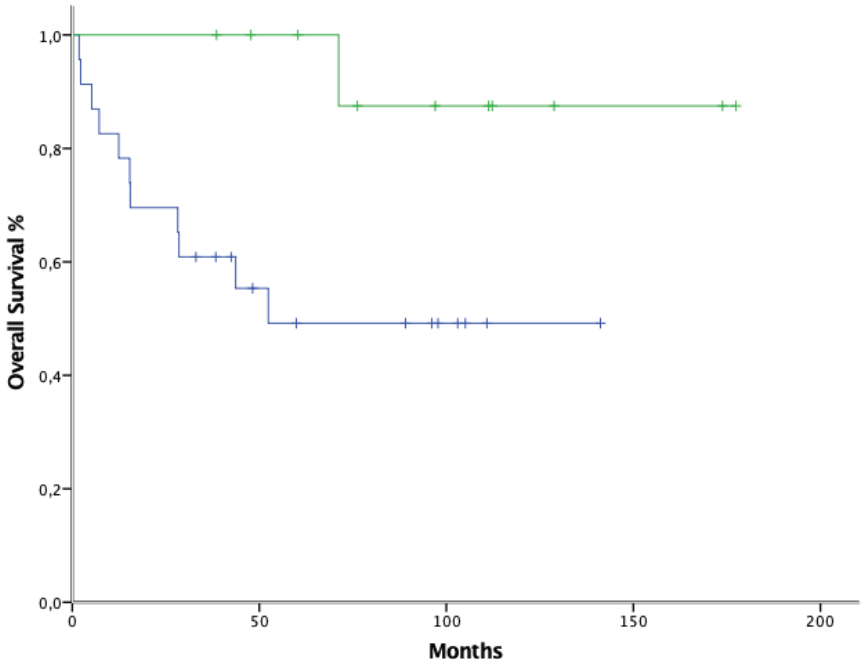
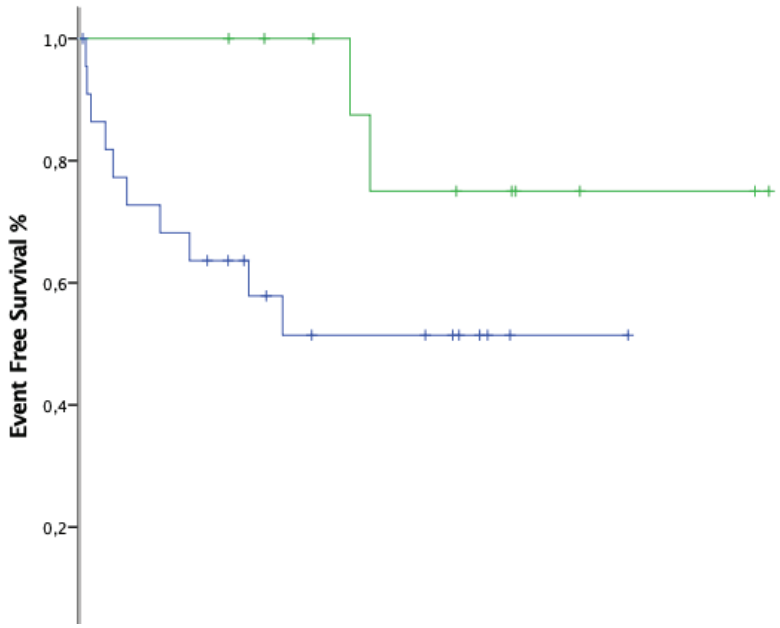


FIGURE 5. **Event Free Survival according to time to relapse or primary refractory to R-CHOP.**



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DOI: 10.46765/2675-374X.2023V4N2P194

OVERCOMING DIFFICULTIES IN DONOR SELECTION FOR PEDIATRIC ALLOGENEIC TRANSPLANTATION IN A RESOURCE LIMITED COUNTRY

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Received: 12 Jan 2023 • Revised: 12 May 2023 • Accepted: 19 May 2023.

ABSTRACT

Objective: Describe the actions taken by our program to gain access to worldwide transplant donors, select and procure the preferred donor for our patients, and perform the transplant timely. **Methods:** We worked on three aspects to gain unlimited access to unrelated donors: hiring and training transplant nurse coordinators, fluid communication and collaboration with registries and cord blood banks, and careful planning of the transplant procedure to avoid delays. We start a donor search immediately after we indicate the transplant. Our donor preference is matched sibling (MSD), matched unrelated (MUD), single antigen mismatched unrelated (MMUD), and cord blood (UCB). We gave a haploidentical donor transplant in case of no donor or procurement delays. We analyzed donor usage and time to transplantation in our program from 2014 through 2022. **Results:** We transplanted 166 children between 2014 and 2022. 19% of patients had an MSD, 28% found a MUD, 19% an MMUD, and 24% a UCB. 10% received a haploidentical transplant. Unrelated donors increased from 26% in 2014-2018 to 61% in 2019-2022. DKMS donor centers provided 60% of the products. The mean time to transplantation was 68 days for related donors (MSD and haploidentical) and 74 days for unrelated donors (MUD, MMUD, UCB). Conclusion: We overcame donor selection difficulties with specific actions, accessing all available donors and transplanting patients timely.

Keywords: Transplantation, Homologous. Pediatrics. Blood Banks.

INTRODUCTION

Allogeneic stem cell transplantation (SCT) is performed worldwide for the treatment of a wide variety of life-threatening blood-related diseases in children and adults. A matched sibling is the preferred donor, but only 20-25% of patients have such a donor. Alternative donors include matched and mismatched unrelated (MUD and MMUD), mismatched related (haploidentical), and unrelated umbilical cord blood (UCB). Choosing the best alternative donor for when more than one is available is a highly debated topic. MUDs are the first source of stem cells for pediatric ASCT in most centers and teams in developed countries where there is broad experience in children with results that match those with MSD . CBUs are used in children preferably for some diseases () and MMUD continue to be used in children with malignant and non-malignant diseases. Haploidentical transplant activity has increased rapidly, allowing patients without an unrelated donor to get a timely ASCT . Moreover, transplants with highly mismatched unrelated donors have proved encouraging results constituting a good alternative in pa-

tients without a MUD or haploidentical donor, especially in ethnic minorities. Many studies comparing survival for different donor options in children show similar results. Still, many other outcomes remain controversial, such as acute and chronic graft versus host disease (GvHD) incidence, the impact of disease stage and conditioning intensity on survival, non-relapse mortality, and relapse incidence . Ongoing prospective trials will answer some of these topics. Centers in resource-limited countries face many challenges when selecting unrelated donors. A perceived low chance for a match, lack of familiarity with the search process, complex logistics for countries far away from large donor centers, lack of trained staff in search and coordination, and high upfront cost are some of those challenges. Based on these issues, many centers in Latin America have moved away from unrelated donors to haploidentical SCT with post-transplant cyclophosphamide. Others do not consider or discourage unrelated SCT and thus limit options for patients in choosing the best donor. Hispanic minorities are historically underrepresented in international donor registries, but recent data from the NMDP has shown that up to 80% of Hispanic patients may find either a fully matched or one antigen/allele mismatched donor in the registry. On the other hand, several reports of haploidentical SCT in pediatric malignancies from centers in Latin America have shown its advantages, feasibility, and encouraging results[7,8]. As the field moves along, it is important for individual centers in the region to consider all transplant options and overcome the difficulties in accessing registries and procuring stem cell products, as well as gaining experience in transplantation with unrelated donors, allowing the best donor choice for each patient.

The pediatric SCT program at our institution started with MSD transplants in 1989. Cord blood became available in 1996 and became our only source of alternative donors. Unrelated donor registries were reluctant to work with new centers in Latin America until 2008, when National Marrow Donor Program (NMDP) accepted us as a non-network center. This collaboration opened the doors of every donor center and registry in the USA and Europe, and we could access the World Marrow Donor Association (WMDA) database. We began with haploidentical donor transplants after the technique was proven safe and effective in children in 2014. In order to expand our options and procure stem cell products from all registries and cord blood banks, we took specific actions:

Hire and train dedicated transplant nursing coordinators. They are involved from the beginning, educating parents and children about the steps of getting to transplant. They participate actively in donor search and contact the donor center, registry, or cord blood bank. When we identify a donor, nursing coordinators request confirmatory typing and workup of the donor. They coordinate the procedure with the medical team, bone marrow transplant ward, hospital administrators, and ancillary services when needed (radiation oncology, blood bank, among others)

As in most resource-limited countries, no donor registry in Chile provides search and procurement services. We established a collaboration and fluid communication with donor registries and cord blood banks outside our country. Large registries such as Deutsche Knochenmarkspenderdatei (DKMS) and NMDP regularly assign a search coordinator to communicate with the transplant center and respond to requirements during the search process. They also provide expert advice regarding donor-patient matching.

Careful planning of the transplant procedure: in order to get the patient expeditely to transplant from an unrelated donor, we begin the search and procurement as soon as we make the indication, allowing time to complete the process timely. Patients with malignancies receive protocol chemotherapy to obtain or maintain remission, and patients with other diseases, such as aplastic anemia and immunodeficiencies, receive supportive care until conditioning starts.

We report the result of our actions and usage of different donor sources for children transplanted in our center from 2014 through 2022. We compare the search process results over two periods and the time from indication to transplant between related and unrelated donors for patients with aplastic anemia, acute leukemia, and lymphoma.

SUBJECTS AND METHODS

A donor search is initiated in our center as soon as the transplant team reviews the patient's history and the SCT indication is confirmed. We perform high-resolution typing for HLA A, B, C, DRB1, DQB1, and DPB1 on the patient, siblings and parents. We refer samples to the DKMS Life Science Laboratories (Dresden, DE) and receive results in 7 to 10 working days. If an MSD is unavailable, we immediately search for an unrelated donor or cord blood unit in WMDA (https://searchmatch.wmda.info/). We base our search algo-

rithm on donor type, underlying disease, and the expected time to transplant . In brief, our first choice is a fully matched unrelated donor (MUD) followed by either a one antigen/allele mismatched donor (MMUD) with a permissive DPB1 TCE3 mismatch or a cord blood unit with ≥ 5/8 loci high-resolution match and an adequate cell dose (TNC 10e7/kg and CD34 2 x 10e5/kg). We prefer cord blood for infants and small children when we identify a fully matched unit or expect delays in procuring unrelated donors. Other criteria for choosing are younger donor age, no ABO incompatibility, CMV status (we try to avoid negative donors for positive patients), and gender.

The best unrelated donor or cord blood unit is then selected, and we set a tentative date for the transplant according to the disease type and stage. Patients with malignant diseases receive chemotherapy according to the institution's protocol, and those with non-malignant diseases receive supportive care according to the disease. If no unrelated donor or cord blood unit is available in the initial search or stem cell procurement is delayed beyond the defined date, we test the patient for anti-HLA antibodies. Haploidentical donors considered are a sibling, father, or mother in that order. We select donor centers providing the product according to the expected time for collection and shipping and the cost of the product.

We analyzed the distribution of donor types in the entire cohort and compared two periods, 2014 to 2018 vs. 2019 to 2021. We choose the periods coinciding with the establishment of DKMS in Chile, and we compared the distribution of donor types by Fisher exact test.

Time to transplantation was defined as the number of days from transplant indication to stem cell infusion. We analyzed the difference between related (MSD, haploidentical) and unrelated donors (MUD, MMUD, UCB) between 2016 and 2022 for patients with acute leukemia, lymphoma, aplastic anemia, and Severe Combined Immunodeficiency (SCID).

RESULTS

One hundred sixty-six children received an allogeneic SCT at our center from 2014 through 2022. Diagnosis and disease stage are shown in table 1. 106 had malignancies, and 60 had nonmalignant diseases.

Table 2 shows the donor distribution for the entire population divided by period. As expected, 19% of patients had an MSD. We found matched and mismatched unrelated donors for 47% of our patients and a UCB for 24%. Sixteen patients (10%) received a haploidentical transplant. Noticeably, the proportion of unrelated adult donors increased from 26% to 61% in both periods, while the UCB proportion fell from 44% to 11%.

The origin of stem cell products is listed in table 3. We procured 61% of unrelated donors from DKMS. DKMS Chile provided a sizable proportion of products considering that by December 2021, there were only 150.000 registered donors. 45% of our donors originated from Germany and Poland, and we obtained two-thirds of cord blood units from Spain and the US.

The mean time to transplantation in patients with severe aplastic anemia, SCID, acute leukemia, and lymphoma was calculated in 98 patients and compared between related (MSD and haploidentical) and unrelated donors (MUD, MMUD, CBU). The mean time to transplantation was 78 days (range 21 to 166), with no difference between both groups: 68 days for related donors (SD 33.8) and 74 for unrelated donors (SD 30.7). 46% of transplants were done within 60 days from the indication in the related donor group compared to 33% in the unrelated donor group (Fischer exact test p=0.26).

DISCUSSION

In the era of universal donor availability, transplant teams confront different options. Donor choice for patients without an MSD is a controversial topic. MUDs continue to be the preferred choice, as reported by CIBMTR and EBMT, both in children and adults [6,7]. Transplant teams in resource-limited counties face extra challenges when selecting an unrelated donor due to obstacles in procuring stem cell products from unrelated adult and cord blood donors. Haploidentical donor transplantation has emerged in Latin America as an alternative for those centers with limited access to donor registries and cord blood banks, limited search experience, delays in product procurement, and product cost. Haploidentical donors have allowed many more patients to access a transplant and are therefore being more used. Nevertheless, there is also broad experience with unrelated transplantation in the region, especially in countries with national registries, such as Brazil, Argentina, and Chile. Despite regional shortcomings, many centers continue to prefer unrelated donors for their patients when they are available. .

Few studies have directly compared outcomes with different donor types for pediatric transplantation. The Brazilian Society for Cell Therapy and Bone Marrow Transplantation recently published the overall activity and outcome for transplant indications in

the country from 2012 to 2022, reflecting the increase of haploidentical transplantation in children and adult patients. The authors found a trend for better survival in children with acute myeloid leukemia for haploidentical donors and for unrelated donors in lymphoblastic leukemia patients. However, the numbers were limited, follow-up was short, and differences were non-significant. Most studies of haploidentical donor transplants for pediatric malignancies in the region have been single-arm oriented to demonstrate the advantages and feasibility of the procedure, with promising results. Studies from Brazilian groups showed good outcomes of haploidentical ASCT in children with ALL, aplastic anemia and immunodeficiencies.[16,19] Other studies from Latin America have reported similar outcomes for transplants with MSD or URD[17]. Centers in countries with limited access to donor centers have recurred to haploidentical and cord blood transplantation [18,17].

Our report provides data to confirm that with a trained team, planning, and collaboration, we could overcome the obstacles to procuring stem cell products from donor centers, registries, and cord blood banks outside our country. Some authors have advocated for a restrictive approach to allogeneic transplantation in countries with limited resources where centers should avoid unrelated adult or cord blood donors in favor of haploidentical donors and prefer reduced intensity conditioning to avoid complications and cost (8). As attractive as this approach may look, we must compare its long-term survival outcomes against standard practice in our countries. This comparison should also look carefully at the relative costs of different procedures. The analysis must look not only at the product's upfront cost but also at short- and long-term post-transplant complications such as viral reactivation, hemorrhagic cystitis, and GvHD, for whom modern therapy in our countries may come at a high cost or not be available [17].

Our team established collaborations with all donor centers where we found matching donors and obtained stem cell products on time. This work was done through direct contact and constant communication between our transplant coordinators, donor center staff, and cord blood banks. Most of our donors came from the most prominent donor centers in the world, DKMS and NMDP. As expected, we found a sizable number in DKMS Chile (23%). Nevertheless, 43% came from Germany and Poland, countries with a tiny Hispanic population, probably explained by the over 11 million donors in both countries, the relatively high proportion of western European ancestry of Chilean patients, and the preference of our center.

Time to transplantation is quoted by transplant centers as a crucial factor in the outcome, especially for patients who need an urgent or tightly scheduled transplant[7]. With an early start of the donor search and careful planning, we did not find a difference in time to transplantation between recipients of related and unrelated donors diagnosed with acute leukemia, severe aplastic anemia, or SCID. Scheduled chemotherapy protocols for leukemia before transplantation allowed us to complete the donor search, receive the unrelated donor product, and transplant the patient simultaneously as a related donor, either a sibling or haploidentical. 22 of 24 patients with aplastic anemia received a transplant as upfront therapy. We scheduled a haploidentical transplant if we could not identify an adequate unrelated donor on the patient's first search or if we projected the stem cell product shipment to be more than 60 days.

In conclusion, centers in resource-limited countries such as Chile may access unrelated adult donors and cord blood units with dedicated staff, fluid communication with donor centers, and careful planning of the search and procurement of the product. With the addition of haploidentical donors, every child needing a transplant should proceed to it, and regional centers should try to access all donor types as the field moves. Future studies in the region will need to compare outcomes considering multiple variables derived from the patient (age, disease, stage, conditioning, GvHD prophylaxis) and the donor (age, relationship, match grade). The analysis should include conventional outcomes (survival, relapse, GvHD), post-transplant complications, and cost, both upfront and related to post-transplant complications.

Acknowledgments: We acknowledge transplant coordinators working with our team in donor registries worldwide, especially Sybille Ohngemach, Sandra Salamanca from DKMS, and Emily Carey from NMDP. We also thank Dr. Alexander Schmidt for his thoughtful review of the manuscript.

TABLE 1. Patient´s diagnosis

Congenital hematologic diseases	Blackfan Diamond anemia	6
	Severe congenital neutropenia	2
	Chediak Higashi	1
	Familial Hemophagocytic Lymphohistiocytosis	2
Congenital immunodeficiencies	SCID	5
	Hyper IgM	4
	Wiskott Aldrich	3
	Chronic granulomatous disease	2
	APDS 1	1
	Cartilage Hair Hypoplasia	1
	Leukocyte adhesion deficiency	1
	IPEX	1
	GATA 2 Emerger	1
	X linked proliferative disease (EBV +)	1
	STAT 1 GOF	1
Inborn errors of metabolism	X linked adrenoleukodystrophy	2
	Mucopolysaccharidosis I	2
Severe aplastic anemia		24
Acute lymphoblastic leukemia	CR1	23
	CR2	27
	CR3, not in remission	18
Acute myeloid leukemia	CR1	16
	CR2	6
	Not in remission	3
Chronic myeloid leukemia	Chronic phase	2
Myelodysplasia		5
Hodgkin´s lymphoma		2
Non-Hodgkin´s lymphoma		4

TABLE 2. Donor selection by period

	Total population n	%	2014-2018 (65) n	%	2019-2022 (101) n	%	Difference between periods
MSD	32	19	14	23	18	17	P= 0.2
MUD	47	28	11	18	36	35	P= 0.0173
MMUD	31	19	6	10	25	24	P=0.0065
UCB	40	24	29	48	11	11	P<0.0001.
Haplo	16	10	5	8	11	11	P= 0.45

TABLE 3. Origin of stem cell products

DONOR CENTERS	n
DKMS Germany	27
DKMS Chile	18
Be the Match	17
ZKRD (Germany)	4
DKMS Poland	3
REDMO (Spain)	3
INCUCAI (Argentina)	2
Ezer Minion (Israel)	2
France Graffe de Moelle	1
Anthony Nolan (UK)	1
CEDACE (Portugal)	1
Cord Blood Banks	
Be the Match (US)	12
REDMO (Spain)	11
NCBP (New York)	4
Banco de Vida (Santiago)	3
France Graffe de Moelle	3
ZKRD (Germany)	3
Austria, Belgium, Canada, UK	1 each

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PERIPHERALLY INSERTED CENTRAL VENOUS CATHETER IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS: FEASIBILITY AND OUTCOME

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Received: 20 Mar 2023 • Revised: 20 Apr 2023 • Accepted: 18 May 2023.

ABSTRACT

Objectives: This study describes our experience using PICC in patients submitted to autologous stem cell transplant (ASCT) regarding the time of use, withdrawal reasons, and complications. **Methods:** A retrospective cohort of 143 patients from 2017 and 2019, with a PICC inserted before the ASCT. **Results:** Regarding baseline disease, 104 (73%) of patients had multiple myeloma. The median days of use was 15 (1 – 37) per catheter. More than 80% of PICC remained in place after D+15, and 112 (78%) patients had the PICC removed at discharge. Only 13 (9%) patients had replacement of the PICC. The rates of central line associate bloodstream infection and thrombosis were 1.36 and 1.36 events per 1,000 PICC days, respectively. **Conclusions:** PICCs were successfully remained until discharge, with manageable rates of complications. All procedures were executed by nurses at the bedside. We concluded that PICC is a safe and feasible alternative to CVC for ASCT.

Keywords: Nursing; Catheterization, Peripheral; Hematopoietic stem cell transplantation; Catheter-Associated Infections; assessment, outcomes

INTRODUCTION

The use of peripherally inserted central venous catheters (PICC) in hematological patients has been growing, and reports in different scenarios have been published.[1-5] Patients with hematological diseases need safe and prolonged vascular access since they undergo intense treatments, high demand for blood products, and long and frequent hospitalizations.[6,7] Central venous catheters (CVC) are essential for treating patients with hematological malignancies and stem-cell transplant recipients. There is a variety of CVCs used in daily practices. Still, the most used long-term devices include surgically implanted cuffed tunneled central venous catheters, peripherally inserted CVCs (PICCs), and percutaneous non-cuffed or tunneled catheters.[6,8] The best type of vascular access selection should be based on the patient's and treatment's characteristics and the patient's preferences and safety. Factors to be analyzed are expected time of use, ease and security in the implantation, maintenance routines, comfort for the patient, and cost.[9]

PICC has advantages over other long-term vascular devices: lower risk of complications related to insertion, allows local compression in patients with coagulation disorders or thrombocytopenia and can be easily inserted and removed in an outpatient setting without the need for surgical intervention. However, there are some reports of thrombosis in the same population.[10]

OBJECTIVE

To describe our experience using PICC in patients with hematological diseases submitted to autologous hematopoietic stem cell transplantation concerning the time of use, reasons for exchange or withdrawal, and complications.

