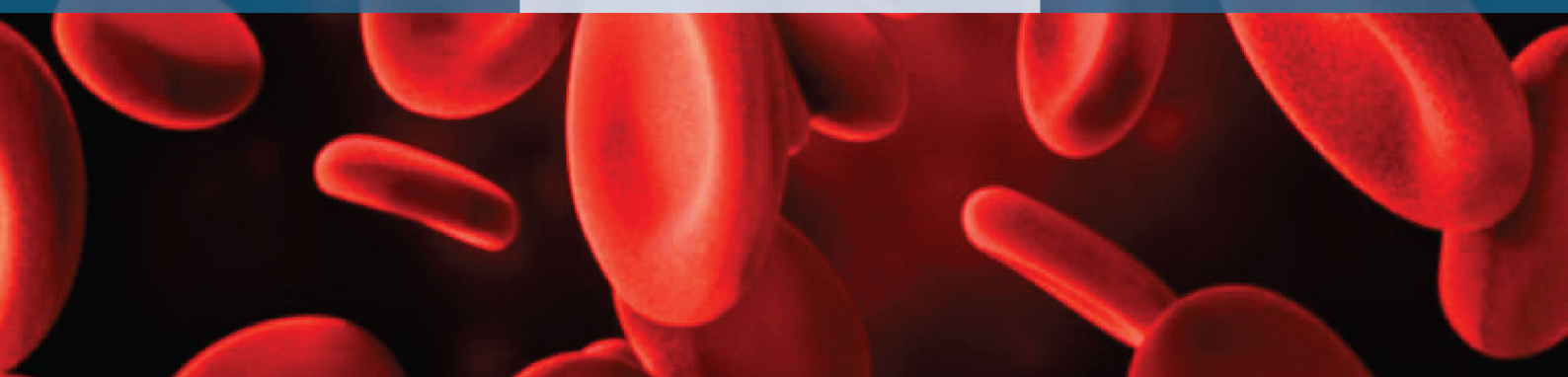
ISSN 2675-374X
DOI: 10.46765/2675-374X.2021v2n2

JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY

JBMTCT

5TH EDITION

SBTMO
SOCIEDADE BRASILEIRA DE TERAPIA CELULAR E TRANSPLANTE DE MEDULA ÓSSEA



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JBMTCT
v.2, n. 2
Apr - Jun, 2021

JBMTCT - Journal of Bone Marrow Transplantation and Cellular Therapy

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The JBMTCT, Journal of Bone Marrow Transplantation and Cellular, is an official publication of the Sociedade Brasileira de Transplante de Medula Óssea (SBTMO).

Cataloging-in-Publication data

Journal of Bone Marrow Transplantation and Cellular Therapy – JBMTCT

Rio de Janeiro, Brazilian Society of Bone Marrow Transplantation, v. 2, n. 2, Apr./Jun., 2021.

111 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, 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

DOI: 10.46765/2675-374X.2021v2n2p103

THE IMPORTANCE OF THE ACCESSIBILITY TO CELL THERAPY IN BRAZIL

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Running title: ACCESSIBILITY TO CT IN BRAZIL

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Due to the undeniable importance of cell therapy (CT) in current medicine [1-4], especially in the area of onco-hematology, some initiatives were taken by SBTMO, the first of which was the incorporation of the name TC to the name of our society, considering that the Hematopoietic Stem Cell Transplantation (HSCT) itself is one of the most successful treatments with CT. Another important decision was the creation of a working group to discuss in greater depth these issues, having as the first concrete act the publication of the Brazilian Consensus on CT in the latest edition of the SBTMO magazine.

Continuing these actions, a regional meeting was held on 27 and 28 May, 2021, with the VIII Fani Job Hematology Meeting, coordinated by Professor Lúcia Silla, from Porto Alegre, with a topic exclusively dedicated to CT. Dr. Lúcia is internationally renowned for her dedication to research with Natural Killer (NK) cells [5] but she held an event in a comprehensive way, covering all current aspects, involving Gene Therapy (GT) and CAR-T-cells.

Several points were addressed, from pre-clinical studies, cell expansion platforms, licensing and manufacturing of cells for NK and CAR-T cell, infusion of donor lymphocytes and their interrelationship with the CAR-T cell, in addition to aspects of these therapies in Europe and in the United States.

Another very relevant issue was the discussion of clinical trials in advanced therapies presently going on in Brazil, including representatives of centers from the northeast, southeast, and south of the country, with the special participation of Dr Renata Parca from ANVISA and Dr Antonio Carlos Campos de Carvalho.

Another great lesson we had was listening to the experience of Barcelona in the development and licensing of CAR-T cell products by Dr Alvaro Urbano Ispizua, a model that draws attention for its excellence and for the possibility of covering several hospitals in Spain, as well as being an example in cooperative work, which we believe is essential at this time to improve accessibility.

We ended the last day with a panel of 28 participants, in addition to the audience, who actively participated with questions and comments, with Dr. Carmem Bonfim as the transplant and pediatrics representative, who made excellent contributions.

The discussion on academic and industrial CT was a huge learning experience for all of us.