METHODS

This study was performed at a tertiary care hospital with 300 beds, including hematology and autologous and allogeneic stem cell transplant unit with 26 single-bed rooms with high-efficiency particulate air (HEPA) filters and positive pressure. Our center has a dedicated nurse team for the insertion and maintenance of PICC since 2015. The PICC catheter has been the primary central venous access (CVC) option in newly diagnosed acute leukemia patients and an alternative to short-term CVC for ASCT.

For this study, we reviewed the data regarding all consecutive PICCs inserted from 2016 and 2019 in patients submitted to ASCT.

This research was conducted following the Declaration of Helsinki and was approved by the Institution's Ethical Committee (CAAE no.54941216.0.3001.5455 – Comite de ëtica em Pesquisa – Hospital Nove de Julho).

PICC INSERTION AND REMOVAL

A group of trained nurses performed the PICC insertion under ultrasound-guided visualization. According to the manufacturer's instructions, the insertion occurred using the modified Seldinger technique and maximum precautionary barrier. The professional chooses the insertion site following the preferred sequence: basilica, cephalic, braquial, cubital, and jugular veins. The final position of the PICC tip (lower third of the superior vena cava) was confirmed by chest radiography before its use. PICC insertion occurs before the conditioning regime or stem cell infusion (D zero) and aims to be maintained until discharge after hematopoietic recovery. In 2018, the nurse team modified the fixation methods, PICC-cover, and shorted the length of lines connected to PICC due to some accidental CVC removal.

Formal indications for immediate PICC removal are suspected or documented infection, suspected or documented thrombosis in the PICC site, and discontinuity of a need for vascular access. The study also captured cases of catheter loss due to other causes.

PICC-RELATED OUTCOMES

The following outcomes were described: exit site and central line-related bloodstream infections (CLABSI), time in place, clinical or documented thrombosis, needs for replacement by accidental extraction, and removal by medical request.

The rate of CLABSI was reported as the number of events per 1,000 catheter-days.

CLABSI were defined by the BSI criteria of the Centers for Disease Control and Prevention (CDC).[11] All events were classified as complicated or uncomplicated CLABSI (regarding a resolution of fever in < 72h and no evidence of endocarditis or suppurative thrombophlebitis.[12]

The criteria to suspect clinical thrombosis was the evidence of pain, hyperemia, edema, or an increase in the brachial circumference of the punctured limb. If there was a suspicion of thrombosis, confirmation by venous doppler from the CVC site was necessary. There was no systematic investigation of thrombosis in individuals without clinical suspicion.

Data were reported as frequencies, medians, and intervals. Time to event was calculated by Kaplan and Meier. All data were analyzed using the SPSS program.

RESULTS

A total of 143 autologous recipients (58% of the sum of ASCT performed in the study period) had a PICC inserted per protocol before stem cell infusion. The most frequent baseline disease was multiple myeloma (n = 104; 73%), and the cohort's median age was 58 years. (Table 1)

The median day of PICC insertion was D-3 (ranging from D -10 and D zero) before ASCT infusion. The median time of the first PICC in use was 15 (1 – 37) days of use per catheter. In Figure 1, we showed the overall PICC survival after ASCT infusion. More than 80% of PICC remained in place after D+15.

Regarding catheter removal, 112 (78%) patients had the PICC removed only at discharge. Causes of early PICC removal were persistent fever (n=11), accidental removal (n=7), mechanical failure (n=5), documented exit-site or CLABSI infection (n=4), documented thrombosis (n=3), and intensive care unit transference by physician description (n=1).

The accidental removal occurred days before stem cell infusion in 6 of 7 events. Six events occurred before and one after 2018. Regarding mechanical failure/lumen obstruction, 4 of 5 events occurred in the first three days of PICC insertion and all four before stem cell infusion.

During the hospitalization, 13 (9%) patients had replacement of the first PICC. The reasons for replacement were accidental removal by patient (n=6), fever protocol (n=3), mechanical failure (n=2), infection (n=1) and local thrombosis (n=1).

CLABSI was documented in 3 (2.1%), with 1.36 infections per 1,000 PICC days. The events occurred 12, 13, and 15 days after PICC insertion, all during neutropenia (D+4, D+5, and D+7 after ASCT). The microbiological etiologies were *Staphylococcus epidermides* in all three events. All events were treated with antibiotics and the removal of CVC. All cases were classified as uncomplicated CLABSI. In one patient, there was an exit-site infection, and the patient had the catheter removed. The discharge occurred in D+14 in two and D+7 in the other, similar to the other patients who did not develop CLABSI (median for discharge D+13, p=0.97).

Thrombosis occurred in 3 (2%), resulting in a rate of 1.36 per 1,000 PICC days. Two of three cases occurred in myeloma patients. The event was documented after 6, 7, and 14 days in use and on Days -1, +3, and +10 of ASCT. The discharge occurred in D+12 in two and D+14 in the other, similar to the other patients who did not develop thrombosis (median for discharge D+13, p=0.99). All catheters were removed, and the event was considered mild (non-complicated) by a doppler scan.

DISCUSSION

In our experience, PICC was a feasible and safe central venous access for hematological patients submitted to ASCT. About 80% of the cohort experienced only one CVC during the ASCT hospitalization. Nurses inserted and removed all PICCs at the bedside, with a low incidence of complications. The replacement rate was less than 10%, and the early losses were more related to mechanical or accidental events. There were few cases of infection and thrombosis. They occurred more lately and were managed with no severe complications.

PICC has been an alternative central venous catheter to hematopoietic patients. [5, 13, 14] Bellesi and collaborators had already evaluated PICC as alternative venous access in individuals undergoing ASCT [1]. The authors concluded that PICC was a safe alternative for their population. After their results, several other centers started this approach, mainly because PICC has a low risk of complications related to insertion and removal, it can be inserted and managed by nurses, and it is related to comfort for the patient. Benvenuti et al., in a small number of pediatric patients, suggested that PICCs were a safe and effective alternative to conventional central venous catheters in pediatric patients receiving stem-cell transplantation.[15] The same was noted in the present cohort. Nurses inserted all PICCs in a bedside local, and most patients (80%) completed the ASCT hospitalization without needing PICC early removal until discharge.

The American Society of Clinical Oncology (ASCO) guideline for venous catheters during cancer care states: "There is insufficient evidence to recommend one type of CVC routinely for all patients with cancer. The choice of the catheter should be influenced by the expected duration of use, the chemotherapy regimen, and the patient's ability to provide care. The minimum number of lumens essential for managing the patient is recommended. These issues should be discussed with the patient". In its guideline, PICC was an alternative.[6]

In our cohort, most events of PICC replacement were due to accidental losses and occurred within a few days after insertion. Other studies also reported dislodgement of PICCs, resulting in early losses (varied from 5 - 15%).[1, 16, 17] After our preliminary results, the team modified the fixation methods, PICC-cover, and shorted the length of lines connected to PICC, with a significant event reduction.

The recommendations for CVC placement in cancer patients have been performed as an elective procedure, guided by ultrasound, by well-trained providers who regularly use the landmark method. A CVC care clinical bundle is recommended for the placement and maintenance of all CVCs to prevent infections. These recommendations may have a high success rate and low incidence of acute and chronic complications.[6, 12, 18]

CLABSI is a significant concern in all patients with CVC inserted, and previous reports of PICCs used in patients with hematologic diseases, who are compromised hosts, have indicated that the incidence of CLABSI is approximately 1-6 cases per 1,000 catheter days, and use of a PICC did not increase the occurrence of CLABSI compared with a conventional CVC. [17]

Although we had PICC-CLABSI events, the frequency was acceptable compared to other types of CVC

CLABSI in our center. Important that none was classified as complicated or increased hospitalization. The frequency of CLABSI in cancer patients is estimated at 0.5–10 per 1000 CVC-days, and it varies by baseline disease, disease phase, neutropenia, and other factors.[5,14] Morano et al. addressed specific PICC-CLABSI in a hematological cohort, and their results showed that the main risk for CLABSI was the underline disease. In their cohort, acute leukemia patients had more risk for PICC-BSI.[13] In our cohort, infection events were not related to baseline disease, but our patients mainly were multiple myeloma and lymphoma patients, non-neutropenic at CVC- insertion. A multicenter cohort with a large number of hematopoietic patients studied if PICC indwelling time contributes to increased CLABSI. They noted that the rates of PICC-CLABSI remained constant, regardless of PICC indwelling time.[14]

Another concerning complication is CVC-related thrombosis. The incidence of CVC-associated thrombosis in patients with cancer varies in different series, from 27% to 66% when routine screening with venography is performed. Most patients with CVC thrombosis are asymptomatic. Reported rates of symptomatic thrombi vary widely, from 0.3% to 28%.[6, 19] Symptomatic venous thrombosis rates associated with PICC lines range from 1 to 4%. PICC – side location and catheter diameter have been associated with this complication.[13, 17, 20, 21] We documented three cases (1.36 per 1,000 PICC days). Even though multiple myeloma patients have increased thrombosis rates, no association between thrombosis and baseline disease was observed. In our cohort, all insertions were made by eco-guided techniques, and we could not associate the event with time after transplant or thrombocytopenia.

Our study is subject to the general limitations of an observational design, which means that information bias may have been introduced: although most of our database was kept prospectively. Other limitations are the sample size and the single center location. As strengths, we assessed the occurrence of CLABSI based on CDC definitions, which is a rigorous method and therefore adds to generalizability.

The use of peripherally inserted central venous catheters (PICC) has been growing in different scenarios, but more data needs to be reported on transplant patients. This study shows the experienced of PICC in more than 100 consecutive autologous patients.

ASCT patients should be cared for with the right competence at all levels, and multidisciplinary teamwork is necessary. The engagement of a nurse team in transplant programs is essential, and our data reinforce that the nurse team can be responsible for venous catheter insertion, manutention, and removal. Early losses and late complication rates were manageable and did not increase hospitalization or outcome. Unlike other types of CVC, PICC care can be managed by nurses at the bedside, bringing commodity to the patient and team.

In summary, our study showed that PICCs was successfully inserted and remained without indication of replacement in 80% of our patients until discharge from ASCT. Early losses and late complication rates were manageable and did not increase hospitalization or outcome. All procedures were managed by nurses at the bedside, bringing commodity for patient and team. We concluded that PICC is a safe and feasible alternative to CVC for Autologous stem cell transplant recipients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DOI: 10.46765/2675-374X.2023V4N2P200

CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: BRAZILIAN SUMMARY SLIDES - 2023

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Received: 05 May 2023 • Revised: 16 May 2023 • Accepted: 19 May 2023.

ABSTRACT

The first hematopoietic stem cell transplantation (HSCT) program in Latin America started in 1979 at the federal university hospital in Curitiba, Paraná, Brazil. Over the years, the number of centers performing transplants in our country has increased significantly generating the need to know the results of this treatment modality. Understanding the HSCT scenario in Brazil is still challenging, since not all Brazilian centers report data to the Center for International Blood and Marrow Research (CIBMTR). Despite the improvement in the number of reporting centers over the past few years, infrastructure and trained data managers are still lacking. The partnership between the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) and the CIBMTR enabled the establishment of the Hematopoietic Stem Cell Transplantation Brazilian Registry (HSCTBR), using the CIBMTR Data Back to Center (DBtC) tool to retrieve Brazilian HSCT data in a standardized and organized way. Since then, it has been possible to gather country-level data on HSCT demographics and transplant outcomes. Between 2012 and 2022, complete information on 9,868 transplants were reported to the CIBMTR from 40 Brazilian transplant centers. The consolidation of the HSCTBR using CIBMTR infrastructure allowed the development and regular update of the Brazilian Summary Slides. Despite the differences in the number of cases and follow-up time, the results in this study were similar to those presented in the United States (US) Summary Slides. In this paper we present the 2023 SBTMO-CIBMTR Summary Slides prepared by the SBTMO data managers (GD-SBTMO).

Keywords: Data Management. Hematopoietic Stem Cell Transplant. CIBMTR. SBTMO. Brazilian Summary Slides.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is often the only curative option for several malignant and non-malignant hematological diseases, as well as extending the survival of a number of patients[1]. Brazil has a large HSCT program, with 126 teams across 86 transplant centers recognized by the Brazilian Ministry of Health.

The first national results on this treatment modality were published in 1985[2]. In 1997, a Brazilian center took part for the first time in an international multicenter study[3]. Throughout the following years, national multicenter studies were developed. Back then, the first steps for the establishment of the Hematopoietic Stem Cell Transplantation Brazilian Registry (HSCTBR) had already begun[4].

Before the publication of the First Brazilian Summary Slides in 2021[5], the Brazilian Association of Organ Transplants (ABTO), established in 1995, while profiting from a strong collaboration with the SBTMO, was the only data source regarding the number of HSCTs performed each year in the country. In 2022, 3,991 transplants were reported to the ABTO: 1,462 allogeneic and 2,529 autologous HSCTs[6]. The overall survival (OS) of these patients is public and serves as a global benchmark for national HSCT outcomes.

A total of 295,682 autologous and 287,972 related and unrelated allogeneic transplants performed around the world between 1970 and 2021 were reported to the CIBMTR[7]. Despite the existence of our summary slides,[8,9] understanding the HSCT scenario in Brazil is still challenging, since not all Brazilian centers report data to the CIBMTR, besides the fact that there is a lack of infrastructure and of trained data managers (DM). Therefore, over the years, thanks to a working group composed of physicians and DMs, coupled with the collaboration of the CIBMTR and the SBTMO, strategies such as continuing education in data management and direct communication channels were developed to support DM training and HSCT centers in the affiliation process to the CIBMTR. These actions underly the increasing number of Brazilian centers currently reporting to the CIBMTR.[10]

The partnership between the SBTMO and the CIBMTR has allowed access to the tools available in the registry, such as the DBtC, which enables the uniform retrieval of data sent by the Brazilian transplant centers to the CIBMTR. Part of the data inserted can thus return to the registered centers in a standardized, de-identified and codified manner, rendering analyses of the outcomes of transplants performed in the country more effective. The consolidation of the HSCTBR using CIBMTR infrastructure and the

accessibility to these data is essential for our public health administration.

OBJECTIVE

Our objective is to understand the Brazilian HSCT demographics and outcomes using the DBtC tool to retrieve the data reported to the CIBMTR, as well as to regularly update and publish them as the Brazilian HSCT Summary Slides. We also aimed to compare our data to those of the US Summary Slides over a similar period of time.

METHODS

Data from 10,107 transplants performed across 40 Brazilian centers between 2012 and 2022 and reported to the CIBMTR were extracted from their portal using the DBtC tool. Of those, 9,868 transplant records had complete data for analysis (4,454 autologous and 5,414 allogeneic HSCTs). The raw data were imported into the Power BI Desktop (PBI). Functions were updated to count the number of transplants performed and the number of participating centers, to translate columns into Portuguese, to categorize and appropriately classify diseases, to group the variables, and to run the global survival analyses.

Patients were classified as pediatric (0-17 years of age) and adults (≥ 18 years of age). Allogeneic transplants were categorized as matched related donor, mismatched related donor (including haploidentical and related donors with one mismatch), and unrelated donor. Grafts were classified as bone marrow (BM), peripheral blood stem cells (PBSC) and umbilical cord blood (CB). The disease stage for Acute Leukemias was classified as 1st remission, 2nd and further remissions, and active disease. Myelodysplastic Syndrome (MDS) was divided into Early Stage, subdivided into refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), and MDS with del(5q) alone, or Advanced Stage, including refractory anemia with excess blasts (RAEB) and Chronic Myelomonocytic Leukemia (CMML). Patients with Lymphoma were categorized as chemosensitive and chemoresistant disease by the response to treatment prior to the HSCT.

Classification of conditioning therapy was based on the agents and doses used: myeloablative conditioning (MAC) for patients who received total body irradiation (TBI) ≥500 cGy in a single dose or >800 cGy in fractionated doses; busulfan >9 mg/kg oral or ≥7.2 mg/kg IV; or melphalan >150 mg/m^2 as a single agent or in combination with other drugs. Conditioning regimens not fulfilling the criteria for MAC, were classified as reduced intensity/non-myeloablative (RIC/NMA)[11,12].

Causes of death were categorized using the standard classification from the DBtC application. The main causes of death from 2018 to 2022 were separated between deaths from 0-100 days and deaths >100 days up to 3 years after HSCT. For the analysis of OS, only 1st HSCTs were selected, and patients with no follow-up data after HSCT or with errors in survival time were excluded (table 1).

Graphics were generated by PBI and exported to Microsoft PowerPoint for publication. OS was estimated by the Kaplan Meier method, and the log-rank test was used to compare survival between groups. Survival analyses were performed using R Statistical Software (Version 4.2.1).

Ethics approval was obtained from the national Institutional Review Board (IRB) in 2019 (Conep CAAE: 65575317.5.1001.0071, principal investigator Dr. Nelson Hamerschlak).

RESULTS

Between 2012 and 2022, 9,868 HSCTs were reported to the CIBMTR from 40 Brazilian centers (table 2), 21 (52%) of which located in the state of São Paulo; 4 in Paraná, 4 in Minas Gerais, 3 in Rio de Janeiro; 3 in Rio Grande do Sul; and 1 center of which in each of the following states: Ceará, Distrito Federal, Rio Grande do Norte, Pernambuco, and Santa Catarina.

The number of active CIBMTR centers increased over the past years in the country, reaching 34 in 2022 (figure 1), which has contributed to the increase in the total number of Brazilian HSCTss registered with the CIBMTR since 2016. In 2022 1,668 transplants were performed (figure 2).

Between 2012 and 2022, 41% of the allogeneic HSCTs performed in Brazil used a matched related donor, followed by an unrelated donor (30%) and a mismatched related donor (29%). However, during the past 3 years, the main type of allogeneic transplant performed in the country was from mismatched related donors (figure 3).

Regarding the graft source for allogeneic transplants, BM was used in most pediatric transplants, while PBSC comprised the main source in adults from 2018 onwards (table 3).

Mismatched related donors were used to treat acute myelogenous leukemia (AML; 32%), followed by acute lymphoblastic leukemia (ALL; 24%) and non-

-malignant diseases (23%); 52% of them used MAC and 48% used RIC/NMA.

The main indications for HSCT in Brazil in 2022 among all age groups were multiple myeloma (MM; 494; 30%), followed by AML (229; 14%), non-Hodgkin lymphoma (NHL; 205; 12%), ALL (204; 12%), and Hodgkin disease (HD;169; 10%) (figure 4). In pediatric allogeneic HSCT, the main diseases were ALL (37%), other non-malignant disorders (23%), and AML (15%). In adults, the main indications for allogeneic transplants were AML (35%), ALL (23%) and MDS (11%). Acute leukemias continue to be the main indication for allogeneic HSCT, but since 2016, there has been an increase in its use for MDS/MPN and lymphomas. The main indications for autologous HSCT remain stable, with the greatest share being that of multiple myeloma and lymphomas.

Among patients with Acute Leukemias, 51% of those with AML and 47% of those with ALL were in 1st remission. Most HSCTs were performed from matched related donors in both AML (45%) and ALL (37%) (table 4).

Infections were the leading cause of death in the first 100 days after all types of transplants: autologous (71%), matched related donor (54%), unrelated donor (57%), and mismatched related donor (56%) allogeneic HSCTs. The most common cause of death after the first 100 days post-HSCT was relapse of the primary disease in both autologous (66%) and matched related (44%), unrelated (43%), and mismatched related donor (47%) allogeneic transplants.

For survival analyses, the median follow-up was 24 months in allogeneic and 13 months in autologous HSCT. Patients with Acute Leukemia who underwent transplantation with active disease had lower survival rates compared to those at other stages (table 5).

Adults had higher survival rates after HSCT from matched sibling donors when undergoing HSCT for AML (p=0.192; figure 5), ALL (p=0.006; figure 6) and MDS (p=0.013; figure 7), but donor type had no impact in pediatric patients with Acute Leukemias.

The 2-year survival for MDS was similar regardless of disease risk and donor type (figure 8). Patients with Chronic Myeloid Leukemia (CML) had a 2-year OS of 63% with a matched related donor, 51% with a mismatched related donor, and 60% with an unrelated donor (p=0.583) (figure 9). Patients with myelofibrosis had a survival of 63% in 2 years (figure 10). Donor type had no impact in children with aplastic anemia, which differed from adults, who had higher survival after HSCT from matched sibling donors (p=0.001) (figure 11).

Patients undergoing autologous HSCT to treat chemosensitive lymphomas had a significantly better 2-year OS than those with chemoresistant disease: 87% versus 77% in HD (p=0.073) and 76% versus 53% in NHL (p=0.001) (figure 12). The 2-year OS was 83% for patients with multiple myeloma (figure 13), and age at HSCT had no impact on the 2-year OS (figure 14).