It was very important to know the initiatives of Brazilian groups, such as genetic studies and clinical studies with NK already developed at the Hospital de Clínicas de Porto Alegre, in addition to the efforts of the Faculty of Medicine of Ribeirão Preto, in partnership with Butantan Institute to develop a vector for CAR-T cells, preclinical studies at Fiocruz, clinical studies at Hospital Albert Einstein and Hospital São Rafael with CAR-T-cells. Which validates the need to carry out a national consortium for the growth of CT across the country.

The standards generated by CONEP and ANVISA, along with the definitions of remuneration for this work and cooperation were also addressed, so that they are officially made feasible, and among these initiatives, the beginning of official negotiations between SBTMO and international partners, such as the experience of Prof. Alvaro Urbano Ispizua in Barcelona and the collaboration of Dr Marcos de Lima from Ohio university.

With this aggregating and inclusive spirit, understanding the need to join forces so that we can have a robust CT program in Brazil as we presently do in HSCT, the meeting was concluded by Dr Lucia Silla with the participation of the president of SBTMO, Dr. Nelson Hamerschlak and the future president Dr. Fernando Barroso.

THE PARTICIPANTS WERE:

- Lucia Silla (RS): UFRGS
- Martin Bonamino: INCA and FIOCRUZ
- Virginia Picanço e Castro (SP): Blood Center of Ribeirão Preto
- Edina Poletto (RS): Universidade Federal do Rio Grande do Sul
- Karina Tozatto Maio (SP): HCFMUSP e HIAE
- Dean A. Lee, MD PhD: Nationwide Children's Hospital/The Ohio State University
- Belinda Simões: Senior consultant technical university Munich
- Lucila Kerbauy (SP): HIAE
- Roberto Giugliani (RS): Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil
- Sang Han (SP): Escola paulista de medicina, Universidade federal de São Paulo (EPM-UNIFESP)
- Úrsula Matte (RS): UFRGS and HCPA
- Hans Kolb: Universitaets-Klinik, Munich
- Andrea Velardi, MD (Itália): University Hospital, Italy
- Marcos de Lima: Ohio State University
- Nelson Hamerschlak: Hospital Israelita Albert Einstein
- Álvaro Urbano Ispizua (Espanha): Hospital Clínic de Barcelona
- Renata Parca: Anvisa
- Antônio Carlos Campos de Carvalho (RJ): Carlos Chagas Biohys
- Marco Salvino (BA): UFBA
- Vanderson Rocha: HCFMUSP
- Jose Mauro Kutner (SP): Hospital Israelita Albert Einstein
- Karina Tozatto Maio (SP)
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- Milena Soares (BA)
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DOI:10.46765/2675-374X.2021v2n2p44

C-REACTIVE PROTEIN IN AUTOLOGOUS STEM CELL TRANSPLANTATION: PREDICTION OF CLINICAL COMPLICATION

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Running title: C-REACTIVE IN AUTOLOGOUS TRANSPLANTATION

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ABSTRACT

Objective: The aim of this study was to evaluate C-reactive protein (CRP) as a predictor of complications during autologous stem cell transplant (HSCT). Methods: We analyzed a cohort of 340 transplants. Correlation analyses were performed, including CRP obtained before HSCT, on Day+3, Day+6, Day+9, after Day+11, and at the onset of febrile neutropenia, and the following outcomes: bacteremia, severity of mucositis, length of neutropenia and hospitalization, and death. Results: the median age was 54 years old (ranging from 20 to 75), and 62% and 20% were multiple myeloma and non-Hodgkin lymphoma cases, respectively. The median CRP levels increased from D+3 to D+9 and after that decreased progressively until discharge. CRP levels were associated with bacteremia, mucositis grade, length of neutropenia and hospitalization, and death. Variation in CRP values from D+3 to D+6 predicted complications. Mortality was associated with D+9 CRP levels (19 vs. 7.9 mg/dL; p<0.01), and a ROC curve area of 0.83 (95% CI 0.7 – 0.95) to predict mortality. At a cut-off of 8.5mg/dL, D+9 CRP had 83% and 79% sensitivity and specificity, respectively.
Conclusions: In this study, CRP dynamics were associated with several HSCT complications. CRP levels curve could be applied to indicate poor outcomes during HSCT.

Keywords: autologous stem cell transplant; complication; febrile neutropenia; C-reactive protein

INTRODUCTION

Hematopoietic stem cell transplant (HSCT) is an essential and potentially curative treatment option for several malignant hematological disorders. It is considered standard of care for multiple myeloma patients and rescue therapy in relapsed lymphoma patients. Although HSCT has been considered a safety procedure compared to other types of transplant, multicenter cohorts had reported the mortality related to this procedure to be around 2- 5% [1]. The most prevalent cause of death is related to infection episodes, mainly bacterial sepsis during neutropenia [2,3]. Mucositis is another frequent and sometimes severe complication of HSCT conditioning chemotherapy. Although mucositis is not commonly directly related to mortality, the severity of mucosal damage is a significant risk factor for infection, bleeding and contributes for prolonged hospitalization length, higher costs and worst quality of life [4,5].

Some serum biomarkers, such as procalcitonin, IL-6, and C-reactive protein (CRP) have been applied in order to early identify potential clinical complications and to guide medical staff to intensify clinical support for those in high-risk. Their impact in predicting outcomes was validated in critical care patients, and

neutropenic patients [6-8]. Also, C-reactive protein is a widely used biomarker, and considered a low-cost exam.

In this study, we describe the dynamics of CRP during HSCT and its correlation with pre-transplant characteristics, and infectious and non-infectious clinical outcomes.

METHODS

This observational study was conducted in two centers (Hospital Universitário Clementino Fraga Filho [HUCFF], Federal University of Rio de Janeiro, Brazil, and Complexo Hospitalar de Niteroi [CHN]. HUCFF is a tertiary care hospital with 200 beds, including a hematology and hematopoietic cell transplant (HSCT) unit with eight single-bed rooms equipped with high-efficiency particulate air (HEPA) filter and positive pressure, and five double-bed rooms without HEPA filter. CHN is a tertiary care hospital with ~400 beds, including a hematology and hematopoietic cell transplant (HCT) unit with eight single-bed rooms equipped with HEPA filter and positive pressure, and 12 single-bed rooms without HEPA filter. Both institutions' Ethical Committees approved this study ("Comitê de Ética em Pesquisa do Hospital Universitário Clementino Fraga Filho" and "ProCEP – Comitê de ética em Pesquisa da ESHO Empresa de Serviços Hospitalares – Hospital Pro-Cardiaco"). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

For this analysis, we selected all patients admitted between 2012 and 2016 who fulfilled the following criteria: a) high dose chemotherapy for HSCT conditioning; b) at least two measures of CRP performed during the HSCT hospitalization period; and c) at least 18 years old. Patients were included more than once when submitted to a second HSCT during the period of enrollment. Patients were followed from the conditioning period until discharge after engraftment or death. The cohort was described regarding demographic characteristics (age, gender), underlying disease and type of conditioning regimen. The following clinical outcomes were analyzed: 1) bacteremia, 2) severe mucositis (by the Common Toxicity Criteria of National Cancer Institute World Health Organization), 3) length of neutropenia 4) length of hospitalization, and 5) death. All data were collected prospectively, as part of an extensive database of stem cell transplant recipients.

Neutropenia was defined as an absolute neutrophil count (ANC) <500/mm3, and Bone marrow recovery as at least two consecutive ANC >500/mm3, obtained on two different days. Grade 3 or 4 were considered severe mucositis. Fever was defined as an axillary temperature ≥38o C. In the case of fever during neutropenia (febrile neutropenia), blood cultures were drawn, and the patients were immediately started on intravenous (IV) Cefepime unless a previous episode of febrile neutropenia documented a Cefepime-resistant Gram-negative organism. In this case, a carbapenem (imipenem or meropenem) was started. Blood cultures were repeated if the fever persisted, recurred, or as clinically indicated. Modifications in the empirical antibiotic regimen were performed according to cultures' results and the patient's clinical course. Additionally, febrile neutropenia episodes were defined as fever of unknown origin (FUO), bacteremia, microbiologically documented infection without bacteremia, or clinically documented infection. Bacteremia was defined as presence of positive blood culture either with a single organism or polymicrobial infection. Microbiologically documented infection without bacteremia was defined as the presence of pathogen in fluid or tissue suspected to be involved with the infection. Clinically documented infection was when a site of infection was diagnosed by signs or radiological features (e.g., cellulitis, pneumonia) but no microbiological documentation was achieved.

CRP values were expressed in mg/dL, and the negative reference value by the manufacturer is was < 0.3mg/dL. As an observational study, CRP samples were drawn at the discretion of clinicians. For the present study, we analyzed CRP values collected in the following interval periods, related to the stem cell reinfusion ("D Zero"):

- before HSCT CRP: admission day until D-2
- D Zero CRP: D-1 until D+1
- D+3 CRP: D+2 until D+4
- D+6 CRP: D+5 until D+7
- D+9 CRP: D+8 until D+10
- After D+11 CRP: after D+11 until discharge

Finally, samples were drawn close to febrile neutropenia (FN CRP) and engraftment (engraftment CRP) were also included in the analysis.

CRP single values and the dynamic of values variation between interval periods were analyzed as outcomes' predictors. All statistical analyses were performed using the SPSS for Windows software (version 21.0.1, SPSS, Inc., USA). The Chi-square test was used to compare proportions, and the Mann-Whitney test

to compare continuous variables; Spearman test was used to correlation analyses, and Receiver Operating Characteristic (ROC) curve to define sensitivity and specificity values. P values <0.05 were considered statistically significant.

RESULTS

A total of 340 stem cell transplants were performed during the study period in 338 patients. Two patients had two HSCT performed. The median age of the group was 54 years old (ranging from 20 to 75), and 53% were male. Baseline diseases were more frequently Multiple Myeloma (62%), Non-Hodgkin Lymphoma (20%), and Hodgkin Lymphoma 17%. Three patients had other baseline diseases (Acute Myeloid Leukemia and germinative tumor in 1 and 2 cases, respectively). Demographic and clinical characteristics are shown in Table 1. Febrile neutropenia (FN) was documented in 299 (88%), and bacteremia in 80 cases (26,7% of FN). Severe mucositis was observed in 26% of patients. Seven patients from the cohort died during hospitalization (2%).