DISCUSSION

This was a cross-sectional, register-based study which aimed to understand the Brazilian HSCT demographics and outcomes across 40 Brazilian centers over the past 10 years using the DBtC tool to retrieve the data reported to the CIBMTR from 2012 to 2022. Data from 10,107 transplants, of which 9,868 HSCT records had complete data for analysis, were extracted from the CIBMTR portal using this tool.

Our study, using the DBtC data, included more allogeneic than autologous transplants reported to the CIBMTR, but, according to the ABTO, there is a greater number of autologous HSCTs performed in the country. The reason for this difference is the larger number of affiliated centers in the CIBMTR performing allogeneic transplants. However, as more centers are increasingly affiliated over the years, more autologous rather than allogeneic transplants have already been reported since 2021.

We observed an increase in the number of transplants with mismatched related donors since 2012, along with a decrease in unrelated CB transplants during the same period, most likely due to the use of haploidentical donors with post-transplant cyclophosphamide to prevent graft-versus-host disease.

Comparing our data with those of the US Summary Slides published on the CIBMTR website[13], matched related donor HSCT is the main type of transplant performed in Brazil, while unrelated donor HSCT predominates in the US.

In pediatric patients, the main source was BM in Brazil, following the same trend in the US. In contrast, there has been an increase in PBSC use over the years, and this graft source has now been the choice for adult recipients since 2018 in Brazil - and since 2000 in the US - for all types of allogeneic HSCTs.

The HSCT indications are very similar between both countries: in Brazil, in 2022, the main indications for

HSCT were MM, AML, NHL, ALL, and HD, as compared to MM, AML, NHL, MDS/MPN and ALL in the US in 2020.

Another important comparison was the cause of early death 0 to 100 days after transplantation: in Brazil, the main cause of early mortality was infection for autologous, matched related donor, mismatched related and unrelated donor allogeneic HSCTs, while in the US, it was the primary disease for autologous and unrelated donor transplants and organ failure for matched and mismatched related donor HSCTs.

Comparing the 2-year OS in our study with the 3-year OS in the US Summary Slides, the Brazilian data are similar to the survival rates reported by US centers (table 6), despite the socioeconomic differences between these countries.

The Brazilian Summary Slides and further de-identified data are fully available to active centers in the HSCTBR through the SBTMO data request flow (figure 15).

CONCLUSIONS

The partnership between the SBTMO and the CIBMTR made the HSCTBR possible by use of the DBtC application. Data analysis on HSCTs performed across Brazilian centers, resulting in the Brazilian Summary Slides, contributes to a better understanding of HSCT outcomes, thereby rendering the results available to centers as a national and international benchmark. The Brazilian Summary Slides are updated twice a year and published on the SBTMO website. Despite the differences in the number of cases and follow-up time, the results in this study were similar to those presented in the US Summary Slides.

FUTURE PERSPECTIVES

The consolidation of the HSCTBR over the past few years has shown positive results, such as the increase in the number of Brazilian centers affiliated to the CIBMTR and the progressively higher qualification of DMs. However, there is still a lot to be done. A greater commitment of each HSCT center in the country ought to be made in order to improve transplant activity registry, including the regular reporting of long-term follow-up data, coupled with DM continuing education, thus fostering data quality improvement within our national registry. Government support (through resources, infrastructure, and qualification) is also essential to achieve these goals. Such tireless efforts will enable the consolidation of the HSCTBR, which, in the long run, will result in the provision of better care to our patients.

ACKNOWLEDGEMENTS

The accomplishment of this work was only possible thanks to the efforts of many invaluable professionals throughout Brazil's HSCT history: Dr. Ricardo Pasquini, one of the pioneers in HSCT in Latin America; SBTMO, for the support provided to Brazilian data managers, including several incentives, especially during the establishment of the Data Managers Working Group (GD-S-BTMO); Dr. Nelson Hamerschlak and Dr. Vergilio Antonio Rensi Colturato, both of whom have continuously encouraged these initiatives in the country since 2016; Dr. Marcelo Pasquini, who provides us with a direct contact with the CIBMTR and has brought and kept on bringing updates and teachings from the research records; Monique Ammi, who has always been active in the Brazilian centers' affiliation process and promptly answered hundreds of questions in Portuguese, directing them to the right person when she could not help, also contributing to DM education and support; HSCT multidisciplinary teams across the country, all of which directly or indirectly enable the continuing development of this work; All the patients who underwent this treatment modality and contribute to scientific research by making their data available.

TABLE 1. Exclusion criteria for overall survival

Total	**9,868**
Exclusion criteria	**n**
Patients without follow-up update	1,656
Error in survival time	59
≥2nd HSCT	817
Complete data	**7,333**

TABLE 2. HSCT centers

Participants Centers
A.C. Camargo Cancer Center
Albert Einstein Hospital
Associação Hospitalar Moinhos de Vento
Bio Sana's Serviços Médicos
Bio Sana's São Camilo
Centro De Pesquisa Clinica Hospital 9 De Julho
Centro de Pesquisas Oncológicas Dr. Alfredo Daura Jorge (CEPON)
Complexo Hospitalar de Niterói
CTMO-HCFMUSP
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Fundação Pio XII - Hospital de Câncer de Barretos
Hospital Amaral Carvalho
Hospital das Clínicas - Faculdade de Medicina de Botucatu, UNESP
Hospital de Clínicas - UFPR
Hospital de Clínicas de Porto Alegre
Hospital Erasto Gaertner
Hospital Leforte Liberdade
Hospital Mãe de Deus
Hospital Monte Sinai
Hospital Nossa Senhora das Graças - IP
Hospital Pequeno Príncipe
Hospital Samaritano
Hospital São Camilo - Mooca
Hospital São Camilo - Pompéia
Hospital São Camilo - Santana
Hospital Sírio Libanês
Hospital Universitário Clementino Fraga Filho, Univ. Fed. RJ
Hospital Universitario da Universidade Federal de Juiz de Fora
Hospital Universitário Walter Cantídio/UFC
Instituto da Criança - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (ITACI)
Instituto de Cardiologia do Distrito Federal - Unidade de TMO Pietro Albuquerque
Instituto de Oncologia Pediátrica - GRAACC
Instituto Nacional de Câncer
Natal Hospital Center
Real e Benemérita Sociedade de Beneficiência Portuguesa de São Paulo
Real Hospital Português
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UFMG Hospital das Clínicas Servico de Transplante de Medula Óssea
UNICAMP - Hemocentro
Universidade Federal de São Paulo - Hospital São Paulo

TABLE 3. Source of cells used by donor type, age and year of HSCT

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Patients <18 Years											
Matched Related Donor (N=417)											
PBSC	2%	4%	2%	3%	9%	5%	6%	8%	3%	14%	15%
BM	93%	88%	96%	94%	91%	93%	88%	90%	97%	86%	82%
CB	5%	8%	2%	3%	0%	2%	6%	2%	0%	0%	3%
Unrelated Donor (N=735)											
PBSC	5%	3%	16%	12%	7%	7%	12%	4%	25%	28%	32%
BM	55%	74%	78%	75%	85%	87%	80%	88%	72%	58%	64%
CB	40%	23%	6%	12%	7%	6%	8%	8%	3%	14%	4%
Mismatch Related Donor (N=602)											
PBSC	24%	10%	27%	14%	25%	21%	34%	25%	24%	24%	24%
BM	76%	90%	73%	86%	75%	79%	66%	75%	76%	76%	76%
Patients ≥18 Years											
Matched Related Donor (N=1,812)											
PBSC	49%	47%	43%	51%	46%	52%	53%	56%	65%	65%	72%
BM	51%	53%	57%	49%	54%	48%	47%	44%	35%	35%	28%
CB	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Unrelated Donor (N=862)											
PBSC	40%	31%	39%	52%	51%	47%	58%	55%	59%	82%	75%
BM	43%	62%	61%	45%	49%	53%	42%	44%	37%	18%	25%
CB	17%	7%	0%	3%	0%	0%	0%	1%	4%	0%	0%
Mismatch Related Donor (N=986)											
PBSC	18%	33%	40%	34%	40%	44%	62%	66%	73%	75%	80%
BM	82%	67%	60%	66%	60%	56%	38%	34%	27%	25%	20%

TABLE 4. Acute Leukemia by disease stage, donor type and HSCT year

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
AML											
Disease Stage											
1st complete remission	36%	45%	48%	45%	59%	51%	54%	55%	52%	53%	57%
2nd or subsequent complete remission	36%	27%	38%	40%	31%	30%	27%	25%	30%	21%	25%
Relapsed disease/Never in CR	28%	27%	14%	15%	10%	19%	19%	20%	17%	26%	18%
Donor Type											
Matched Related Donor	51%	57%	68%	48%	50%	50%	44%	43%	44%	35%	38%
Mismatch Related Donor	16%	6%	8%	17%	23%	24%	33%	33%	41%	49%	45%
Unrelated Donor (BM/PBSC)	28%	27%	20%	33%	27%	26%	22%	25%	15%	15%	17%
Unrelated Donor (CB)	5%	9%	4%	1%	0%	0%	1%	0%	0%	1%	0%
ALL											
Disease Stage											
1st complete remission	45%	41%	54%	58%	52%	41%	52%	39%	42%	44%	51%
2nd or subsequent complete remission	50%	53%	39%	40%	39%	51%	34%	48%	49%	45%	36%
Relapsed disease/Never in CR	5%	6%	8%	2%	9%	8%	15%	13%	9%	11%	12%
Donor Type											
Matched Related Donor	45%	53%	51%	43%	40%	36%	39%	31%	33%	28%	27%
Mismatch Related Donor	7%	3%	3%	8%	16%	25%	25%	29%	40%	50%	51%
Unrelated Donor (BM/PBSC)	31%	35%	45%	43%	42%	38%	34%	35%	25%	21%	22%
Unrelated Donor (CB)	17%	9%	1%	6%	1%	1%	2%	5%	1%	1%	0%

TABLE 5. Overall survival of AML/ALL patients

	N	OS in 2 years (%)	p
AML			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	74	47.9% (35.1-59.6)	
Mismatch Related Donor	73	60.2% (44.8-72.6)	0.269
Unrelated Donor	75	58.3% (45.5.69.0)	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	506	54.9% (49.9-59.5)	
Mismatch Related Donor	271	48.4% (41.0-55.4)	0.192
Unrelated Donor	224	54.1% (46.6-61.0	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	35	56.5% (37.6-71.7)	
2nd or subsequent complete remission	23	48.7% (26.7-67.6)	0.484
Relapsed disease/Never in CR	16	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	344	63.8% (57.9-69.1)	
2nd or subsequent complete remission	94	38.0% (26.6-49.4)	<0.001
Relapsed disease/Never in CR	68	31.2% (19.4-43.8)	
Mismatched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	25	77.4% (53.9-90.0)	
2nd or subsequent complete remission	34	64.7% (41.2-80.8)	0.406
Relapsed disease/Never in CR	14	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	155	57.1% (47.1-65.9)	
2nd or subsequent complete remission	70	46.3% (31.9-59.6)	<0.001
Relapsed disease/Never in CR	46	19.7% (7.4-36.2)	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	32	78.1% (57.1-89.7)	
2nd or subsequent complete remission	27	57.4% (36.1-73.9)	0.036
Relapsed disease/Never in CR	16	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	92	67.5% (55.3-77.1)	
2nd or subsequent complete remission	87	55.7% (43.8-66.1)	<0.001
Relapsed disease/Never in CR	45	22.6% (10.3-37.8)	

B. ALL

	N	OS in 2 years (%)	p
ALL			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	119	57.9% (47.3-67.2)	
Mismatch Related Donor	122	47.9% (35.7-59.1)	0.293
Unrelated Donor	232	60.8% (53.6-67.2)	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	260	55.8% (49.3-61.8)	
Mismatch Related Donor	110	50.4% (40.7-59.3)	0.006
Unrelated Donor	143	43.6% (35.1-51.7)	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	37	67.7% (48.8-80.9)	
2nd or subsequent complete remission	65	52.4% (38.0-64.9)	0.349
Relapsed disease/Never in CR	17	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	225	63.6% (56.3-70.1)	
2nd or subsequent complete remission	64	32.4% (20.1-45.3)	<0.001
Relapsed disease/Never in CR	13	-	
Mismatched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	24	76.0% (50.8-89.5)	
2nd or subsequent complete remission	86	45.0% (31.1-57.9)	0.128
Relapsed disease/Never in CR	12	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	97	58.4% (46.2-68.8)	
2nd or subsequent complete remission	50	41.9% (25.8-57.1)	0.074
Relapsed disease/Never in CR	8	-	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	68	72.0% (57.8-81.8)	
2nd or subsequent complete remission	141	57.8% (48.7-65.9)	0.033
Relapsed disease/Never in CR	23	41.7% (15.6-66.2)	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	101	47.3% (35.8-57.9)	
2nd or subsequent complete remission	54	44.1% (29.8-57.4)	0.478
Relapsed disease/Never in CR	14	-	

TABLE 6. Comparison overall survival – Brazil and USA

A. Acute leukemia

	Brazilian Registry (2012-2022)		US Summary Slides (2009-2019)	
	N	OS in 2 years (%)	N	OS in 3 years (%)
AML				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	35	56.5% (37.6-71.7)	391	69% (65-74)
2nd or subsequent complete remission	23	48.7% (26.7-67.6)	133	68% (60-77)
Relapsed disease/Never in CR	16	-	75	30% (21-43)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	344	63.8% (57.9-69.1)	5,317	58% (57-60)
2nd or subsequent complete remission	94	38.0% (26.6-49.4)	1,226	54% (51-57)
Relapsed disease/Never in CR	68	31.2% (19.4-43.8)	1,721	31% (29-33)
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	32	78.1% (57.1-89.7)	368	66% (61-71)
2nd or subsequent complete remission	27	57.4% (36.1-73.9)	212	64% (57-71)
Relapsed disease/Never in CR	16	-	118	34% (26-44)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	92	67.5% (55.3-77.1)	7,441	56% (55-57)
2nd or subsequent complete remission	87	55.7% (43.8-66.1)	1,940	54% (52-57)
Relapsed disease/Never in CR	45	22.6% (10.3-37.8)	2,463	31% (30-33)
Mismatched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	25	77.4% (53.9-90.0)	172	63% (56-72)
2nd or subsequent complete remission	34	64.7% (41.2-80.8)	99	61% (51-73)
Relapsed disease/Never in CR	14	-	71	37% (27-50)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	155	57.1% (47.1-65.9)	1,977	53% (50-55)
2nd or subsequent complete remission	70	46.3% (31.9-59.6)	572	55% (51-60)
Relapsed disease/Never in CR	46	19.7% (7.4-36.2)	706	28% (25-32)
ALL				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	37	67.7% (48.8-80.9)	317	79% (74-84)
2nd or subsequent complete remission	65	52.4% (38.0-64.9)	464	70% (66-74)
Relapsed disease/Never in CR	17	-	38	57% (43-76)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	225	63.6% (56.3-70.1)	2,302	64% (62-66)
2nd or subsequent complete remission	64	32.4% (20.1-45.3)	640	45% (41-49)
Relapsed disease/Never in CR	13	-	249	37% (31-44)
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	68	72.0% (57.8-81.8)	312	80% (75-84)
2nd or subsequent complete remission	141	57.8% (48.7-65.9)	421	64% (60-69)
Relapsed disease/Never in CR	23	41.7% (15.6-66.2)	40	68% (54-84)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	101	47.3% (35.8-57.9)	2,425	64% (62-66)
2nd or subsequent complete remission	54	44.1% (29.8-57.4)	765	46% (43-50)
Relapsed disease/Never in CR	14	-	253	36% (30-42)
Mismatched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	24	76.0% (50.8-89.5)	137	75% (67-83)
2nd or subsequent complete remission	86	45.0% (31.1-57.9)	233	63% (57-70)
Relapsed disease/Never in CR	12	-	23	28% (14-57)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	97	58.4% (46.2-68.8)	771	69% (65-73)
2nd or subsequent complete remission	50	41.9% (25.8-57.1)	344	47% (42-54)
Relapsed disease/Never in CR	8	-	99	28% (20-39)

B. MDS and Aplastic Anemia

	Brazilian Registry (2012-2022)		US Summary Slides (2009-2019)	
	N	OS in 2 years (%)	N	OS in 3 years (%)
MDS (Adults)				
Matched Related Donor				
Disease Stage				
Low risk	99	56.4% (45.3-66.1)	677	52% (48-56)
High risk	96	56.7% (45.2-66.7)	1,693	46% (44-49)
Unrelated Donor				
Disease Stage				
Low risk	52	51.8% (35.2-66.1)	1,133	49% (46-52)
High risk	46	43.4% (27.7-58.0)	2,997	46% (44-48)
Aplastic Anemia				
Patients Age 0-17 Years				
Donor type				
Matched Related Donor	59	83.8% (71.1-91.3)	504	98% (96-99)
Mismatched Related Donor	61	73.6% (58.8-83.7)	110	86% (80-93)
Unrelated Donor	70	80.7% (69.0-88.3)	337	90% (95-99)
Patients Age ≥18 Years				
Donor type				
Matched Related Donor	147	83.8% (76.6-88.9)	625	84% (81-87)
Mismatched Related Donor	46	70.8% (55.0-82.0)	177	80% (74-86)
Unrelated Donor	77	56.5% (44.0-67.2)	581	77% (74-81)