A total of 1761 CRP tests were included in the analyzes. The median samples collection per patient was 5, ranging from 2 to 7. At admission, 158 (66%) patients had CRP levels above the normal reference. The median level of Before HSCT CRP was 0.48mg/dL (ranging from <0.01 to 15), and decreased on D Zero (median 0.38md/dL) (p<0.01). (Table 2) In the post-transplant period, the median variation from D+3 to D+6 CRP was 3.23 mg/dL (- 7.6 – +31) which represented a fourfold increase, and only 11% of patients had a decrease in CRP values on this period. After D+9 and engraftment, there was a decrease in the CRP median (p<0.01). On discharge, CRP medians remained higher than on D Zero levels (p<0.01). (Figure 1)

Febrile neutropenia was documented in 299 transplant recipients. Only in one patient, FN CRP was not collected at the onset of FN.CRP levels at the onset of FN were higher in patients with documented bacteremia compared to others (5.5 vs. 2.69 mg/dL, respectively: p=0.01). When testing FN CRP to predict bacteremia using the ROC curve, the area under the curve (AUC) obtained was 0.63 (CI 95% 0.55 – 0.7), with no cut-off value with a reasonable sensitivity or specificity to be considered. Patients who developed bacteremia had statistically higher CRP levels at D+6, D+9, and D+11 than patients without bacteremia (p<0.05 for all).

Patients with severe mucositis had higher median CRP levels on D+6, D+ 9 and after D+11 (p<0.05 for all). The best linear relationship between CRP and mucositis grade was obtained with the D+6 CRP (r=0.4; p<0.01). Median D+6 CRP in patients with severe mucositis was higher compared to those with grade 1 and 2 (14.9 and 2.9 mg/dl, respectively; p<0.001), and the AUC obtained was 0.76 (CI 95% 0.69 – 0.83).

Length of both neutropenia and hospitalization had statically significant correlations with D+3, D+6, D+9 and after D+11 CRPs. The stronger linear relation was obtained with the D+6 CRP (r=0.39; p<0.001 for both outcomes).

When comparing the CRP of patients that died with those discharged, there was an associated-on D+9 (19 vs. 7.9 mg/dL) and D+11 (14.5 vs. 3.4 mg/dL) CRP levels (p<0.01 for both). The D+9 CRP AUC was 0.83 (95% CI 0.7 – 0.95) to predict mortality (Figure 2), and a cut-off of 8.5mg/dL the D+9 CRP had 83% and 79% of sensitivity and specificity, respectively.

The CRP variation from D+3 to-D+6 was associated with bacteremia, severe mucositis, and length of neutropenia and hospitalization (p values < 0.01). Areas obtained by the ROC curve were similar to those reached with single point CRP values, for instance, CRP variation from d+3 to D+6 and FN CRP had both AUC of 0.62 to predict bacteremia. For severe mucositis, CRP variation from D+3 to D+6 and D+6 CRP had both AUC 0.7. Although the CRP variation from D+3 to D+6 was not statistically associated with mortality, in patients who died and were discharged it was 9.3 vs. 3.2 mg/dL (p=0.62), respectively.

DISCUSSION

Our study was intended to describe the correlation between the CRP absolute values and variations in its dynamic in patients undergoing HSCT, and to search for possible cut off values for prognostic outcomes. We found a correlation with a four-fold increase between the median variation of CRP from D+3 and D+6 and the outcomes of mucositis (grade 3 and 4), bacteremia, increased neutropenia duration, and more extended hospitalization. We also found a statistically significant correlation between the D+9 CRP and death (>8.5mg/dL with 83% and 79% respectively of sensitivity and specificity), but no reasonable cut off value on the ROC curve was noted.

Regarding preconditioning CRP values, we found no correlation with any outcomes we were studying. The literature has some confronting data over the CRP predicting capabilities when measured before HSCT. AKI et al. found, in a cohort of allogeneic transplan-

tation patients, that prior conditioning CRP values were associated with validating prognostic scores (HCT-CI, EBMT), and had a significant impact on overall survival [6]. CRP equal to or higher than 10mg/L (or 1.0 mg/dL) had a significant effect on overall survival, as well as serum ferritin and the HCT-CI risk score. Another study, by Andrew S. Artz et al., confirmed the previous results and suggested levels over than 0.367mg/dL as a threshold for transplant-related mortality [9]. In a study performed in lymphoma patients submitted to autologous stem cell transplant, CRP levels before HSCT had significant survival impact with special emphasis on disease status at the procedure [10]. In our data, including only autologous recipients, prior conditioning CRP was over 0.3mg/dL (or 3mg/L) in 66% of patients. A significant association with mortality was only observed considering later collected samples (D+9 and D+11 CRP sample). CRP collected on D+9 had the best performance to predict mortality. Considering 8.5mg/dL (or 85mg/L) as a cutoff, CRP on D+9 had sensitivity and specificity of 83% and 79% respectively. This threshold is very higher than those described by Aki and Artz in allogeneic patients [6,9].

Regarding febrile neutropenia and bacteremia, despite a significant difference between CRP values of patients with and without bacteremia, no cut off value had a good performance to predict the outcome. The same results were observed for severe grades of mucositis. The role of systemic inflammatory markers in febrile neutropenia was addressed in several studies [11-14], with conflicting results. These studies demonstrated that, although CRP levels were higher in patients with complicated febrile neutropenia episodes than non-complicated episodes, there were better markers to be applied, such as procalcitonin (PCT), presepsin, and others. A meta-analysis reported by Wu et cols [15], concluded that PCT was a highly specific but less sensitive marker of bacterial infection in patients with FN, while CRP was a highly sensitive but less specific marker for bacterial infection. In a study by Karin SR Massaro et al. [14], CRP was compared to procalcitonin (PCT) in febrile neutropenic patients, and PCT levels had a better association with severe infection than CRP concentration to distinguish presence and absence of disseminated infection, but neither biomarkers had an association with mortality. In another study including febrile neutropenia patients, CRP was combined to MASCC risk index to predict the risk of death within 30 days [16]. The combination of the inflammatory parameter (cut-off of 15mg/dL) and the clinical index successfully identified patients with a high risk of death. In a more recent study including only stem cell transplant recipients, Igor Stoma et al. [17] showed that CRP samples collected 4-hour after the onset of febrile neutropenia were significantly associated with Gram-negative bacteremia. The optimal cut-off value of 16.5mg/dL had an average diagnostic value (AUC:0.71) but a low sensitivity (40%). In this consideration they did not recommend CRP as a routinely biomarker for sepsis. In our study, CRP dynamic variation had interesting associations, with potential clinical applicability. We found a median increment of 3mg/dL from the D+3 to the D+6 CRP, and very few patients (~10%) had decrease in CRP values during this period. The D+3-D+6 variation had a significant correlation with several outcomes (bacteremia, mucositis, duration of neutropenia and hospitalization), but no prediction of mortality. In our data, the CRP variation from D+3 to the CRP from the onset of febrile had no significant association to the development of bacteremia.

The use of antibacterial prophylaxis with quinolones was decided at the discretion of the clinicians. To overcome this limitation, we performed a complementary analysis that revealed no difference in the FN CRP level in patients with or without antibacterial prophylaxis. (p=0,946). Quinolones prophylaxis had no association with occurrence of bacteremia (p=0,165) in this cohort.

This study has some limitations inherent to its retrospective design leading to some missing information from a small number of patients. Nevertheless, the data obtained was considered statistically sufficient to assume relations between the HSCT complications and the dynamic of CRP as pointed out.

The study successfully accessed the dynamic of CRP in HSCT recipients and its association with outcome. CRP levels showed associated with several outcomes, with huge variations. Although there was no cut-off point reasonable to be taken for any of these outcomes, CRP dynamic may be used as possible early red flag markers for patients more prone to complications during HSCT.

CONCLUSION

CRP levels were associated with bacteremia, mucositis grade, duration of neutropenia and hospitalization, and death. Variation in CRP from D+3 to D+6 was an interesting predictor of complications, although the best prediction of mortality was a sample collected on Day+9.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

This study was approved by institution's Ethical Committees from both centers ("Comitê de Ética em Pesquisa do Hospital Universitário Clementino Fraga Filho" – Reference Number CAAE 51013315.0.0000.5257, and "ProCEP – Comitê de Ética em Pesquisa da ESHO Empresa de Serviços Hospitalares – Hospital Pro-Cardiaco"- Reference Number CAAE 51013315.0.3001.5533). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The Ethical Committee did not request informed consent as only retrospective data were included and all details that might disclose the identity of the subjects under study should be omitted.

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TABLE 1: Characteristics of 340 autologous stem cell transplants

	N = 340
CENTER, N (%)	
1	51 (15)
2	289 (86)
CONDITIONING REGIMEN, N (%)	
MELPHALAN	211 (62)
BEAM	111 (33)
BUCYVP	10 (3)
CBV	4 (1)
OTHERS	4 (1)
FEBRILE NEUTROPENIA, N (%)	299 (88)
UNKNOWN ORIGIN	192 (64)
CLINICALLY DOCUMENTED	24 (8)
MICROBIOLOGICALLY DOCUMENTED	83 (28)
WITHOUT BACTEREMIA	3
WITH BACTEREMIA*	80
DUE TO GRAM NEGATIVE BACTERIA	35
DUE TO GRAM POSITIVE BACTERIA	46
MUCOSITIS, N=236 (%)	
MUCOSITIS > GRADE 2	171 (72)
MUCOSITIS > GRADE 3	61 (26)
DURATION OF NEUTROPENIA IN DAYS, MEDIAN (RANGE)	6 (3 – 36)
DURATION OF HOSPITALIZATION IN DAYS, MEDIAN (RANGE)	19 (8 – 64)
DEATH, N (%)	7 (2)