FIGURE 1. Brazilian active centers in the CIBMTR by year

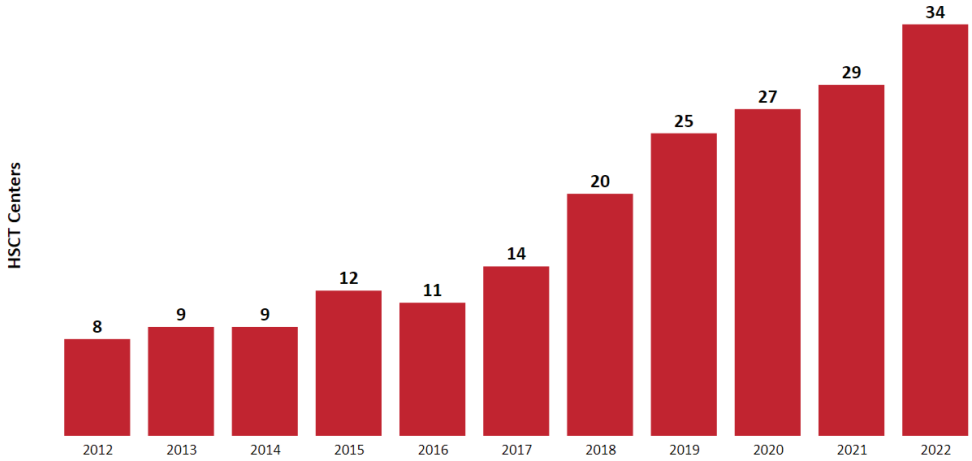


FIGURE 2. Transplants performed in Brazil and reported in the CIBMTR

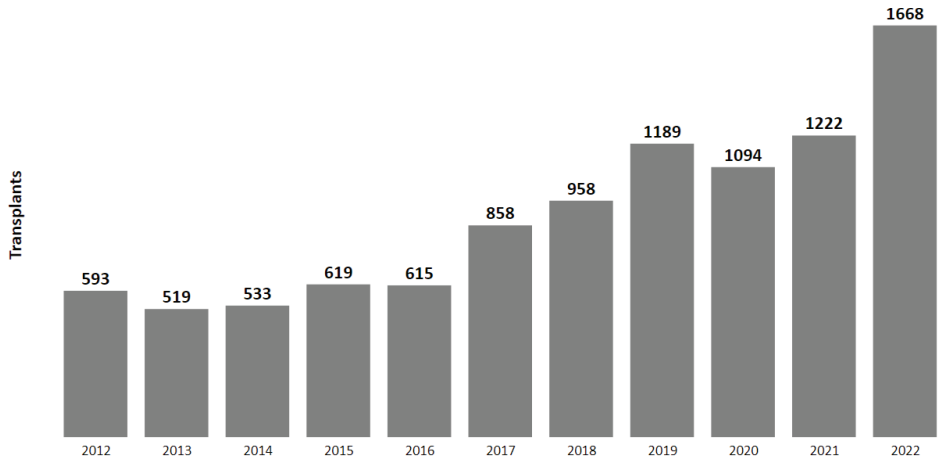


FIGURE 3. Relative proportion of allogeneic HSCT in Brazil by donor type

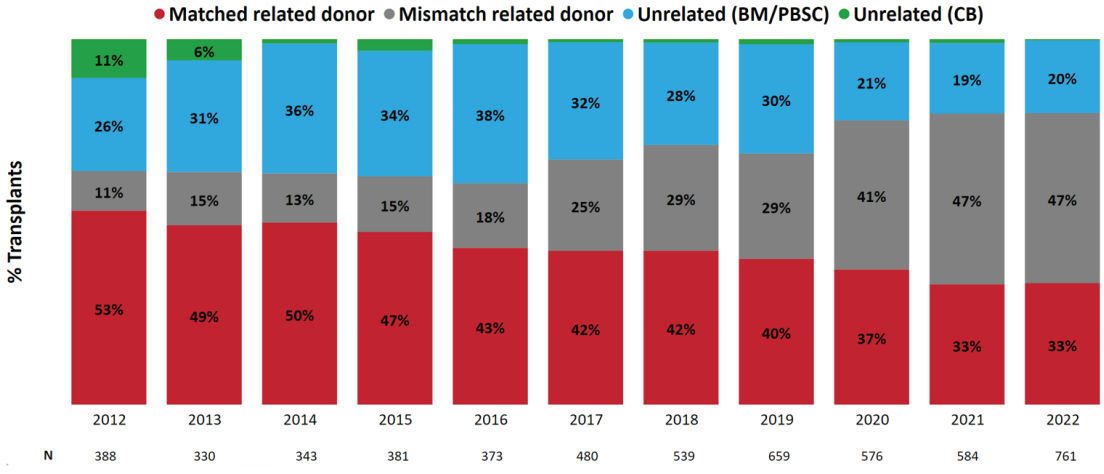


FIGURE 4. **Global indications for HSCT in Brazil, 2022 (n=1,668)**

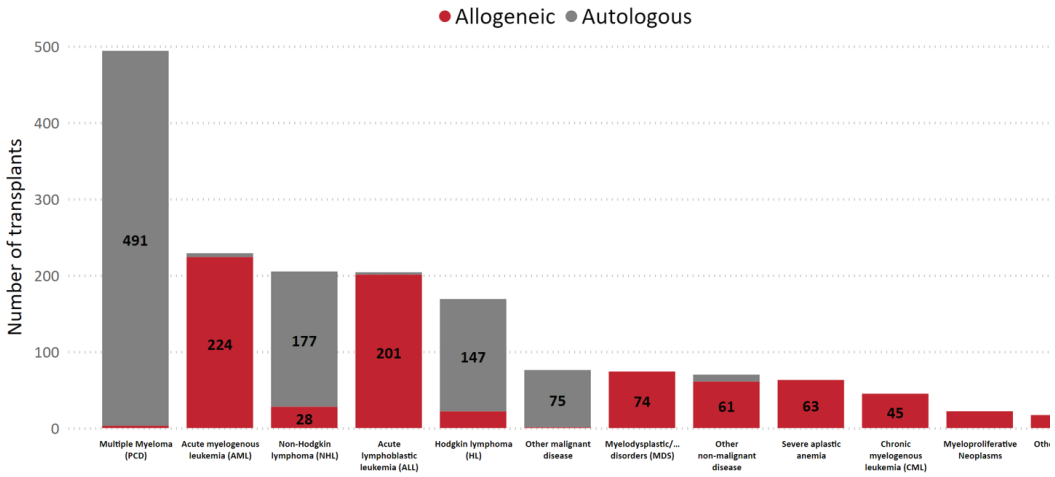


FIGURE 5. **AML, overall survival after 1st allogeneic HSCT by donor type**

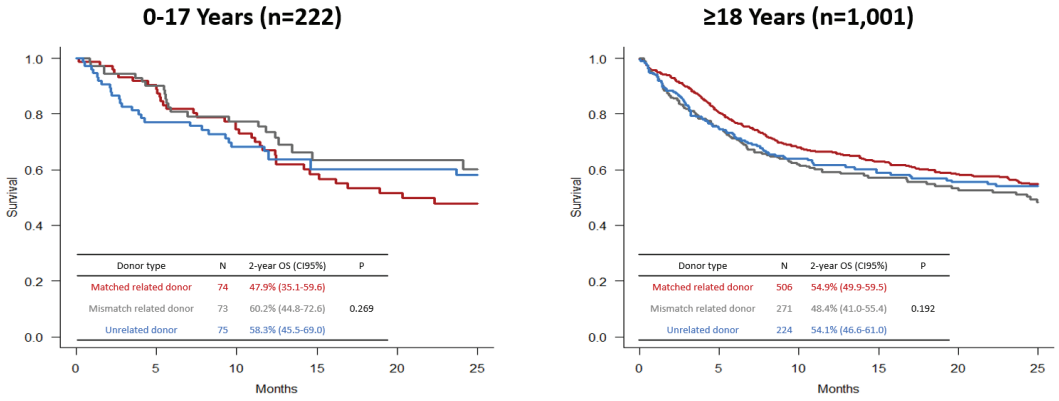


FIGURE 6. **ALL, overall survival after 1st allogeneic HSCT by donor type**

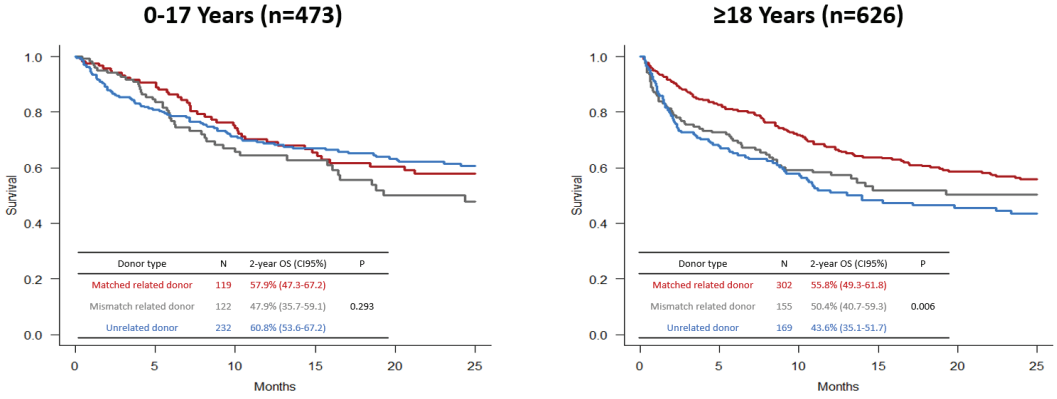


FIGURE 7. **MDS, overall survival after 1st allogeneic HSCT by donor type**

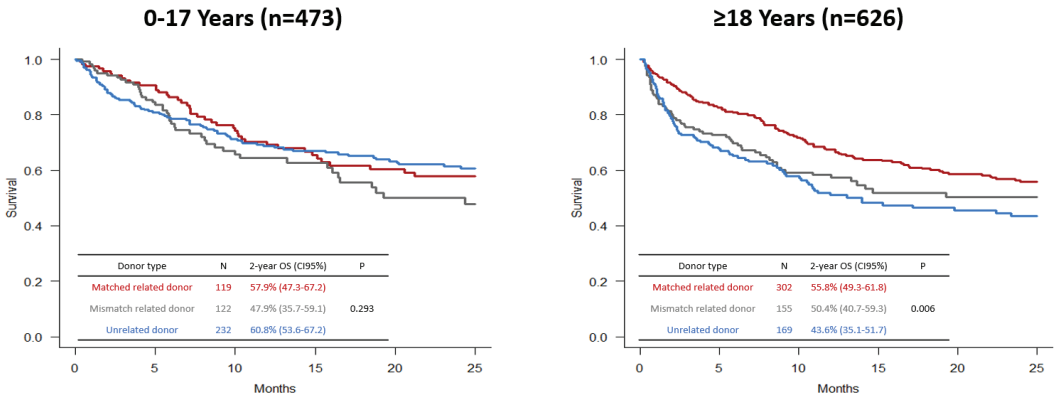


FIGURE 8. **MDS, overall survival after 1st allogeneic HSCT by disease stage**

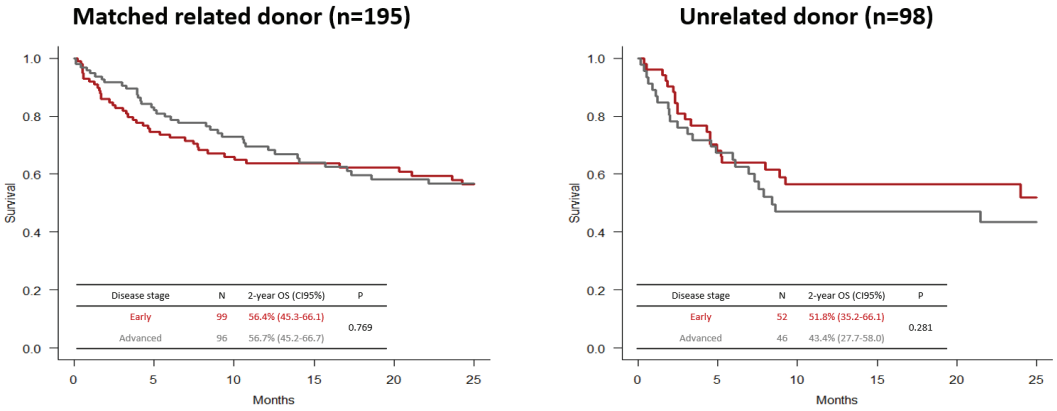


FIGURE 9. **CML, overall survival after 1st allogeneic HSCT by donor type**

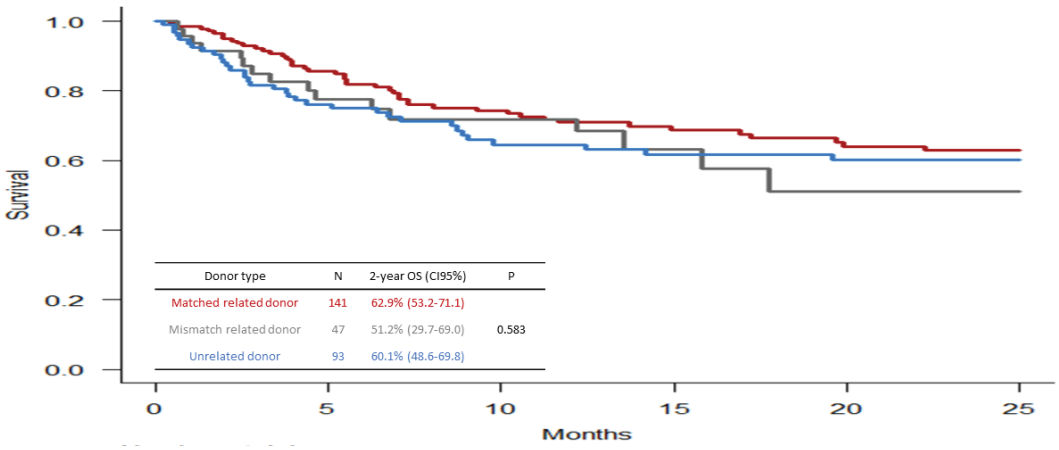


FIGURE 10. **Myelofibrosis, overall survival after 1st allogeneic HSCT**

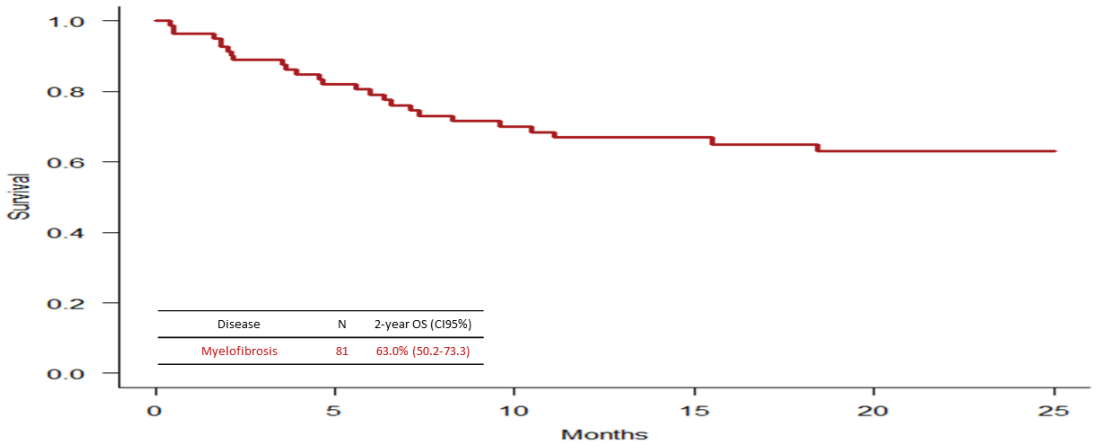


FIGURE 11. **Aplastic Anemia, overall survival after 1st allogeneic HSCT by donor type**

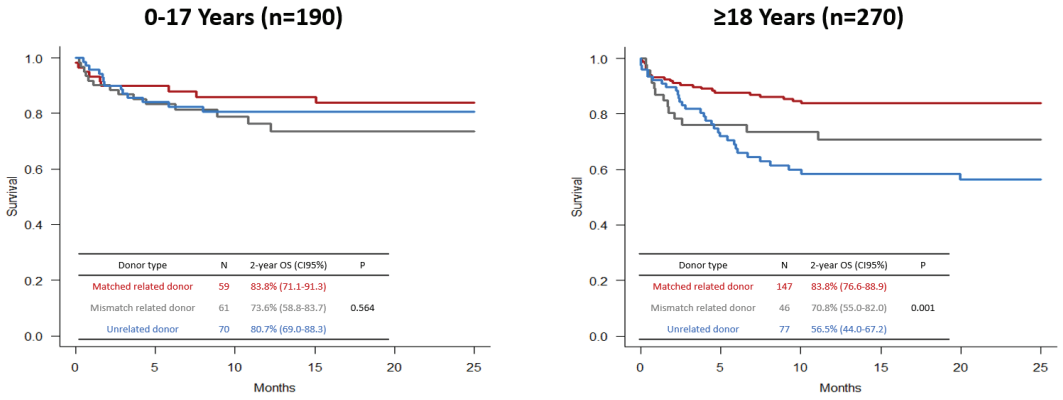


FIGURE 12. **Lymphomas, overall survival after 1st autologous HSCT**

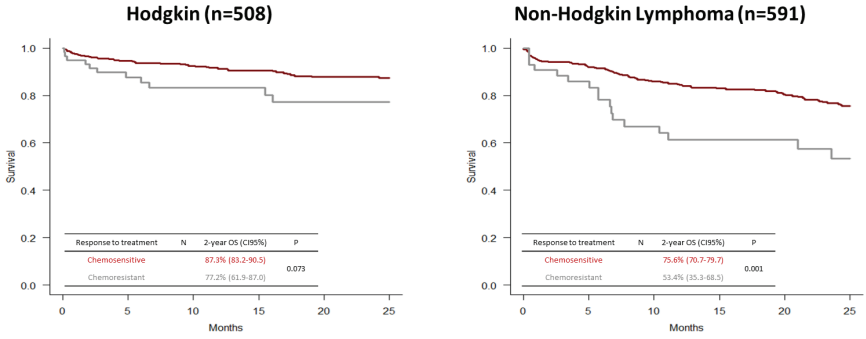


FIGURE 13. **Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HSCT**

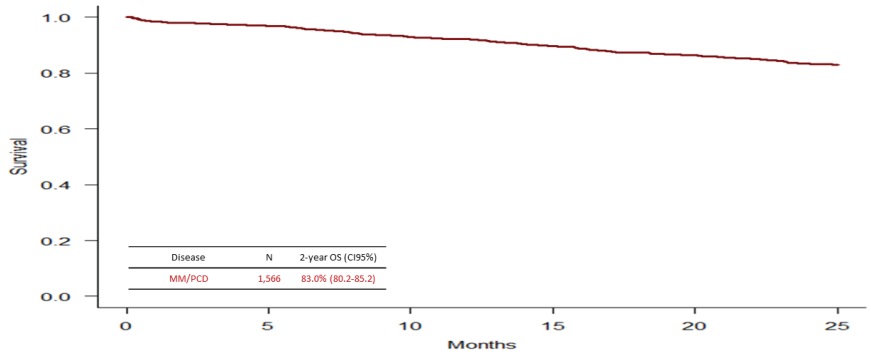


FIGURE 14. **Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HSCT by age at HSCTautologous HSCT**

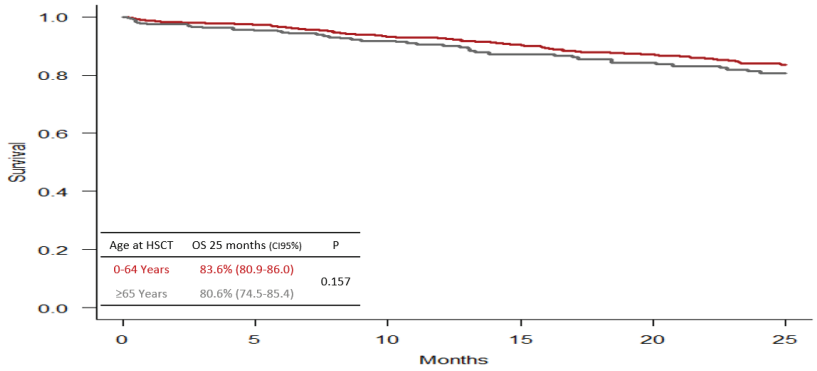
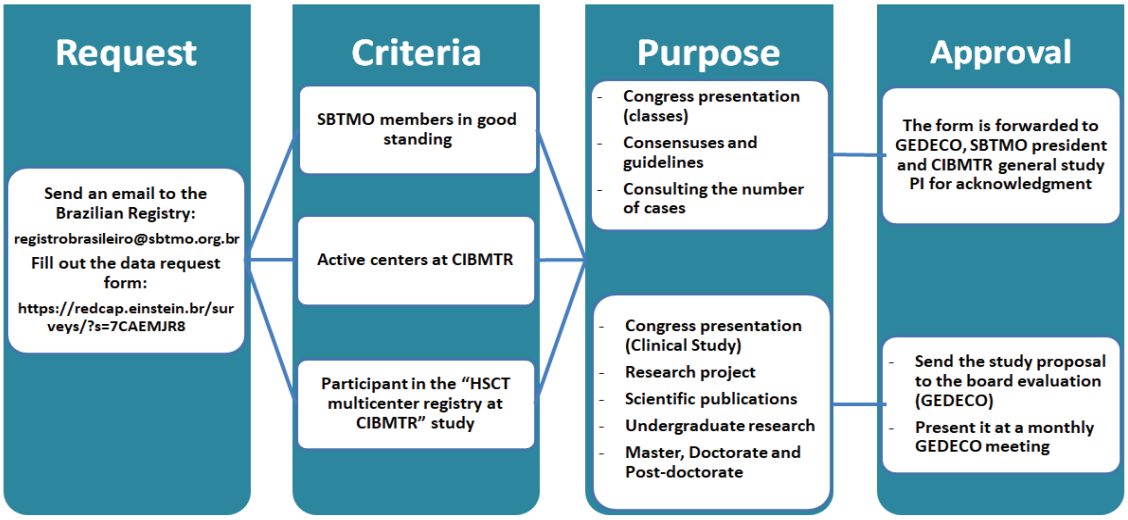


FIGURE 15. **Data request flow**



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DOI: 10.46765/2675-374X.2023V4N2P185

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMA IN BRAZIL: REAL-LIFE DATA

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Received: 05 Dec 2022 • Revised: 16 May 2023 • Accepted: 24 May 2023.

Following the creation of a working group between the CIBMTR, Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO), Bone Marrow Association (AMEO) and *Data Managers Working Group* (GTGD), the Brazilian Bone Marrow Transplantation Registry (RBTMO) was stablished based on cooperation models already used by the CIBMTR with other countries, such as Canada and Japan. Due to this effort, the regular functioning of the RBTMO has currently allowed Brazilian hematopoietic stem cell transplantation (HSCT) centers to report and benchmark their data for specific purposes such as the current report on non-Hodgkin lymphoma (NHL)[1].

NHL represents the second most frequent indication of HSCT in the United States[2]. In Brazil, according to RBTMO data, NHL is the fourth most transplanted disease, which probably demonstrates a characteristic of the Brazilian registry that has only recently received information from centers with a greater volume of autologous HSCT compared to allogeneic ones.

Patients without complete data in the registry were excluded from this study. A total of 778 autologous (n= 616) and allogeneic (n=68) HSCT recipients for NHL were reported to the CIBMTR and now included in the RBTMO between 2008 and 2020. The numbers of HSCT reported for NHL has increased significantly since 2017. The median age of the entire cohort was 51 years (3-76 years) to autologous HSCT and 46 years (4-47 years) to allogeneic HSCT and most were male. Diffuse large B-cell lymphoma (*DLBCL*), not otherwise specified (NOS) was the most common diagnosis for recipients of autologous HSCT, while T-cell NHL were frequent diagnosis for the allogeneic HSCT group, although it compounds a very heterogeneous group, encompassing several subtypes of mature T cell neoplasms[3].

The most frequent conditioning regiment for the autologous group was BEAM (Carmustine, etoposide, cytarabine and melphalan), while fludarabine-based regimens was the main regimen for the allogeneic HSCT. The OS for patients undergoing allogeneic HSCT was 54% at 2 years, donor type had no impact on OS rates for allogeneic HSCT, but CR was also important, with 65.3% of OS in 2 years, with a trend to longer survival (p= 0.057).

For patients transplanted for DLBCL NOS, the 2-year OS was 70.3% after autologous HSCT, and the 3-year OS of 68 ± 1% reported by the CIBMTR for North American patients[2]. The 2-year OS after allogeneic HSCT for this histological subtype was 48.6% which appears comparable to the 46% ± 2% reported by the CIBMTR.

Mantle cell lymphoma (MCL) was the second mostly common NHL subtype transplanted, since autologous HSCT is part of first-line therapy for this subtype of NHL[4]. The 2-year OS was 85.2% for 114 patients who underwent autologous HSCT for this subtype, a very similar result to that reported by the CIBMTR, 83% ± 1% in 3 years[2]. Only 10 patients were evaluated for OS rate after allogeneic HSCT in MCL, which was 65.6%, a value that may be overestimated due to the small number of cases.

Follicular lymphoma (FL), which represents second most prevalent subtype in our country, was the third most common indication for HSCT for B-cell NHL[4]. In the autologous HSCT, the 2-year OS of RBTMO data was 83.1% in the 2008 to 2020 period, comparing to 84% ± 2% of 3-year OS of CIBMTR reported from between 2016 to 2018[2]. Once again, allogeneic HSCT had its analysis hampered by the small number of cases.

Peripheral T-cell lymphomas (*PTCL*) is a rare subtype of NHL, equivalent only to 4% of NHL in our environment[4]. Among autologous HSCT for PTCL, OS was superior to the literature[(5)], probably due to a selection bias in patients' arrival for autologous HSCT and also because we included ALK+ anaplastic lymphomas, which are often excluded from the analysis. Allogeneic HSCT is more important in peripheral T-cell lymphomas (*PTCL*), which was the group most frequently submitted to this type of transplant, with 51.1% OS in 2 years, similar to international literature[6].

This report while initial and small, demonstrates similar overall survival rates for patients treated with autologous or allogeneic HSCT for NHL in Brazil are similar to those reported by other international large centers and by the CIBMTR. Moreover, it shows the value of collaboration with centers with a longer tradition in reporting HSCT data, such as those in the USA and Europe, are capable of foster the beginning of a similar work, in other countries like Brazil.

TABLE 1: Characteristics of patients with NHL submitted to first autologous HSCT and overall survival according to histological subtypes and remission status at transplant

Characteristic	**n/%**	**2-years OS** (p value)	
Total No. of patenits	616	-	
Age, years, median (range)	51 (3-76)	-	
Sex, n/%			
Male	370/60	-	
Female	246/40	-	
NHL histological subtype, n/%*			
DLBCL	161/36.6	70.3	
MCL	114/25	85.2	
FL	45/10.2	83.1	
PTCL	64/14.5	73.7	
Complete remission at transplant, n/%*			
Yes	288/65.4	82.3	(<.001)
No	151/34.6	62.5	

* 440 patients with complete data

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DOI: 10.46765/2675-374X.2023V4N2P192

CARDIOTOXICITY AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT): LONGITUDINAL AND OBSERVATIONAL STUDY

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Received: 21 Dec 2022 • Revised: 16 May 2023 • Accepted: 24 May 2023.

ABSTRACT

Objectives: To assess incidence and extent of early cardiotoxicity after autologous hematopoietic stem cell transplantation (AHSCT). **Methods**: Study carried out in two bone marrow transplant centers, in public and private hospital, located in interior of Minas Gerais, Brazil. All patients who underwent AHSCT at centers between March 2018 and May 2019 and October 2019 were included. Altered results were classified according to Brazilian Cardio-Oncology Guidelines. **Results**: Of the 36 patients evaluated, seven (21.2%) had cardiotoxicity on echocardiography, with mean left ventricular ejection fraction decreasing from 71.53 to 64.75% before and after conditioning (p = 0.00013). Clinical cardiovascular alterations were associated with advanced staging and time of more than one year between diagnosis and AHSCT (p=0.01 in both cases). Specific clinical signs of congestion were correlated with radiotherapy to the mediastinum and a dose >400 mg of doxorubicin before AHSCT (p=0.02 and p=0.01, respectively). **Conclusions**: Thus, higher incidence of cardiac injury was observed after AHSCT, which was related to type of pre-transplant therapy. This fact reflects our limitations and leads us to seek improvements in cardiovascular assessment of patients undergoing AHSCT, in order to reduce morbidity and mortality associated with myocardial injuries in these patients.

Keywords: Cardiotoxicity. Risk factors. Hematopoietic Stem Cell Transplantation.

INTRODUCTION

We are currently experiencing longer survival of cancer patients, which is due to advances in cancer therapy and adequate clinical support for patients[1]. Despite this, complications still occur, especially in post-HSCT patients due to intensive chemotherapy[2], such as high-dose cyclophosphamide and total body irradiation, in addition to pre-HSCT therapeutic exposure, which often includes anthracyclines, alkylating agents, and cardiac radiotherapy[3,4,5]. Other risk factors for cardiac damage independent of cancer therapy include advanced age, smoking, systemic arterial hypertension (SAH), and obesity[4].

Congestive heart failure (CHF) is one of the most serious and common adverse effects following chemotherapy and may occur in the immediate post-transplant period or months later[6]. High rates of morbidity and mortality associated with this complication have been described and may even lead to the need to interrupt treatment and compromise proper disease control[6,7].

Considering that the detection of cardiovascular risk in the subclinical phase is necessary to prevent morbidity and mortality in these patients, our study aimed to evaluate the incidence and extent of cardiotoxicity in the early phase after AHSCT with echocardiographic examination and troponin I (TnI) determination. We focused on detecting clinical signs of cardiotoxicity during hospitalization and associated these signs with prior cardiovascular risk factors unrelated to chemotherapy.

MATERIAL AND METHODS

After ethics and research committee approval and patient consent to participate in the study, all patients who underwent AHSCT at two bone marrow transplant centers from March 2018 to May 2019 and October 2019 were included and evaluated. Patients with insufficient information were excluded.

Echocardiograms (Echo) were performed using the one-dimensional method corrected by the Teicholz formula, using the two-dimensional technique before the start of conditioning chemotherapy and thirty to sixty days after chemotherapy. For the definition of cardiotoxicity, a reduction in left ventricular ejection fraction (LVEF) of more than 10% was considered according to the criteria of Brazilian Guidelines on Cardio-Oncology, described below[7]:

- **Grade I:** asymptomatic reduction of LVEF between 10% and 20%.
- **Grade II:** LVEF reduction greater than 20% or below normal (LVEF: 50%).
- **Grade III:** symptomatic heart failure

Laboratory dosing of TnI was performed before conditioning chemotherapy, during the period of neutropenia (neutrophils less than 500 mm^3) and 30 days after the conditioning protocol. An increase in TnI levels above the normal range was considered a sign of cardiotoxicity. The methods used to detect TnI were immunochromatography and chemiluminescence.

To analyze the deterioration of cardiac output based on LVEF in echocardiography, the Shapiro-Wilk test was used to test normality, followed by the non-parametric Wilcoxon test and the parametric Paired T-test.

To describe the profile of the sample, frequency tables were constructed and the Fisher's test was used to assess the association between the risk factor variables and the outcome. Outcome variables included the difference between LVEF before and after AHSCT, arterial hypertension, hypotension, signs of congestion, and clinical changes in the cardiovascular system after AHSCT.

Correlation analysis was performed between the presence of grade I and II cardiotoxicity on the echocardiogram and changes on physical examination suggestive of cardiac congestion and several risk factors independent of or related to cancer therapy, including: age, obesity, smoking, concomitant cardiovascular disease, cancer diagnosis, advanced staging, previous chemotherapy with cyclophosphamide and doxorubicin, mediastinal radiotherapy, lack of complete response before AHSCT, cardiovascular complications during cancer treatment, mobilization for stem cell collection with cyclophosphamide, cellularity of progenitor cells with CD34 labeling, time between diagnosis and AHSCT, and conditioning protocol for AHSCT with high-dose cyclophosphamide.

R Core Team software (2018) was used for statistical analysis, assuming a significance level of 5% ($p \leq 0.05$).

RESULTS

Thirty-six patients who underwent AHSCT during the study period were evaluated. The mean age was 49.9 years (23 - 69 years), and most patients were female (52.7%). Some clinical characteristics of the disease and treatment are described in Table 1.

On physical examination during hospitalization for AHSCT, clinical changes related to the cardiovascular system, such as tachycardia, hypertension, hypotension, edema, and lung sounds, occurred in 86% (n = 31) of patients after conditioning chemotherapy. Thirty-one percent (n = 11) of patients had more specific signs of congestion.

A significant association was found between cardiovascular changes with advanced staging and time between diagnosis and transplantation ($p = 0.01$ and $p = 0.01$, respectively). There was a trend toward greater development of clinical changes in the cardiovascular system in patients who underwent chemotherapy protocols containing anthracyclines and/or alkylating agents prior to AHSCT ($p = 0.08$).

The clinical changes more specifically related to signs of congestion, such as third heart sound, progressive lower limb edema, pulmonary crackles and jugular turgence, showed a significant correlation with radiotherapy in an area involving the heart ($p = 0.02$) and use of doxorubicin in a dose greater than 400mg pre-AHSCT ($p = 0.01$).

Thirty-three patients underwent echo before and 30 to 60 days after AHSCT, of whom 7 (21.2%) had cardiotoxicity on examination, 4 with grade I cardiotoxicity and 3 with grade II. The corrected LVEF values observed in echocardiogram examinations before AHSCT and 30 to 60 days after this treatment were recorded and the difference between these values was then calculated. At the second examination, there was a decrease, maintenance, or increase in LVEF compared with the first examination, and the 10 patients who had an increase in LVEF were excluded from the analysis. A significant difference between the mean echo values before and after conditioning was detected by the paired t-test ($p = 0.00013$) under the normality assumption, with 71.53±6.67% and 64.75±7.65% for the echo values before and after conditioning, respectively (Figure 1).

Twenty-one patients (56.7%) underwent TnI examination before AHSCT, at nadir time after conditioning chemotherapy and 30 days after treatment. Of these, only one patient had an abnormality on examination at the time of neutropenia associated with high-grade atrial fibrillation with hemodynamic instability, and one patient had a positive test 30 days after transplantation. Neither event was associated with early change in LVEF on echo after AHSCT.

DISCUSSION

The cardiotoxicity of chemotherapeutic agents has gained importance as these treatments improve survival in cancer patients. Cardiovascular symptoms associated with alkylating agents usually occur within the first week and month of therapy[9,10]. In accordance to the literature, we found signs of early cardiotoxicity, approximately 4 to 6 weeks after AHSCT[9].

Regarding clinical findings of cardiotoxicity, we found more signs of congestion in patients who had taken doxorubicin at a dose greater than 400 mg prior to AHSCT ($p = 0.01$) and also in those who had undergone radiotherapy to an area that included the heart ($p = 0.02$). Advanced staging and a time between diagnosis and AHSCT of more than 1 year also showed a correlation with clinical signs related to the cardiovascular system ($p = 0.01$ and $p = 0.01$, respectively), probably because these patients received a greater number of cycles and lines of therapy and consequently a higher dose of treatment with cardiotoxic potential.

Although it has been described that atrial fibrillation can be caused by the use of melphalan,[11] we believe that this was not the only reason for the arrhythmia in the only patient in our series who had such an arrhythmia, since it occurred after a stem cell infusion in which dimethyl sulfoxide (DMSO) was used as a cryopreservative, which also has arrhythmogenic potential.

Echocardiography and troponin measurement are methods that can help detect cardiotoxicity in AHSCT[12]. Chung et al.[9] studied 39 patients undergoing AHSCT and observed a decrease in LVEF in 31% (n=10) of them, a value very similar to our study, in which signs of cardiotoxicity, assessed by echo, were found in 21.2% (n=7) of the sample of 36 patients. A tendency to cardiotoxicity was observed in patients who had received chemotherapy with anthracyclines or alkylating agents prior to AHSCT (p=0.09), which has also been demonstrated in previous studies[1,11].

Similar to Morandi et al., we did not find an association between the use of high-dose alkylating agents used in AHSCT and cardiac dysfunction, in contrast to studies from the 1970s and 1980s in which combined therapy regimens with cyclophosphamide resulted in an incidence of up to 43% cardiotoxicity, which was due to the use of high-dose cyclophosphamide (up to 7 g/m^2) in a non-fractionated administration regimen[11].

All patients who had grade II toxicity in echo (n=3) underwent AHSCT more than 1 year after diagnosis. This indicates that the likelihood of cardiotoxicity is related to the greater number of prior therapies (p=0.06), consistent with the literature in which left ventricular dysfunction has been associated with three or more lines of chemotherapy prior to AHSCT[13].

Chung et al. demonstrated a reduction in mean LVEF from 62% at baseline to 55% at 6 weeks after conditioning chemotherapy and transplantation,[9] which is very similar to our results regarding reduction in LVEF.

Of the 21 patients who underwent TnI testing, only two showed changes in test results within 30 days of high-dose chemotherapy. This is likely due to the lack of standardization of diagnostic tests and better determination between monitoring intervals, which is not yet well defined in the literature[8].

The occurrence of cardiotoxicity does not appear to be related to high-dose conditioning chemotherapy but rather to therapeutic exposure prior to AHSCT, with exposure to anthracyclines and alkylating agents being independent risk factors for CHF.

Therefore, identification of patients at increased cardiovascular risk through surveillance measures allows implementation of early treatment.

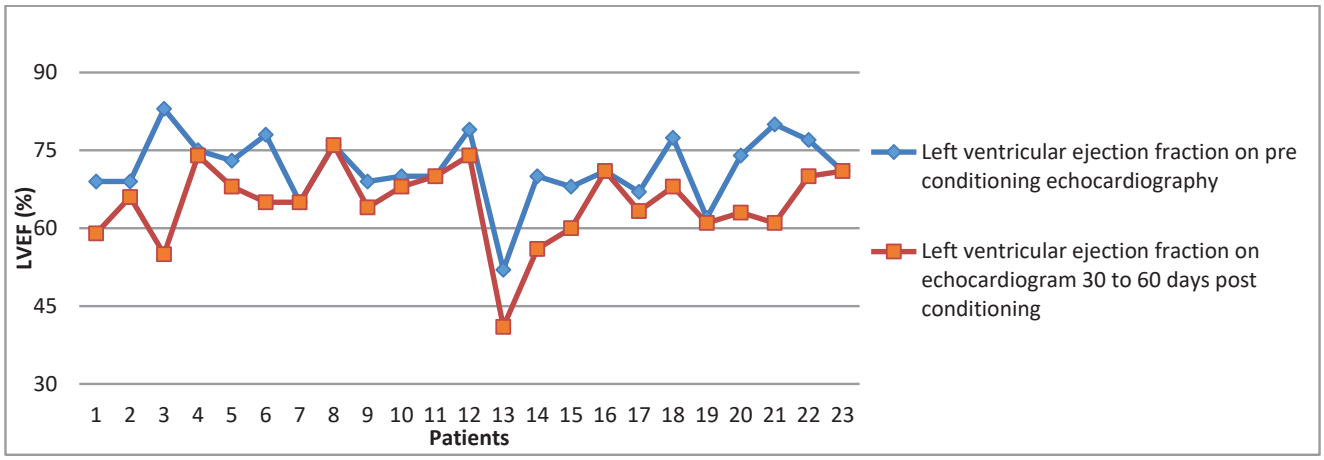
Real-life studies, such as ours, are the best way to represent the population we typically deal with in our daily clinical practice[14]. However, prospective studies with a larger number of patients and standardized tests are needed to detect signs of cardiac dysfunction that are still in the subclinical phase or when cardiac injury is not yet irreversible. The analysis of this study will allow us to propose ways to improve the cardiovascular assessment of patients undergoing AHSCT and consequently reduce cardiac toxicity in our setting.

TABLE 1. Population characteristics and clinical alterations in the cardiovascular system after autologous hematopoietic stem cell transplantation.

	Clinical changes of the cardiovascular system after conditioning chemotherapy		
	Yes N (%)	No N (%)	P value
Advanced stage of disease			
Yes	22 (71.0)	0 (0.0)	0.01366
No	9 (29.0)	4 (100.0)	
Pre-transplant chemotherapy including anthracycline or alkylating agents			
Yes	29 (93.5)	3 (60.0)	0.08429
No	2 (6.5)	2 (40.0)	
Time lapse between diagnosis and transplant			
≤365 days	6 (19.4)	4 (80.0)	0.01515
>365 days	25 (80.6)	1 (20.0)	

Chi-squared test.

FIGURE 1 Echocardiograms performed pre and post conditioning



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DOI: 10.46765/2675-374X.2023V4N2P193

EVALUATION OF A HYDROXYETHYL STARCH SOLUTION FOR DIMETHYL SULFOXIDE REMOVAL FROM MOBILIZED PERIPHERAL BLOOD USING AN AUTOMATED SYSTEM

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Received: 12 Jan 2023 • Revised: 16 May 2023 • Accepted: 24 May 2023.

ABSTRACT

Background and objectives: This study evaluates the efficacy of synthetic colloid hydroxyethyl starch for use as a washing solution to remove DMSO from hematopoietic stem cells cryopreserved grafts in comparison to a crystalloid based solution. **Materials and methods:** We evaluated samples of cryopreserved mobilized peripheral blood (MPB) from 6 (six) patients that had not been used for transplant. For comparison, we used two equal bags of the same collection procedure, allowing the analysis of two different solutions simultaneously. Washing solutions were used: a crystalloid solution (solution 1, sodium chloride 0.9%) and a colloidal solution (solution 2, hydroxyethyl starch 6%), both added with human albumin 2.5%. The washes were performed using the SEPAX2™ (Biosafe) system automated methodology, using the CS-600.1 kit (Biosafe), according to the washing protocol established by the manufacturer. **Results:** The washing solution containing HES showed a statistically significant increase in the recovery of CNT and CD34+/CD45+ cells (p = 0.0313, both), in addition to a greater number of CFU-GM colonies (without statistical significance) when compared to the 0.9% sodium chloride solution. Furthermore, the wash solution containing HES also prevented significant clumping, contrary to what was observed in the wash with 0.9% sodium chloride solution. Conclusion: This work shows that the colloidal washing solution containing hydroxyethyl starch is a good option for DMSO removal procedures in samples of cryopreserved mobilized peripheral blood, maintaining the CD34+ cells viability and functionality and reducing the cell clumping.

Keywords: Cryopreservation. Dimethyl Sulfoxide. Mobilized Blood. Stem cell processing. Hematopoietic Stem Cells. SEPAX 2™.

INTRODUCTION

The first successful bone marrow (BM) transplant, performed in 1957 by Edward Thomas, led to the worldwide use of hematopoietic stem and progenitor cells (HPC) for the treatment of patients with hematologic and non-hematologic diseases, by promoting recovery of the hematopoietic activity after receiving high-dose chemotherapy[1]. In some cases, cryopreservation of the graft is necessary and an essential step for the clinical and therapeutic approach of HPC transplantation.

There are standardized cryopreservation protocols for HPC from different sources that guarantee the viability of these cells after thawing. Successful cryopreservation mainly encompasses the rate of temperature decay of 1 to 3 °C/min during freezing and the combination of cryoprotective agents such

as Dimethyl Sulfoxide (DMSO) (5%) and hydroxyethyl starch (HES - 6%) that prevent formation of ice crystals and preserve the survival of mature granulocytes after thawing, thus avoiding gel formation and macroscopic agglutination caused by cell lysis after thawing, releasing nucleoproteins and lysosomal enzymes, observed when using only DMSO as a cryoprotective agent[2].

Despite the cryoprotective action of DMSO, its use is associated with some adverse events during infusion, due to its dose-dependent toxicity[3,4]. These adverse events are related to allergic reactions, gastrointestinal, renal, cardiovascular, neurological and liver toxicity[5-9]. Based on this, Junior et al recommend that the maximum daily dose of infused DMSO be adjusted to 1 g per kg of body weight[5]. However, these toxic effects can be reduced by removing the DMSO by washing the product after thawing[10]. Over the past two decades, different methods and technologies for DMSO removal have been developed, including the use of different washing solutions, to minimize problems such as cell agglutination, loss of HPC and risk of bacterial contamination[10-17].

In general, the washing solutions that are used to remove DMSO consist of saline or cell culture medium plus osmotic active formulation, such as albumin and/or acid citrate dextrose, or non-permeable macromolecules such as dextran. These agents are not toxic to the cells and provide a hyperosmotic extracellular environment that buffers the hypertonic intracellular compartment created by DMSO, preventing osmotic damage to the cells[6, 10, 13, 14, 16, 18]. However, the increasingly frequent worldwide shortage of critical reagents, such as the qualified dextran, represents a major technical challenge for Cell Therapy Facilities[19], especially when DMSO removal is critical. Thus, this study evaluates the use of synthetic colloid hydroxyethyl starch as a constituent of the wash solution by comparing its performance with a saline-based solution, after DMSO removal using an automated system.

MATERIAL AND METHODS

Samples

Twelve mobilized peripheral blood (MPB) samples from six patients, collected between 2001 and 2014, were used after discarded with the authorization of the medical direction of the Bone Marrow Transplantation Center following the patient's death. The collection of MPB from the patients was done by apheresis 4-5 (four to five) days after administration of Granulocyte colony-stimulating factor human (G-CSF). Samples were selected according to the number of bags available for each patient from the same collection day. Those with a minimum of 2 (two) identical bags were selected for this study, allowing direct comparison of the two methodologies. Each frozen bag contains a concentration of $<3x10^8$ TNC/mL in volume of 100 mL with cryoprotectant solution composed of DMSO 5%, HES 6% and human albumin 2.5% and stored at -80 °C.

Washing solutions

Two washing solutions were evaluated in this study. Solution 1 was a crystalloid-based solution, consisting of sodium chloride 0.9%. Solution 2, was a colloidal solution, containing hydroxyethyl starch 6% (130/0,4) (Voluven™, Fresenius Kabi). Human albumin (Alburex™, CSL Behring) was added to both solutions, to a final concentration of 2.5%.