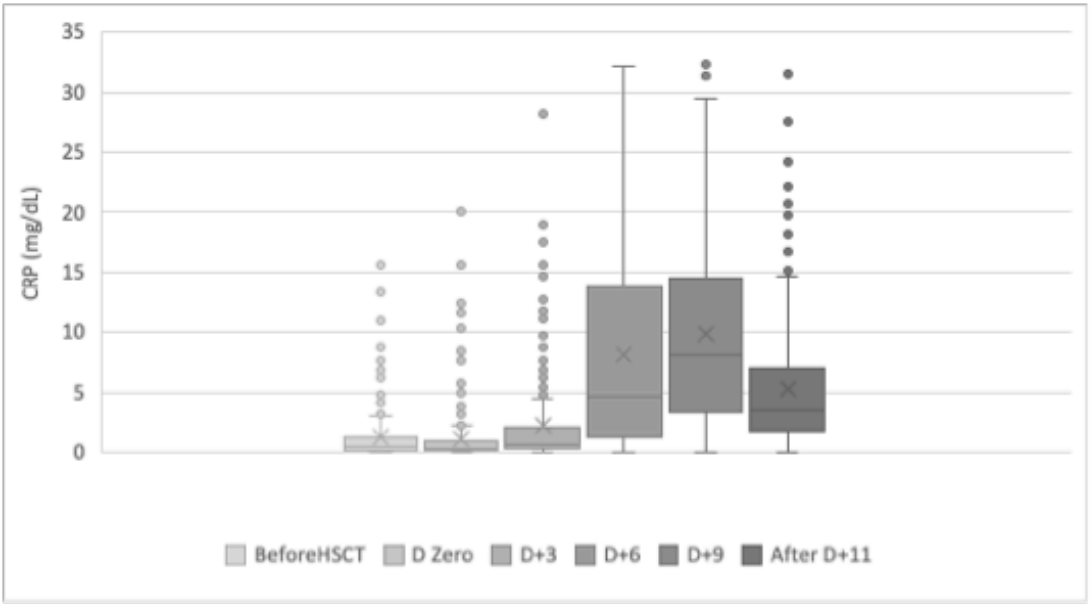
BEAM: BCNU, etoposide, cytarabine and melphalan; CBV: cyclophosphamide, carmustine and etoposide; BuCyVP: cyclophosphamide, etoposide and busulfan *One patient had both Gram-negative and Gram-positive bacteremia

TABLE 2: CRP levels according to sample collection time related to transplant

Time related to infusion (Dzero)	Median (range), mg/dL
Before HSCT, n=238	0.48 (<0.01 – 15)
D Zero, n=239	0.38 (<0.01 – 20)
D+3, n=274	0.71 (<0.01 – 28)
D+6, n=321	4.66 (<0.01– 32,2)
D+9, n=318	8.07 (<0.01 – 32.3)
After D+11, n=276	3.49 (<0.01 – 31.5)
Onset of FN, n=298	3.30 (<0.01 – 27.2)
Engraftment, n=321	4.93 (<0.01 – 31.2)

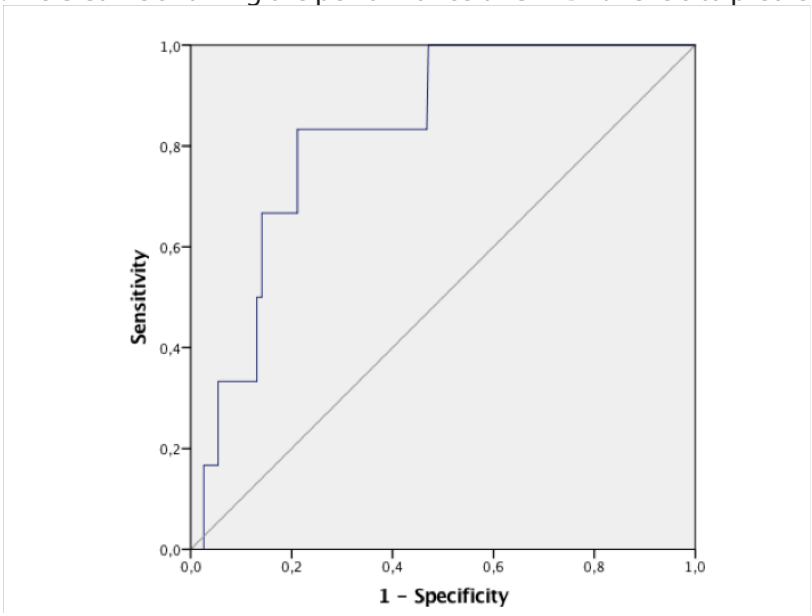
FN: febrile neutropenia; CRP: C-reactive protein

FIGURE 1: CRP variation during autologous stem cell transplant



CRP: C-reactive protein; HSCT: hematopoietic stem cell transplant

FIGURE 2: ROC Curve showing the performance of CRP D+9 levels to predict mortality