Thawing and washing

Grafts were thawed in a water bath at 37° C, an aliquot immediately removed for pre-wash analysis and the bag immediately submitted to the washing protocol. An automated washing methodology was performed with the SEPAX 2™ system (Biosafe) using a specific kit for washing (CS 600.1 kit Biosafe) and following the *SmartWash* v.314 program protocol, as established by the manufacturer. For each bag, a dilution ratio of 1.0 and input and output volume of 100 mL were set, with a total procedure time of around 25 min per sample. For each patient, the thawing of two equal bags and each step of the washing procedure were performed in parallel, using each of the two solutions in two different SEPAX 2™ devices.

Product analysis

As criteria for protocol evaluation and validation, after thawing and washing, the recovery of TNC, number of $CD34^+/CD45^+$ viable cells, number of colonies forming units and cell clumping were accessed. TNC count was performed using an automated hematological counter (ABX Micros 60).

Quantification of HPC $CD34^+/CD45^+$ viable was carried out by flow cytometry, according to the ISHAGE protocol[20] modified to include the viability dye 7-aminoactinomicina D (7-AAD, BD Pharmingen™). *In vitro* diagnostics approved anti-CD45 FITC (2D1 clone, BD Biosciences) and anti-CD34 PE (8G12 clone, BD Biosciences) were used, and samples were evaluated in an Accuri™ C6 flow cytometer (BD Biosciences).

For evaluation of the number of granulocyte-monocyte colony forming units (CFU-GM), 10^4 cells were plated per well in the semi-solid methylcellulose-based Methocult™ H4034 media (Stem Cell Technologies). CFU-GM colonies were identified by their characteristic morphology.

The presence of macroscopic clumps after washing was assessed by visual inspection. As a further quality control of the washing procedure, products were tested for sterility, before the cryopreservation and at the end of the process.

Clinical follow-up

After validation of the washing protocol for DMSO removal, products from 3 patients were submitted to washing. In our center, DMSO washing is not a frequent procedure, however, the establishment of an effective protocol is necessary. Indication criteria are chosen based on experiences with adverse events associated with DMSO during infusion, for example, whether five or more cryobags per patient or patient clinical problems that may increase the risk of adverse events, for example, disease progression, chronic ischemia, heart disease and others. For the clinical follow-up of these patients, number of frozen bags and number of washed bags, source of CPH and number of CD34/Kg cells infused were independently analyzed. In the post-transplant period, it was mainly verified whether there was any adverse event related to the infusion of the washed bags or any change in the graft time. Adverse events evaluated include headache, nausea, vomiting, change in blood pressure, tachycardia, fever, mucositis or irritation of the throat and others. For graft evaluation, the first day was determined by blood counts showing more than 500/mm^3 of neutrophils and 20,000/mm^3 of platelets for 3 consecutive days after 7 days without transfusion.

Statistical analysis

TNC and CD34$^+$/CD45$^+$ cells recovery was calculated using the following fórmula: % Recovery = (Pre-cryo or Post-wash ÷ Post-thaw) x 100

Data was plotted and analyzed using Graph Pad Prism 8.0.1 (GraphPad Software, San Diego, CA, USA, www.graphpad.com) and EXCEL (Microsoft Inc). Descriptive analysis, including calculation of median or mean ± standard deviation (SD) was performed. For each solution, data is expressed as a percentage of the post-thaw results, and comparison between the two solutions was performed by Wilcoxon test's. Differences were considered statistically significant when *p* value was less than 0.05.

RESULTS

TNC, viable CD34$^+$/CD45$^+$ cells and CFU-GM of products washed with both solutions were evaluated pre-cryo or post-thaw and post-wash, Table 1. During the washing of two paired bags, a mechanical problem occurred in one of the Sepax™ device, which performed the washing of the product using solution 1, this data being excluded from the analyses. The parameters were compared in grafts washed with saline-based solution 1 and colloid-based solution 2. Recovery of TNC after thawing and before washing was 35.8 ± 12.1%. After washing, the recovery of CNT was 28.0 ± 11.0% for solution 1 (p = 0.0625) and 39.0 ± 15.1% for solution 2 (p = 0.0313) if compared to pre-cryopreservation, and 82.9 ± 14.9% for solution 1 (p = 0.0625) and 110 ± 30.7% for solution 2 (p = 0.0313) if compared to post-thaw, Table 2.

In the analysis of viable CD34$^+$/CD45$^+$ cells, the mean recovery after thawing was 84.2 ± 58.4%. After washing, the recovery was 43.4 ± 38.3% for solution 1 (p = 0.0625) and 68.7 ± 54.9% for solution 2 (p = 0.0313) if compared to pre-cryopreservation, and 64.6 ± 26.1% for solution 1 (p = 0.0625) and 81.9 ± 18.9% for solution 2 (p = 0.0313) if compared to post-thaw.

The results show recovery of CNT and viable CD34$^+$/CD45$^+$ cells generally higher in products washed with solution 2, being statistically significant.

When comparing the number of CFU-GM colonies after washing with the number obtained after thawing, we observed a greater recovery of the number of CFU-GM in products washed with solution 2, 114.6 ± 21.4% (p = 0.0625), versus solution 1, 73.3 ± 31.0% (p = 0.1250), although there is no statistical significance.

Considering that the storage period in the freezer (-80 ºC) of the analyzed samples was between 1 and 13 years, the viability of CD34$^+$/CD45$^+$ cells was on mean of 67.2% ± 19.2% after thawing. In correlation analysis between CD34$^+$/CD45$^+$ cell viability after thawing and storage period, the results showed a moderate correlation, $R^2 = 0.66$.

Analysis of clumps formation during the wash protocol was performed by visual inspection. Significant cell clumping, that could not be dissolved by manual homogenization, was recurrently observed post-wash in all products washed with solution 1, although these were not a significant problem in products washed with solution 2 (Figure 1). An aliquot of 10 mL of each product was transferred to a conical tube after homogenization, in order to better evaluate the amount of clumps, confirming that they were present in great quantity in products washed with solution 1 (Figure 2A), although nearly absent in those washed with solution 2 (Figure 2B).

All samples selected for this study had negative pre-freeze blood cultures for aerobic and anaerobic bacteria and for fungi. No contamination was observed after washing.

Based on the results obtained, solution 2 was established in the laboratory washing routine to remove the DMSO, in an automated way, using the SEPAX 2 ™ system. In our institution, washing for DMSO removal is not routine, but it is required in situations where there is a need to reduce toxicity related to DMSO due to the patient's clinical condition at the time of transplantation or the excessive number of bags to be infused. Thus, after validation, 3 patients needed to have their product washed before infusion, and the results for each procedure are detailed in table 3. The products cryopreserved for an average of 107 ± 63 days at -80 ºC. After thawing, in a 37 °C water bath, each bag was subjected to the washing process following the established protocol described above.

After washing, TNC recovery and viability were evaluated. For these cases, the analysis of cell recovery after washing was calculated in relation to the number of cells before cryopreservation. Therefore, considering the total number of bags washed for each patient, the mean recovery of TNC, comparing before cryopreservation, was 100 ± 0% for patient 1, 92.9 ± 5.8% for patient 2 and 82.7 ± 15.4% for patient 3. For total cells viability after washing, the means were: 91.5 ± 6.9% for patient 1, 95.7 ± 0.8% for patient 2 and 97.6 ± 0.1% for patient 3.

To guarantee the efficacy and safety of the washing procedure, adjusting it to the number of bags to be thawed and infused and ensuring the quality of the product intended for the patient, this process was performed by 3 professionals. While one operator performed the washing protocol, the second performed the necessary quality control assays, such as evaluation of TNC recovery and viability analysis. A third member of staff was available at the patient's bedside to monitor adverse events during infusion and manage and coordinate the beginning of the washing procedure for the posterior bags, so that all products were infused within 1 hour of thawing.

In clinical follow-up, regarding the proportion of bags submitted to the washing protocol in relation to the total of infused bags, patient 1 only 5% were washed, while patient 2, 60% and patient 3 had all bags submitted to the washing protocol. Due to the small number of patients followed, variability of infusion conditions of washed bags and clinical characteristics of each patient, the impact of the washing procedure on transplantation was evaluated through the graft recovery time for each type of HPC source, occurrence of problems during thawing or washing and adverse events during the infusion. Our team followed each patient during infusion and post-transplantation to assess graft time. There were no problems thawing or washing the bags. For all patients followed, no adverse events were observed during the infusion of the washed bags and, in the post-transplant follow-up, the neutrophil and platelet engraftment times occurred within the expected time for each type of CPH source, 11 days to neutrophils in autologous MPB transplants and up to 32 days for cryopreserved BM, considering a minimum dose of 2-3 x10^6 $CD34^+$ cells/kg[21].

DISCUSSION

To preserve the potential of CPH during cryopreservation, it is necessary to use a cryoprotective agent such as DMSO, which is the most used[22]. However, adverse events may occur during infusion of thawed products and most of them are with DMSO toxicity[5-7]. Nevertheless, there are studies showing that the DMSO removal in MPB samples after thawing, by washing, reduces adverse events without adversely affecting the grafting[10, 15, 16].

To avoid HPC losses as well as to reduce the risk of contamination, several techniques and methodologies have been developed for DMSO removal, replacing the conventional method which is based on manual removal after centrifugation [23]. An automated washing system, such as demonstrated by the present study, provides time sensitive alternative, optimizes the washing process and reduces the risk of contamination due to the closed fluid path[7, 16, 17].

In 2011, Scerpa et al, showed that the automated washing procedure for DMSO removal, using the Sepax™ S-100 system, guarantees a better result in terms of recovering TNC, $CD34^+$/$CD45^+$ cells and total CFU without affecting cell functionality, when compared to the manual centrifugation procedure[24]. In this study, the automated Sepax2™ system has proven an effective method for routine removal of DMSO from MPB cryopreserved grafts after thawing, with the mean recovery of TNC, viable $CD34^+$/$CD45^+$ cells, CFU-GM count as well as maintaining test sterility of cell products. These results are compatible with those obtained by Rodriguez et al, 2004 showing that the wash for DMSO removal from umbilical cord blood units using the Sepax™ system is a secure method for maintaining cell function and a viable option for clinical routine[15]. In addition, according to Huvarová et al 2021[25], washing of cryopreserved transplants using Sepax 2 showed high recovery of hematopoietic cells, did not influence time to engraftment, and resulted in a satisfactory reduction of adverse effects and improved tolerance to the procedure.

Considering the long-term storage time of the samples used in the present work, studies show that MPB subjected to long-term storage at -80 ºC with uncontrolled freezing rate and cryopreservation with 5% DMSO combined with HES, can support hematopoietic reconstitution when compared to that of controlled rate freezing and liquid or vapor nitrogen storage[26-28]. In our analyses, the lower rates of $CD34^+/CD45^+$ cell viability were not associated with longer storage period in freezer -80 °C, the sample with the longest storage period used in the study, 164 months, had 92% cell viability $CD34^+/CD45^+$ after thawing.

For a reliable evaluation of the results, the criterion established for sample selection was that two discarded bags from the same collection day should be available for each patient and that the proper authorization for their use was obtained. With this approach, it was possible to guarantee that the analysis of each evaluated solution was comparable. Therefore, the number of samples available, according to the established criteria, limited the number of samples evaluated in this study.

Our results showed that the washing solution containing HES showed a statistically significant increase in the recovery of CNT and CD34+/CD45+ cells, in addition to a greater number of CFU-GM colonies when compared to the solution of sodium chloride 0.9%. Furthermore, washing solution containing HES also prevented the significant clumping, unlike what was observed in the wash with the sodium chloride 0.9% solution.

Literature shows that cell clumping is a major problem when centrifugation of thawed HPC products is performed[13] and this is likely due to DNA release from the fragilized cells, since DNAse treatment was shown to reduce clumping of cells during the thawing procedure[29]. Since the presence of these cell clumps is associated with clinical toxicity of infused products[6], the use of HES-based washing solutions is clearly advantageous over those constituted of isotonic saline. Thus, Larrea et al 2021, concluded in their study that HES can be used by observing the recipient's renal function to assess the need to adjust the proportion of HES to be used in washing DMSO[30].

Despite the small number, the post-transplant clinical follow-up of patients who had products submitted to the washing protocol showed that solution 2 did not harm the patient. Within the established criteria for analysis, no adverse events were observed in any of the patients during the infusion of washed products or delays in the recovery hematopoiesis. Therefore, the HES-based lavage protocol established in the study can be considered safe for patients, with no impact on infusion or HPC transplant outcomes.

In summary, this study shows that HES-based washing solution is a good choice to remove DMSO from cryopreserved MPB grafts, because it is satisfactory in maintaining the viability and functionality of HPC after thawing and washing. Furthermore, the Sepax 2™ automated system is a good alternative for thawed HPC products wash, allowing a high rate of cell recovery after the procedure and ensuring sterility of the samples. Thus, the proposed washing protocol can be effectively used in clinical HPC transplantation routine and, considering the increasing advances in cell therapy, we can prospect the use of this washing protocol for any product intended for cell therapy. Nevertheless, this HES based solution can even be adapted and validate for manual processing protocols, not restricting the use to automated systems.

Funding Information: The authors declare that the Sepax™ equipment (Biosafe) used for washing products to remove DMSO, as well as the flow cytometer used for the analysis of hematopoietic progenitor cells and cell viability were acquired from an expansion project and work by the Brazilian Network of Umbilical Cord Blood Banks financed by the Ministry of Health and the National Bank for Economic and Social Development (agreement number: 08207521). All consumable materials/reagents used in the study were purchased through a regular purchase made by the National Cancer Institute for the routine of the Cell Processing Center/Umbilical Cord and Placental Blood Bank, with laboratory validation studies being included in the laboratory routine and process quality.

Acknowledgements: The authors must thank Brazilian Ministry of Health and the Banco Nacional de Desenvolvimento Econômico e Social, for supporting the expansion and work of Brazilian Network of Cord Blood Banks, which made possible device acquisition used in this work. All authors participated in the study design and review of the manuscript. Carla, Juliana, Pedro and Luciglei performed the assays. Juliana analyzed the data. Carla analyzed the data, wrote and edited the manuscript. Luis Fernando da Silva Bouzas, responsible for financing the acquisition of equipment.

Disclosure of interests: The authors declare to have no conflict of interest.

TABLE 1. Descriptive statistical analysis

	Pre-cryo (n=6)		Post-thaw (n=6) Solution 1 (n=5)			Post-wash Solution 2 (n=6)					
	Mean ± SD	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range
TNC (x10^9)	43.4 ± 13.1	30.8 - 67.9	14.7 ± 4.4	13.5	10.7 - 21.4	11.2 ± 3.9	12.1	6.8 - 16.8	15.9 ± 5.1	18.9	8.3 - 19.7
Total CD34$^+$/ CD45$^+$ viable (x10^6)	69.8 ± 40.1	8.1 - 128.8	55.3 ± 53.4	46.6	6.4 - 148.2	28.6 ± 29.9	14,0	3.3 – 65.6	48.3 ± 51.8	35.3	5.7 - 142.0
CFU-GM (x10^4)	a	a	34.0 ± 17.1	22.5	21.0 - 53.0	23.4 ± 19.5	16.8	8.5 - 51.5	40.7 ± 24.9	29.0	17.0 - 70.5

[a]Not shown because CFU-GM test was not performed on pre-cryopreservation product

Legend: This table shows descriptive statistics, including mean, standard deviation (SD), median and range of the number of TNC, the number of viable CD34+/CD45+ cells and the number of CFU-GM in the pre-cryo, post-thaw samples and after each washing procedure.

TABLE 2. Descriptive statistical analysis of recovery cells

Cell recovery pre-cryo vs Post-thaw (%)				Cell recovery pre-cryo vs Post-wash (%)						Cell recovery post-thaw vs Post-wash (%)					
			Solution 1 (n=5)			Solution 2 (n=6)				Solution 1 (n=5)			Solution 2 (n=6)		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range
TNC (x10^9)	35.8 ± 12.1	38.0	15.7 - 49.6	28.0 ± 11	30.0	10.1 - 38.2	39.0 ± 15.1	43.5	15.5 - 57.3	82.9 ± 14.9	79.3	63.9 - 102.5	110.0 ± 30.7	100.9	77.6 - 161.9
Total CD34$^+$/ CD45$^+$ viable (x10^6)	84.2 ± 58.4	81.6	11.6 - 163.8	43.4 ± 38.3	40.6	7.5 - 106.4	68.7 ± 54.9	54.4	11.3 - 157.0	64.6 ± 26.1	64.7	31.4 - 100.6	81.9 ± 18.9	86.1	54.6 - 100.6
CFU-GM (x10^4)	a	a	a	a	a	a	a	a	a	73.3 ± 31.0	75.3	40.5 - 102.4	114.6 ± 21.4	121.7	81.0 - 134.3

[a]Not shown because CFU-GM test was not performed on pre-cryopreservation product

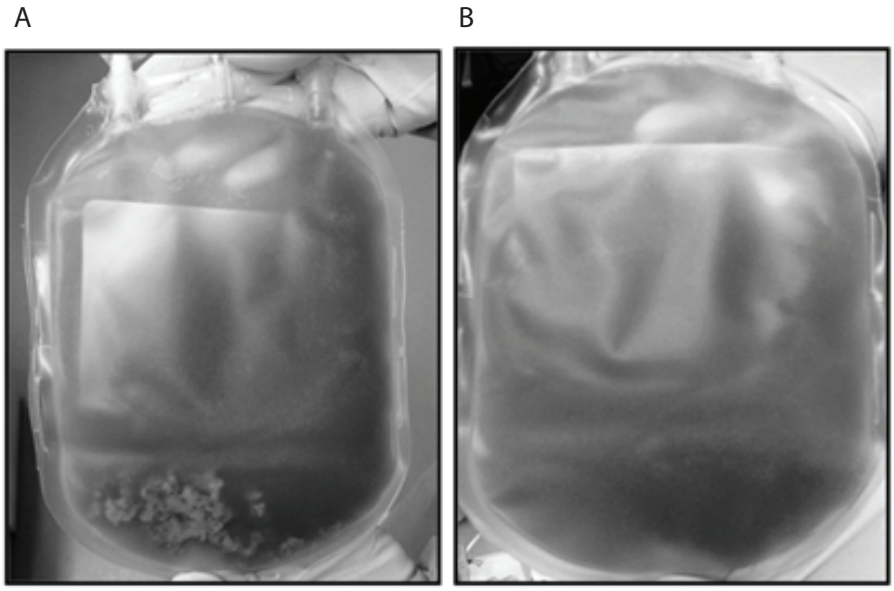
Legend: This table shows descriptive statistics including mean, standard deviation (SD), median and recovery rate range of TNC, CD34+/CD45+ and CFU-GM cells comparing pre-cryo, post-thaw and after each wash procedure.

TABLE 3. Detailed product information of patient washed for DMSO removal

	Patient 1	Patient 2	Patient 3
PATIENT INFORMATION			
Age (years)	60	62	14
Sex	Female	Male	Male
Diagnosis	LNH	MM	LLA-T/B
Transplantation Type	Autologous	Autologous	Alo-NR
Pre-transplant			
Mobilization Regimes:			
1ª mobilization	G-CSF only	G-CSF only	G-CSF only
2ª mobilization	G-CSF only	G-CSF only	-
PRODUCT INFORMATION			
HPC source	MPB/BM	MPB	BM
Total CD34/Kg (106)*	1.56	2.56	4.62
Total dose DMSO(g)/kg	0,85	0,81	0,31
Total cryopreserved bags	10	5	2
THAWING/WHASING/INFUSION			
Problem during thawing	No	No	No
Problem during whashing	No	No	No
Number of washed bags	2	3	2
Adverse reaction during infusion	No	No	No
TNC recovery post-wash (% - per bag)	100 /100	95.7/95.7/87.4	93.6/71.7
TNC viability post-wash (% - per bag)	86.6/96.3	96.2/96.2/95.1	97.7/97.5
Storage time at -80 °C (days)	199	92	64
POST-TRANSPLANT			
Grafting time (days):	14	11	24
GRAFT DATA:			
leukocytes (cels/mm3)	6100	3530	3670
neutrophils (cels/mm3)	3520	2676	1993
monocytes (cels/mm3)	1891	286	1369
Platelets (k/mm3)	32	37	65
erythrocytes (106/mm3)	3.15	2.73	3.26
hemoglobin (g/dL)	8.8	8.24	9.8
hematocrit (%)	27.1	24.27	26.5

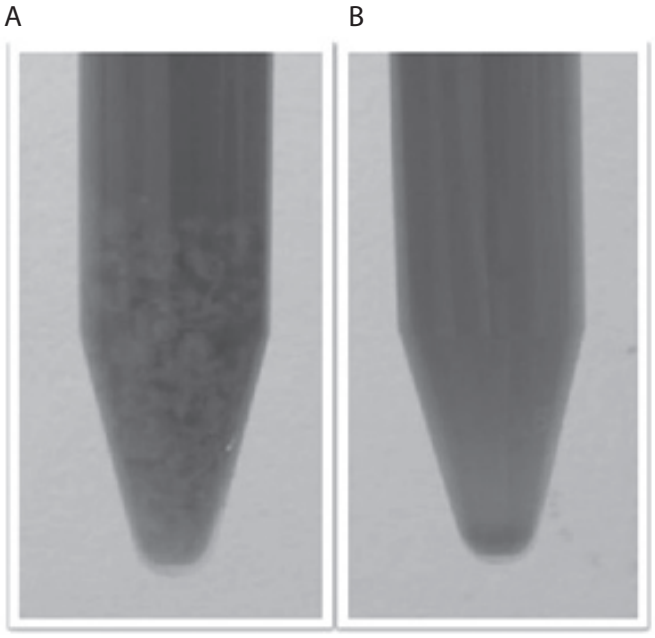
Abbreviations: MM, multiple myeloma; LLA-T/B, acute T and B cell lymphoblastic leukemia; BM, Bone marrow; G-CSF, Granulocyte colony-stimulating factor human; Alo-NR, Unrelated allogeneic.
*Pre-freezing enumeration
Legend: This table shows detailed information about the patients, infused product and post-transplant results.

FIGURE 1. Visual evaluation of macroscopic cell clumps.



Legend: *Figure A shows a large amount of cell clumps in the bottom of a bag of a representative sample subjected to washing with saline solution (solution 1). Figure B shows the absence of clumps in a bag of a representative sample subjected to washing with hydroxyethyl starch solution (solution 2). This result was consistently observed in all samples.*

FIGURE 2. Visual evaluation of macroscopic cell clumps.



Legend: *An aliquot of 10 mL of each sample was transferred to a 15 mL conical tube to better evaluate the amount of cell clumps in each washing protocol. Figure A shows nearly 2 mL of clumps in the bottom of a conical tube containing a representative sample subjected to washing with saline solution (solution 1). Figure B shows the absence of clumps in a conical tube containing a representative sample subjected to washing with hydroxyethyl starch solution (solution 2). This result was consistently observed in all samples.*

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DOI: 10.46765/2675-374X.2023V4N2P198

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS IN BRAZIL: A COHORT

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Received: 04 Apr 2023 • Revised: 24 Apr 2024 • Accepted: 29 May 2023.

ABSTRACT

The allogeneic hematopoietic stem cell transplant (allo-HCT) represents an important therapeutic strategy for acute leukemias, lymphomas and solid neoplasms, also used in benign diseases, such as aplastic anemia and inborn errors of immunity. This treatment requires myeloablative chemotherapy (conditioning regimen) followed by the infusion of donor-derived hematopoietic stem cells. However, this procedure carries some risks, such as infections, graft versus host disease (GVHD) and conditioning toxicity, which may result in transplant-related mortality. Over the decades, due to the increasing life expectancy and new advances in medicine, the cases of patients > 50 years with hematologic diseases that need allogeneic transplant have grown, requiring a comprehensive geriatric assessment as a mechanism for the best treatment option choice. Objective: To apply a clinical frailty score and Karnofsky score in allogeneic hematopoietic stem cell older than 50 years old for three years in Walter Cantídio University Hospital (Fortaleza/Ceará) and in Amaral Carvalho Hospital (Jaú/São Paulo), expecting to recognize the profile of this patients and to demonstrate the relation between the clinical frailty score and overall survived, besides to estimate the contribution of GVHD prophylaxis and relapse in overall survival. Methods: Multicentric, retrospective, descriptive, analytical and quantitative study, acquiring dates by means of exams and medical record from Walter Cantídio University Hospital in Fortaleza/Ceará and Amaral Carvalho Hospital in Jaú/São Paulo. Results: The study selected 252 patients, 147 males and 105 females, sort in gender, disease, HCTCI score, CFS and KPS. In three years, the overall survival in FIT score is 2,46 years, while in FRAILTY score is 1,82 years. About the prophylaxis, the combination of cyclosporine, mycophenolate mofetil, cyclophosphamide had worse results than others prophylaxis. As expected, in case of relapse, there is shorter survival. Conclusion: The elderly population require a geriatric score in order to evaluate the profile of this patients once the allogeneic transplant must happen, then FIT patients has longer survival than FRAILTY patients.

Keywords: Geriatric Health. Bone marrow transplantation. Rating Scales.

INTRODUCTION

The hematopoietic stem cell transplant (HSTH) emerged as a revolutionary strategy in acute leukemia, lymphoma and solid neoplasms treatment, in addiction benign diseases treatment, for example severe aplastic anemia[1]. This treatment requires myeloablative chemotherapy therapy followed by the infusion of hematopoietic stem cells from the own patient or from the donor, who is related or not[2].

The allogeneic hematopoietic stem cell transplant could be the cure for this patient, but it could show bad results in older ages because of the toxicided in the protocols, high relapse risk and difficulties in the access[3].

Because the oldest of the population, there are the identification of more cases of hematological diseases[4], whose has the transplant a way of treatment. Furthermore, it must be necessary the application of strategies to evaluate this patient oldest 50 years old, to stratify who has a real benefit in a hematopoietic stem cell transplant.

The clinical geriatric score analyzed the patient as social support, healthy system access, falls in the last year, medications use, functionality, cognition, self-evaluation, depressive symptoms, nutrition and speed step. According to these criterias, the patient was scored in the scale[5].

METHODOLOGY

It is a retrospective, analytical study and analysis of data proven through exams. The population aged 50 years or older were used as inclusion cells in allogeneic hematopoietic stem transplantation at the University Hospital Walter Cantídio and Hospital Amaral Carvalho from 2009 to 2021. Excluding the individuals whose age was less than 50 years, selected for autologous transplantation or technical conditions that analyzed medical records or for lack of essential records for the work.

They will be used as information contained in medical records and institutional information systems. The data will be sent and through record sheets released in a Microsoft Excel spreadsheet.

Analytical data is analytical using Master and AGHU programs. There will be variables inherent to the patient (age, sex, underlying disease, comorbidities, performance status, geriatric scales, comorbidity score), to the donor (type of donor, age, sex) and to the transplant (transplant date, type of transplantation, cell source, conditioning type, GVHD profile, outcome or sequence from the last day of follow-up). The contracts to be executed correspond dead or alive.

According to these dates, the patients were separated in three groups: fit, unfit and frailty. This classification was based on Critical Frail Scale (CFS), so the grade 1 and 2 are fit, grade 3 is unfit and grade 4 to 9 mean frailty.

RESULTS

The sample collected is composed of 252 patients, 147 of which are male, which corresponds to 58.33% of the total sample. These will be divided according to sex, type of disease, as well as their classifications on the HCTCI, CFS and KPS scales.

Regarding diseases, most patients have AML, namely 100 patients (39.68%), and MDS and CML, as there is a scarcity of therapy with Tyrosine Kinase Inhibitors and difficulty in carrying it out due to the nutritional deficiency of patients in this population, are the other two most prevalent, which are present in 20.24% and 12.70% of patients, respectively.

According to the frequency distribution of variables, such as type of conditioning, cell source and prophylaxis for GVHD (Table 2), a balance is analyzed regarding the type of conditioning used, since myeloablative therapy was used in 118 patients and in 115 of reduced intensity, which in percentage terms is equivalent to 46.83% and 45.63%, respectively.

Regarding prophylaxis, the most used was cyclosporine and methotrexate (CyA+MTX), which was performed in 112 patients, followed by cyclosporine, methotrexate and anti thymoglobulin (CyA+MTX-+ATG) and cyclosporine and mycophenolate mofetil (CyA+MMF) , both applied to 43 patients.

It was observed that 52 patients had relapse, which corresponds to 20.63% of the total number of patients in the study, as seen in graph 1. We also found that 119 patients died, that is, 47.22% of the patients in the study, and among these deaths, the most recurrent cause of death was relapse and infection, where 33.61% and 32.77% of the patients who died had this cause of death, respectively (Graph 2).

The study highlights the relationship between the geriatric CFS score and survival time. We can see that the average lifetime recorded is slightly higher in cases where the score is of fit classification. Time is 2.81 years on average in those with this geriatric rating, down to 2.45 in the frailty category. Accord-

ing to the p-value of the significance test, there is evidence to state that the geriatric classification is related to survival time, so that those with a Fit classification have a longer survival time.

When performing the survival assessment, Fit patients have greater survival than patients with scores classified as Frailty. As for median and mean survival, those who fit into the Fit category have a median of 6.92 and a mean of 6.13 years, those in the Frailty category have a median of 2.95 years and a mean survival of 5.91 years.

However, based on the p-value of the log-rank test, we conclude that there is no statistical significance in the differences in survival probability, regardless of the CFS classification, the expected survival time will be the same. However, having observed that in the first years there is a greater difference in the survival curves, and assuming that after a certain period there are deaths from other reasons independent of our studied objective, it is important to analyze the events considering the events only up to a certain time limit. So, evaluating the 3-year case, we can observe that statistical significance was found, so that patients with a geriatric fit score have greater survival. The median survival time for these is 2.46 years, while for those classified as Frailty it is 1.82 years.

Regarding survival according to the KPS score, practically the same occurs as for the CFS score, with the KPS 60 and 70 categories being the ones that apparently have the highest survival, but with the application of the significance test we can prove that there is no association of these geriatric scores with patient survival.

In Graph 6, we have survival stratified by the variable DRI, noting that there is a certain tendency to decrease survival according to the highest DRI, despite these indications, it was not possible to prove an association between DRI and survival, as we found that there is no evidence enough for us to believe that patient survival changes according to the DRI classification.

Regarding the donor, in all groups the highest survival observed is that of unrelated and the lowest survival is that group whose donors were haploidentical. However, the significance test indicated that there are no significant differences between survival according to the type of donor.

Considering the donor's gender, the median survival of those whose donor was a man is 2.75 years, and the median survival time of these is 6.2 years. The median survival of those whose donor was a woman is 3.73 years, and the mean survival time of these patients is 5.61 years. Despite the differences, there is no significance in these differences, so we cannot say that the sex of the donor influences the survival of patients.

In Table 4, we can conclude that there is no significant association between CFS, KPS scores and donor age with patient survival.

It is possible to observe that up to 1.5 years after BMT there is a differentiation between the survival of HLA 8/8 patients and those of HLA ≤ 7/8, where the survival of patients with HLA 8/8 donors is higher. However, from that point onwards, a decrease in the survival gap appears to begin.

According to Graph 10, we can say that there are also not many differences in the survival of the groups of patients of each type of conditioning, myeloablative and of reduced intensity. In this case, no statistical significance was found about the relationship between survival and conditioning.

Regarding survival in the main cellular sources, we see that there is a small difference in survival up to 6 years after transplantation, after that period the survival is practically the same for these sources, and in this period up to 6 years, the survival of the group with PB source is larger than the BM group. Despite these observations, once again the significance test showed that there was no association between the cell source and the survival of patients undergoing HSCT.

In graph 12, we can quickly see that the group of patients whose prophylaxis was CyA+MMF+CyPT has a lower survival rate, because within approximately 1 year after transplantation, the survival of patients in this group reaches less than 25%, which is below of patients who used other prophylaxis. We observed that the CyA+MMF prophylaxis and other prophylaxis have very close and intermediate survival rates, whereas the CyA+MTX, CyA+MTX+ATG and CyA+MMF+ATG prophylaxis are the prophylaxis of patients who survived the most over time.

We can conclude that CyA+MMF prophylaxis differs from CyA+MTX, such that the survival of patients in the CyA+MTX group is higher and that CyA+MMF+-CyPT prophylaxis differs from CyA+MTX and CyA+MTX+ATG prophylaxis, so that the latter two cause greater survival for patients.

Finally, we analyzed patient survival according to the presence of relapse over time. As expected, we can clearly see in Graph 13 that the group of pa-

tients who had relapse had higher mortality. After one year of transplantation, patients who have not relapsed have an expected survival rate of approximately 68%, while those who have ever relapsed have approximately a 40% survival expectation.

With statistical relevance, the average life span of patients according to the presence of relapse, the average of those who did not relapse is 7.08 years, whereas for those who did, it is only 2.41 years, much lower.

For an even better interpretation of these results, which were significant, it was identified that patients who relapsed patients had 2.45 times higher risk of death than patients who did not, whereas patients whose prophylaxis is CyA+MMF have 2. 09 times more risk of death than patients in the CyA+MTX group, in addition to the fact that patients whose prophylaxis is CyA+MMF+CyPT have a 3.32 times greater risk of death than those in the CyA+MTX group. Such conclusions can be seen in table 5.

In order to summarize the information and tests given in the survival analyses, Table 6 shows the crossing of variables with death, in addition to the log-rank test that compares the survival curves, and the mean and median survival values.

As shown in Table 7, we found that the type of donor variable is significant, which means that an unrelated donor is a protective factor against death, and patients to whom the donor is not related have 0.29 times the risk of death of those whose donor was related.

DISCUSSION

In view of the analyzed data, the importance of applying geriatric scores in the population over 50 years old submitted to allogeneic hematopoietic stem cell transplantation is observed, aiming at the best therapeutic adequacy.

As the population was evaluated as Frailty, the 3-year survival was reduced in relation to the Fit population. The median survival time in Fit patients was 2.46 years, while in Frailty patients it was only 1.82 years.

This demonstration shows the importance of applying geriatric scores to ensure the best therapeutic choice for this patient population.

It is still observed that survival in the CyA+MTX group is higher than the others, with prophylaxis CyA+MTX and CyA+MTX+ATG causing greater survival in patients than CyA+MMF+CyPT. This observation reinforces the better suitability of GVHD (graft versus host disease) prophylaxis in the population over 50 years of age.

It is possible to conclude that those who relapse will have a higher mortality in relation to those who do not relapse, since survival in this group is 7.08 years, while in that group it is 2.41 years.

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TABLE 1 – Frequency distribution of variables: sex, HCTCI, CFS, KPS and disease.

Variables	Frequency	Percentual
Sex		
Male	147	58,33%
Feminine	105	41,67%
Total	252	100%
HCTCI		
0	137	54,37%
1	49	19,44%
2	26	10,32%
3	27	10,71%
4	8	3,17%
5	1	0,40%
6	2	0,79%
7	2	0,79%
Total	252	100%
CFS		
Very fit	6	2,38%
Fit	25	9,92%
Managing well	170	67,46%
Very mild frailty	47	18,65%
Mild frailty	3	1,19%
Moderate frailty	1	0,40%
Total	252	100%
KPS		
60	5	1,98%
70	5	1,98%
80	32	12,70%
90	74	29,37%
100	136	53,97%
Total	252	100%
Disease		
AML	100	39,68%
MDS	51	20,24%
CML	32	12,70%
Ph+ ALL	16	6,35%
Myelofibrosis	14	5,56%
B/T ALL	13	5,16%
CLL	8	3,17%
NHL B	6	2,38%
Aplastic anemia	5	1,98%
MDS/MPN	4	1,59%
Other	2	0,79%
Dendritic cell Leukemia	1	0,40%
Total	252	100%

TABLE 2 - Distribution of frequencies of variables according to type of conditioning, cell source and prophylaxis

Variables	Frequency	Percentual
Conditioning		
Myeloablative	118	46,83%
Reduced intensity	115	45,63%
Sem resposta	19	7,54%
Total	252	100%
Source		
PB	111	44,05%
BM	120	47,62%
CB	1	0,40%
PB+BM	1	0,40%
Sem resposta	19	7,54%
Total	252	100%
GVHD_proph		
CyA+MTX	112	44,44%
CyA+MTX+ATG	43	17,06%
CyA+MMF+ATG	7	2,78%
CyA+MMF	43	17,06%
Other	10	3,97%
CyA+MMF+CyPT	17	6,75%
Sem resposta	20	7,94%
Total	252	100%

FIGURE 1 - Frequency distribution of the occurrence of relapse

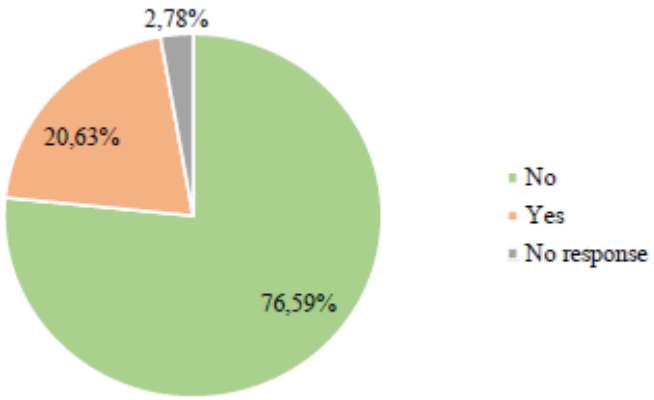

FIGURE 2 - Distribution of frequencies of death and cause of death

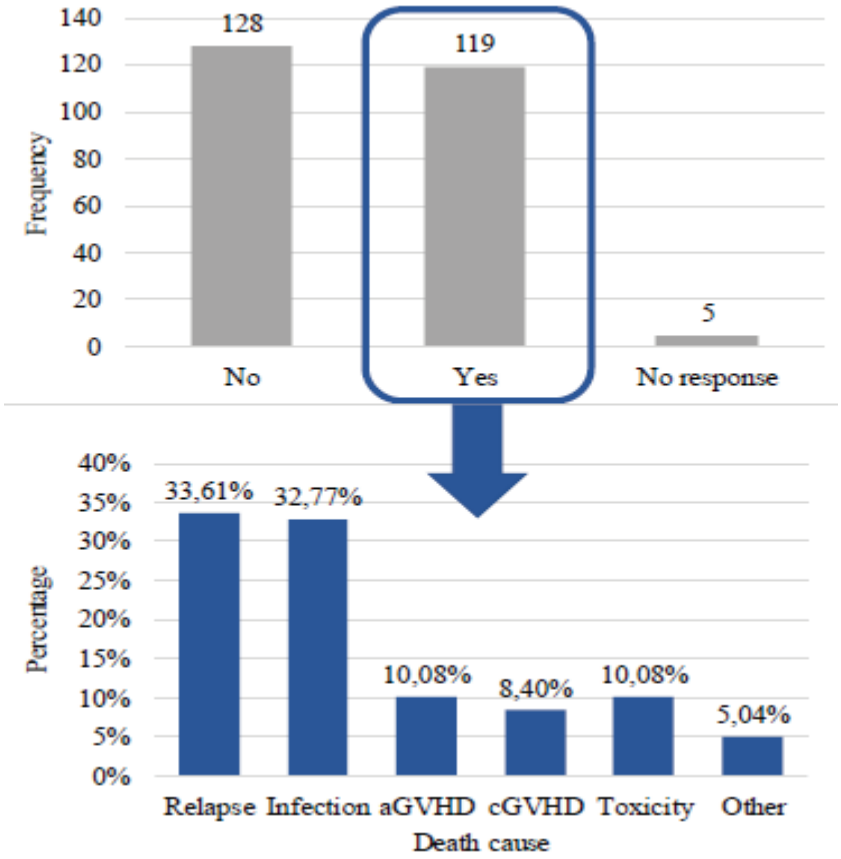

TABLE 3 - Relationship between CFS and survival time (in years)

Survival time (in years)	CFS			P Value
	Fit	Frailty	Total	
Mean	2,81	2,45	2,48	0,019
Standard deviation	2,50	2,88	2,85	
Minimal	0,06	0	0	
Maximum	10,02	12,05	12,05	