DOI:10.46765/2675-374X.2021v2n2p51

IMPACT OF LEAM AND CBV CONDITIONING ON GASTROINTESTINAL TOXICITY AT EARLY PERIODS FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION: A RETROSPECTIVE STUDY

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Running title: GASTROINTESTINAL TOXICITY AFTER LEAM AND CBV

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ABSTRACT

Objectives: To compare the severity of oral mucositis and the frequency of gastrointestinal mucositis, and to observe if there is impact of these adverse effects on overall survival (OS), in patients who underwent CBV (carmustine, BCNU, and VP-16) and LEAM (lomustine, etoposide, Ara-C, and melphalan) conditioning for autologous hematopoietic cell transplantation (aHCT). Method: We collected retrospective data from medical records (n = 120) of transplantation and mucositis in the digestive tract of Hodgkin's and non-Hodgkin's lymphoma patients. Results: The frequency of OM grade 1 was higher in LEAM (36.76%) than in CBV (19.72%, p=0.038). There were no significant differences between the frequency of gastrointestinal mucositis in the two regimens (CBV - 52.11% and LEAM - 63.27%, p=0.305). CBV regimen exhibited lower 1-year overall survival (OS) than did LEAM (p=0.003). Oral mucositis grade ≥2 was associated with reduced OS in the CBV group (p=0.013). CBV regimen (HR=2.98, p 0.005) and oral mucositis grade ≥2 (HR=2.17, p=0.013) interfered negatively on the OS rate. Conclusion: Oral mucositis was more severe in CBV than in LEAM, decreasing the OS rate. Further studies with comprehensive follow-up and toxicity analyses must be undertaken to clarify the safety of LEAM conditioning in the digestive tract.

Keywords: Lymphoma. LEAM. CBV. Oral mucositis. Autologous hematopoietic cell transplantation.

INTRODUCTION

Autologous hematopoietic cell transplantation (aHCT) has been indicated for patients with refractory or relapsed Hodgkin's disease and non-Hodgkin's lymphoma, improving event-free and progression-free survival rates.[1-3] To achieve favorable outcomes, aHCT conditionings must have anti-lymphoma effects.2. High-dose chemotherapy combining cyclophosphamide, BCNU/carmustine, and VP-16/etoposide (CBV); BCNU/carmustine, etoposide, Ara-C/cytarabine, and melphalan (BEAM); or cyclophosphamide, etoposide, Ara-C/cytarabine, and carmustine (BEAC) are examples of conditionings adopted to avoid high-dose irradiation;[2,4] these regimens are selected based on institutional experiences and preferences. An optimal conditioning regimen for aHCT, however, remains a prominent challenge in lymphoma treatment.[5]

Carmustine leads to high lung toxicity, has a high cost, and is in shortage in many countries,[6] including Brazil.[7] This drug has been replaced by lomustine combined with etoposide, Ara-C/cytarabine, and melphalan (LEAM)[6-9] to substitute CBV in aHCT

conditioning. Although promising results are linked to LEAM, including improvement in overall and disease-free survivals[7], its toxicity in the gastrointestinal tract relative to CBV has been poorly investigated. In our institution, LEAM was introduced in 2011 to replace CBV conditioning due to carmustine shortage in the national market. However, we did not know the LEAM toxicity in the gastrointestinal tract of our patients and whether this toxicity would have an impact on overall survival. Therefore, the aim of this study was to compare the severity of oral and gastrointestinal mucositis in lymphoma patients who underwent CBV and LEAM conditionings prior to aHCT, as well as the impact of these toxicities on overall survival (OS).

METHOD

This retrospective study enrolled consecutive Hodgkin's and non-Hodgkin's lymphoma patients who underwent aHCT. The study was approved by the ethics committee of our institution (Project #139-420-2011, CAAE 0102.0.420.000-11) and followed according to the criteria defined by the Declaration of Helsinki. Informed consent from all adult patients and guardians of underage patients was obtained for aHCT-related procedures.

Patient and transplantation characteristics

We examined the medical records from patients who underwent aHCT at the Bone Marrow Transplantation Center of Hospital of Juiz de Fora University, Brazil, between September 2004 and July 2016. Inclusion criteria were: patients diagnosed with Hodgkin's and non-Hodgkin's lymphoma who underwent a conditioning regime with CBV or LEAM, who followed the oral care protocols, and whose records had clear information on oral and gastrointestinal mucositis. Exclusion criteria were medical records with insufficient information about time duration of neutropenia and transplantation, and about oral and gastrointestinal toxicity. Medical records of patients who refused the oral care protocols were also excluded.

Data collection

The data were collected by a single researcher with expertise in bone marrow transplantation. The following information about the patient and the transplantation was collected: age, sex, primary disease, status of the disease (refractory, partial, or complete remission), duration of neutropenia (number of days with neutrophil count ≤500 cells/mm3), and duration of hospitalization (number of days from the first day of conditioning to the day of discharge from the transplantation center). Data on oral mucositis and diarrhea were collected from the first day of the conditioning to the last day in the bone marrow transplantation. Presence of diarrhea related to gastrointestinal mucositis was considered only when non-infectious etiology (confirmed by microbial cultures) and ≥3 daily episodes were registered. We also recorded the presence of prescriptions for artificial nutrition.