FIGURE 3 – **Kaplan Meier survival probability stratified by CFS.**

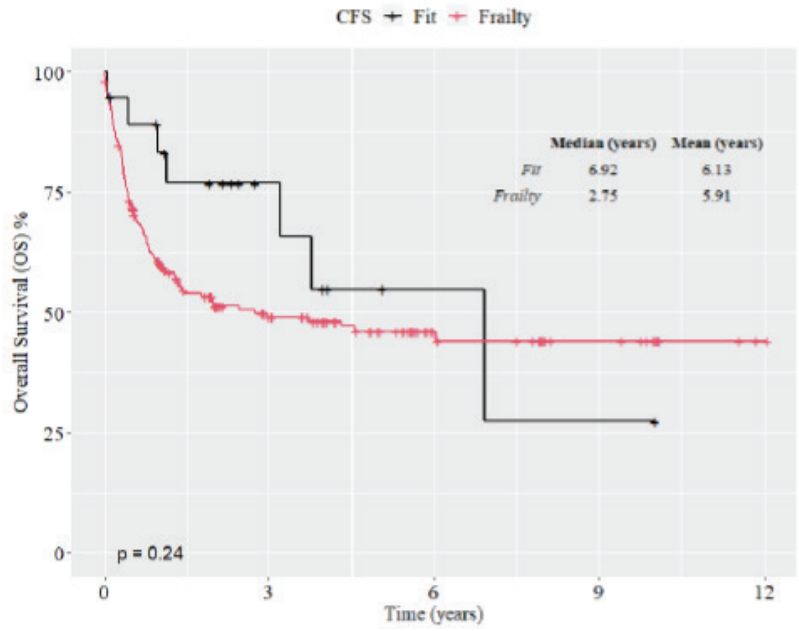

FIGURE 4 – **Kaplan Meier survival probability stratified by CFS (3 years)**

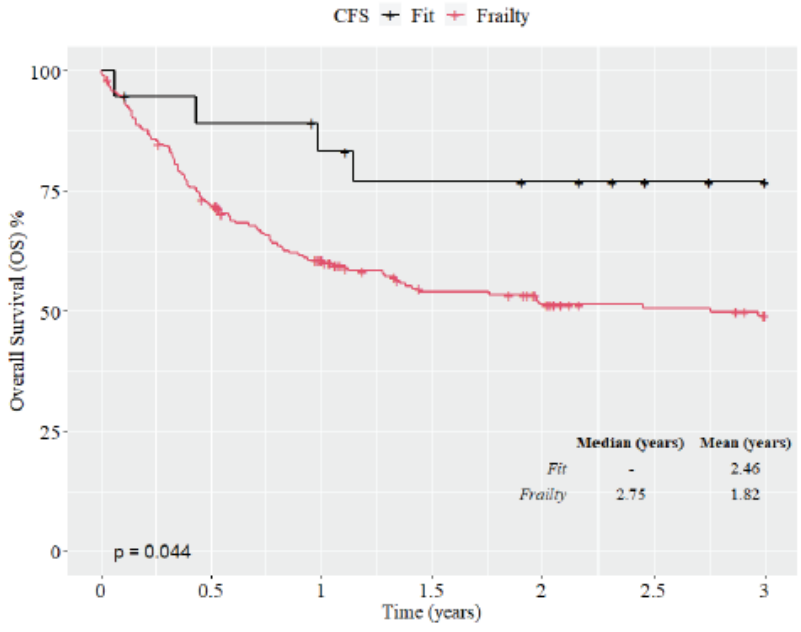

FIGURE 5 - Kaplan Meier probability of survival stratified by KPS

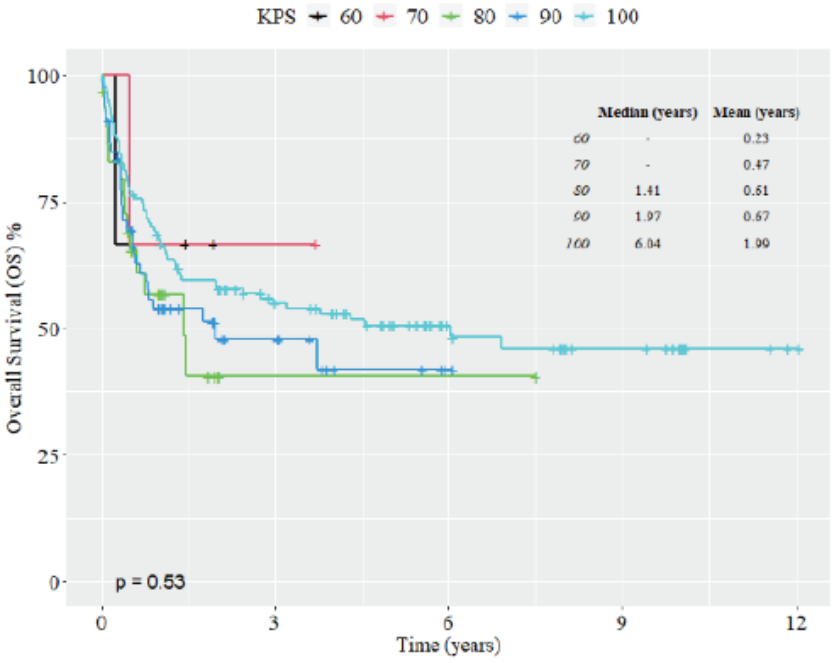

FIGURE 6 - Kaplan Meier probability of survival stratified by DRI

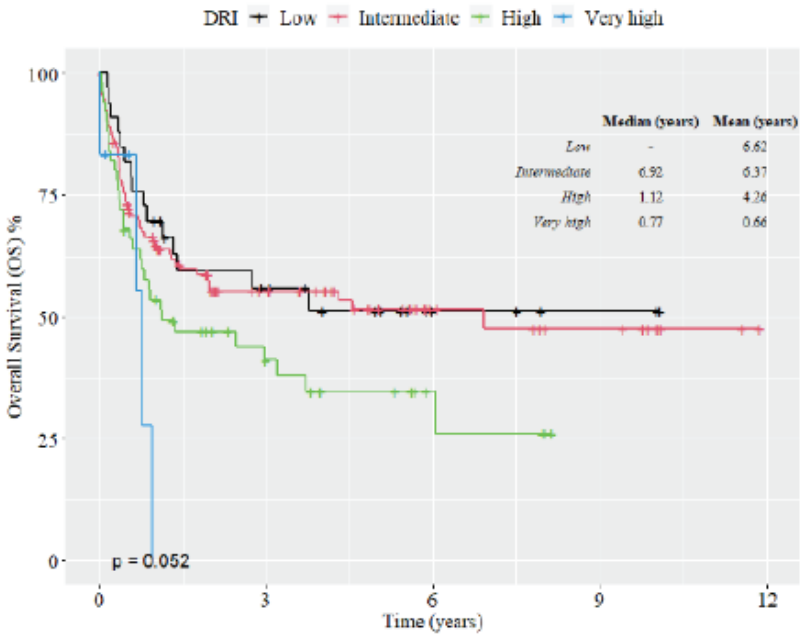

FIGURE 7 – Kaplan Meier survival stratified by type of donor

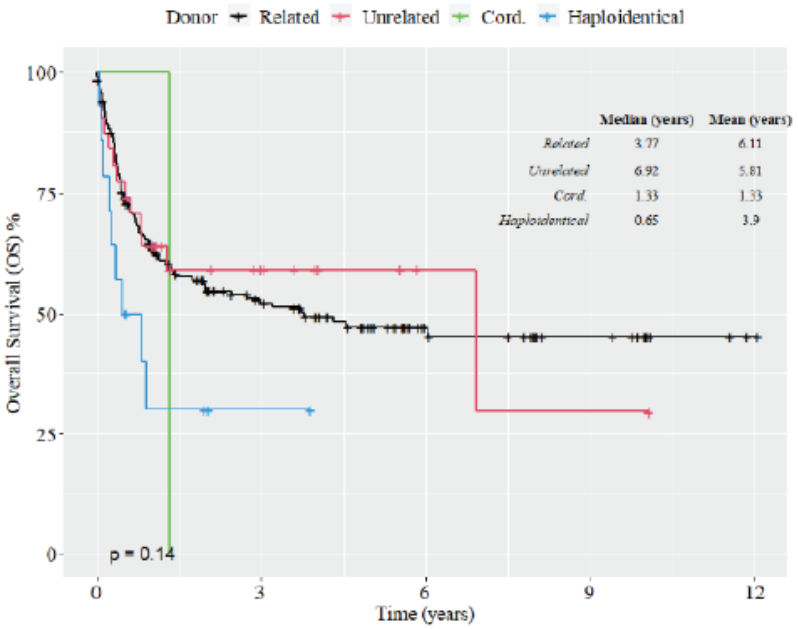

TABLE 4 - Relative risk and confidence interval for CFS, KPS and Age of donors scores

Variables	RR	CI (95%)	P-value
CFS	1,122	(0,83 - 1,51)	0,447
KPS	0,9883	(0,97 - 1,01)	0,28
Donor age	0,9924	(0,97 - 1,01)	0,415

FIGURE 8 - Kaplan Meier survival stratified by gender of donor

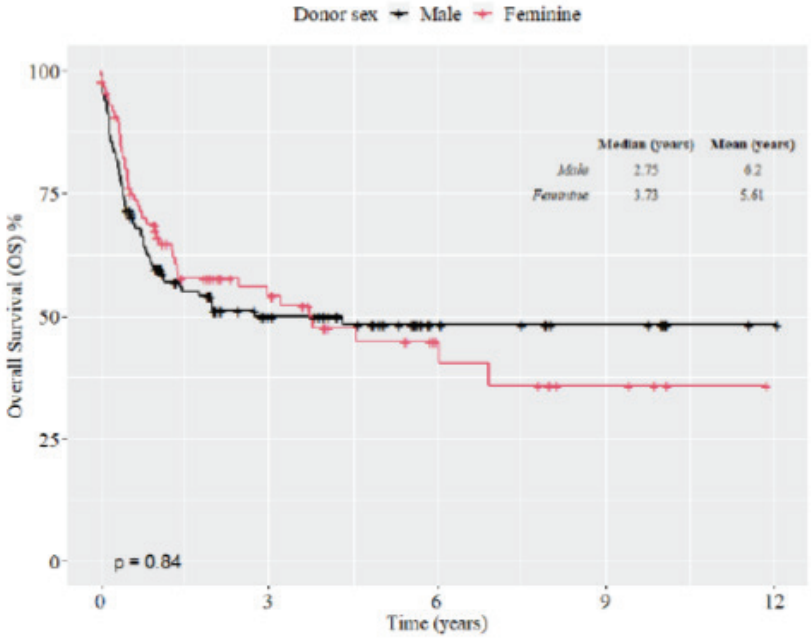

FIGURE 9 - Kaplan Meier survival stratified by HLA donor

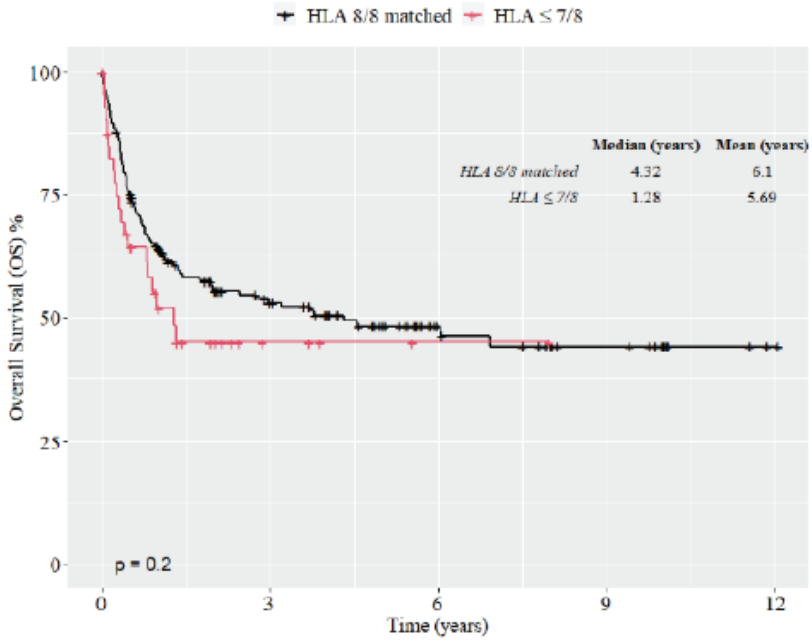

FIGURE 10 - Kaplan Meier survival stratified by conditioning

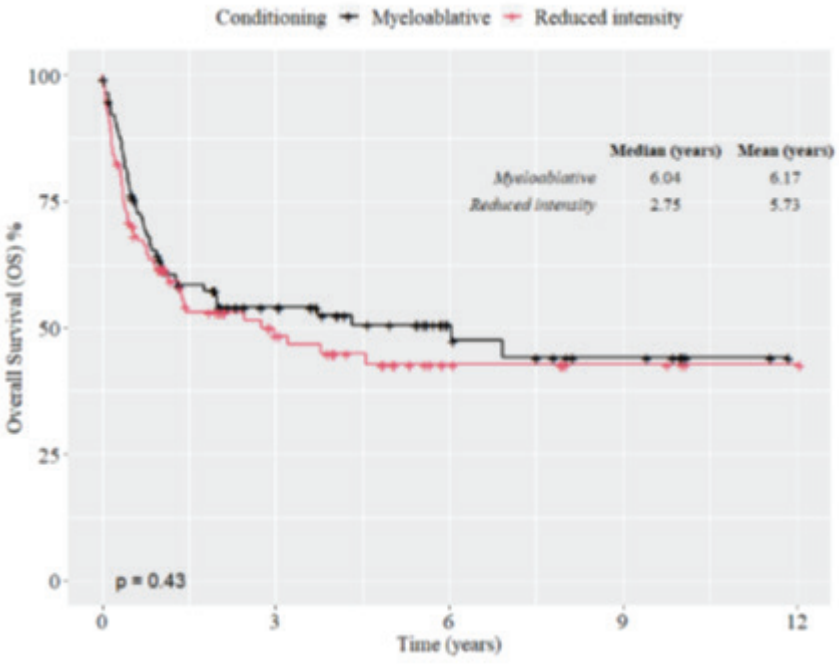

FIGURE 11– Kaplan Meier survival stratified by gender of cell source.

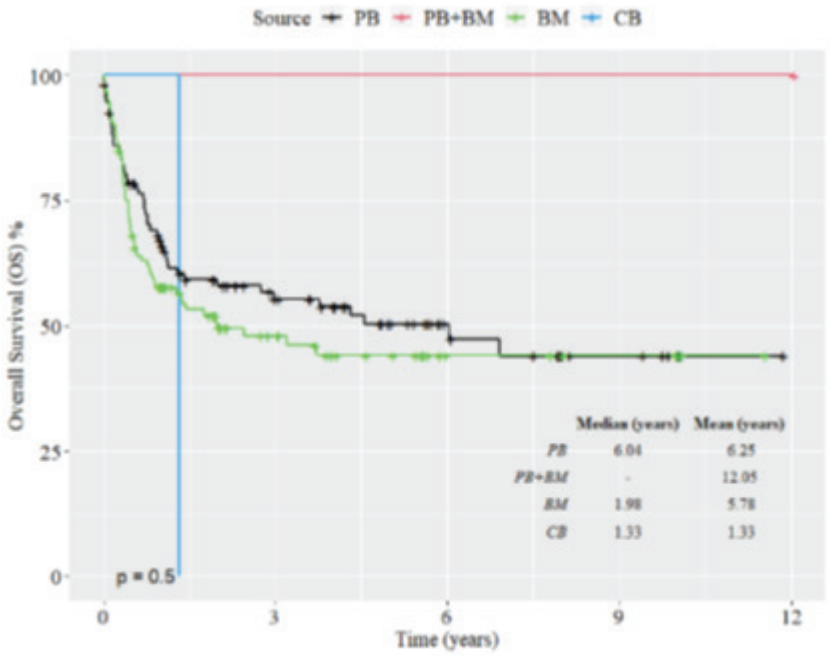

FIGURE 12 - Kaplan Meier survival stratified by GVHD prophylaxis

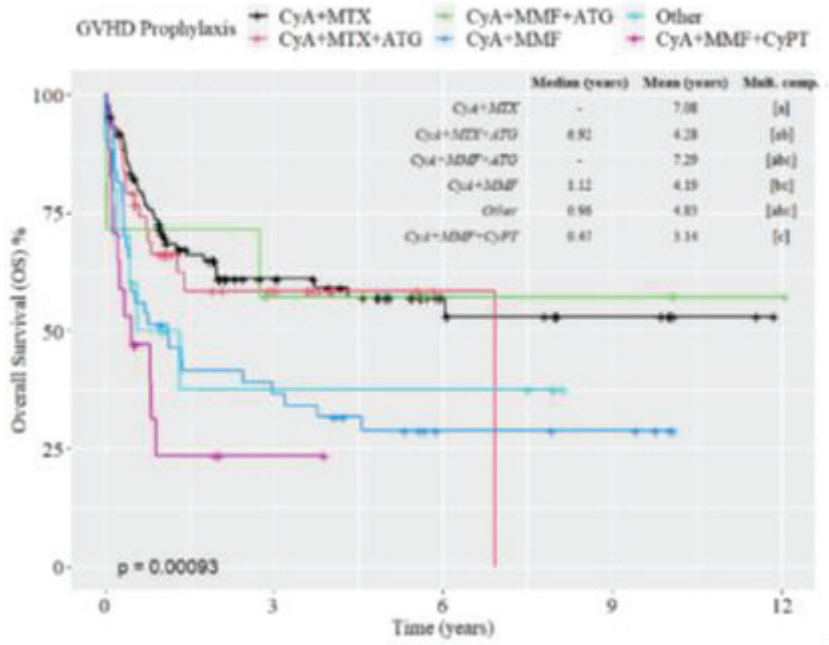

FIGURE 13 – Kaplan Meier probability of survival stratified by relapse.

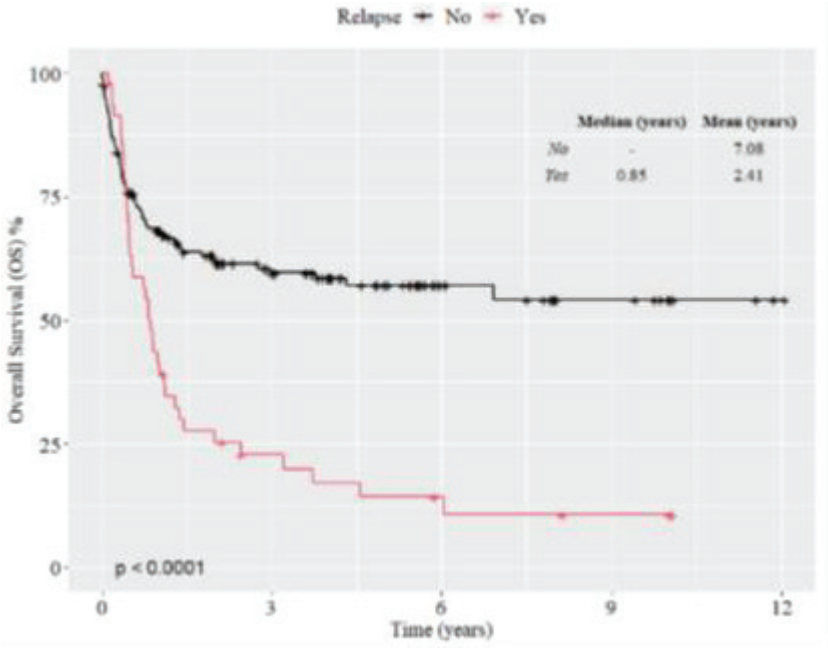

TABLE 5 - Relative risk and confidence interval for relapse and GVHD prophylaxis

Variables	RR	CI (95%)	P-value
Relapse	2,452	(1,66 - 3,63)	**<0,001**
GVHD prophilaxis			
CyA+MTX+ATG	1,174	(0,67 - 2,06)	0,578
CyA+MMF+ATG	1,078	(0,33 - 3,48)	0,901
CyA+MMF	2,094	(1,31 - 3,35)	**0,002**
Other	1,862	(0,79 - 4,39)	0,155
CyA+MMF+CyPT	3,321	(1,74 - 6,35)	**<0,001**

TABLE 6 - Crosses with death, p-value of the log rank test and median and mean survival time.

Variables	Death			Survival time		P-value
	No	Yes	Total	Median	Mean	
Sex						
Male	68 (51,13%)	65 (48,87%)	133 (100%)	3,21	5,76	0,290
Feminine	52 (53,61%)	45 (46,39%)	97 (100%)	4,56	6,17	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
CFS						
Very fit	4 (80%)	1 (20%)	5 (100%)	-	9,11	0,520
Fit	8 (57,14%)	6 (42,86%)	14 (100%)	6,92	5,71	
Managing well	83 (50,61%)	81 (49,39%)	164 (100%)	2,97	5,86	
Very mild frailty	23 (51,11%)	22 (48,89%)	45 (100%)	2,75	5,96	
Mild frailty	2 (100%)	0 (0%)	2 (100%)	-	12,05	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
KPS						
60	2 (66,67%)	1 (33,33%)	3 (100%)	-	0,23	0,530
70	2 (66,67%)	1 (33,33%)	3 (100%)	-	0,47	
80	16 (53,33%)	14 (46,67%)	30 (100%)	1,41	0,61	
90	35 (52,24%)	32 (47,76%)	67 (100%)	1,97	0,67	
100	65 (51,18%)	62 (48,82%)	127 (100%)	6,04	1,99	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
DRI						
Low	18 (54,55%)	15 (45,45%)	33 (100%)	-	6,62	0,052
Intermediate	76 (56,72%)	58 (43,28%)	134 (100%)	6,92	6,37	
High	19 (38%)	31 (62%)	50 (100%)	1,12	4,26	
Very high	2 (33,33%)	4 (66,67%)	6 (100%)	0,77	0,66	
Total	115 (51,57%)	108 (48,43%)	223 (100%)			
Donor						
Related	97 (52,72%)	87 (47,28%)	184 (100%)	3,77	6,11	0,140
Unrelated	18 (58,06%)	13 (41,94%)	31 (100%)	6,92	5,81	
Cord	0 (0%)	1 (100%)	1 (100%)	1,33	1,33	
Haplo	5 (35,71%)	9 (64,29%)	14 (100%)	0,65	3,9	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Donor sex						
Male	76 (52,78%)	68 (47,22%)	144 (100%)	2,75	6,2	0,840
Feminine	44 (51,16%)	42 (48,84%)	86 (100%)	3,73	5,61	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Donor HLA8						
HLA 8/8 matched	99 (52,38%)	90 (47,62%)	189 (100%)	4,32	6,1	0,200
HLA <=7/8	21 (51,22%)	20 (48,78%)	41 (100%)	1,28	5,69	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Conditioning						
Myeloablative	62 (53,45%)	54 (46,55%)	116 (100%)	6,04	6,17	0,430
Reduced intensity	58 (50,88%)	56 (49,12%)	114 (100%)	2,75	5,73	

TABLE 7 - Relative Risk Indices and Confidence Interval for the Cox Multivariate Regression Model

Variables	RR	CI (95%)	P-value
CFS	0,992	(0,71 - 1,39)	0,961
KPS	0,984	(0,96 - 1,01)	0,228
Sex Feminine	0,838	(0,56 - 1,26)	0,394
Donor Unrelated	0,291	(0,1 - 0,81)	**0,018**
Donor Haploidentical	2,076	(0,58 - 7,47)	0,263
Donor Age	0,975	(0,95 - 1)	0,081
Donor HLA <= 7/8	0,543	(0,21 - 1,41)	0,210
Conditioning Reduced intensity	1,008	(0,67 - 1,51)	0,971
Source BM	1,056	(0,69 - 1,62)	0,803

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