LEAM and CBV conditionings

Patients who underwent HCT from 2004 to 2011 received the CBV conditioning; from 2011 to 2016, all the selected patients were exposed to the LEAM conditioning. Patients in the LEAM group received lomustine (300 mg/m2) in D-4, etoposide (1000 mg/m2) in D-3, aracytin (4000 mg/m2) in D-2, and melphalan (140 mg/m2) in D-1. Dosages for LEAM conditioning regimen were according to Dos Santos et al. (9). Hematopoietic cells were infused 24 h following the end of the melphalan conditioning. In CBV group, the patients received cyclophosphamide (1800 mg/m2) from D-6 to D-3 (total of 7200 mg/m2), etoposide (400 mg/m2) every 12 h from D-6 to D-4 (total of 2400 mg/m2), and BCNU (450 mg/m2) in D-2.

Oral care and oral mucositis assessment

All patients received oral hygiene guidance and an oral care protocol for prevention and treatment of oral mucositis. The patients used a soft toothbrush and toothpaste with fluoride, and alcohol-free antiseptic mouthwash for 30 s twice per day. Low-level laser therapy was administered three times per week using a diode laser (gallium indium arsenide, InGaAlP, 660 nm, 0.04 cm2 spot, 100mW, 25J/cm2, 10 s per point, 1 J per point) from the first day of oral mucositis symptoms to the point of complete remission of the lesions.

Oral mucositis severity was recorded daily by a dentist following the World Health Organization grading criteria as follows: 0 – absence of oral lesions; 1 – only erythema; 2 – presence of pseudomembrane or ulceration, but normal oral ingestion is possible; 3 – presence of ulcerated lesions, and only liquid diet is possible by oral ingestion; 4 – presence of ulcerated lesions, and oral ingestion is not possible; necessary artificial nutrition.

Primary and secondary outcomes

The primary outcome was the impact of CBV and LEAM regimens on the severity of oral and gastrointestinal mucositis. The secondary outcome was the impact of oral and gastrointestinal mucositis on overall survival (OS).

Statistical analyses

Numerical and categorical data were shown as median and minimum–maximum, and absolute and relative (%) frequencies, respectively. The medical records were grouped in LEAM and CBV conditionings. Comparisons between the two groups were performed using the Mann–Whitney test and $\chi 2$ test with Bonferroni correction. In each group, we considered duration of neutropenia and transplantation (dichotomized in accordance with the median of days), presence of non-Hodgkin's lymphoma, and disease status (in partial remission/refractory status) as risk factors for oral mucositis grade ≥2 and for presence of gastrointestinal mucositis. The Kaplan–Meier curve was used to measure OS, which was defined as the first day of enrollment in the hospital to the last day of the follow-up registration. Mean follow-up was one and three years in the LEAM and CBV conditioning groups, respectively. We applied log-rank test to compare the OS between the two groups and to verify the impact of oral mucositis and diarrhea in the OS. Cox proportional hazards regression was applied to determine which factor was decisive for OS. We adopted 5% as the level of statistical significance.

RESULTS

From September 2004 to July 2016, a total of 286 aHCTs were performed in our institution. Of these, 128 were performed on patients with a diagnosis of either Hodgkin's or non-Hodgkin's lymphoma. Eight medical records showed inconsistent data, leading to a total of 120 medical records selected for the study.

Patients and transplantation characteristics

Table 1 depicts patient and transplantation characteristics. The CBV and LEAM groups were composed by 71 and 49 patients, respectively. The median age was 34 years, and the majority were male (64.17%). For both groups, the most frequent primary disease was Hodgkin's lymphoma, nodular sclerosis subtype. In the LEAM group, the frequency of patients with complete remission of the disease (51.0%) was higher than in the CBV group (32.4%, $p = 0.009$). In addition, the median duration of neutropenia in LEAM (8.5 days) was significantly lower than in CBV (12 days, $p < 0.001$); a similar result was found for length of hospitalization (LEAM – 18 days vs. CBV – 21 days, $p = 0.014$).

Oral and gastrointestinal mucositis

Table 2 shows the data of oral and gastrointestinal mucositis, as well as of artificial nutrition prescription. Oral mucositis was detected in 52.5% of patients. The frequency of OM grade 1 was higher in LEAM (36.7%) than in CBV (19.7%, $p = 0.038$). Grade 4 oral mucositis was not observed in any group. No significant differences were found in the frequency of gastrointestinal mucositis between the two regimens (CBV – 52.1%, LEAM – 63.3%). The percentage of artificial nutrition prescription was very low in both groups (CBV – 2.8%, LEAM – 2.0%). Analyzing the potential risk factors for oral mucositis grade ≥2 and gastrointestinal mucositis (Table 3), no significant association was found in either group for any variables.

Overall survival

The CBV regimen resulted in lower 1-year OS (mean: 64.0%, 95% CI: 51.4–74.0%) than did the LEAM regimen (mean: 80.0%, 95% CI: 64.0–89.0%, $p = 0.003$; Fig. 1). Oral mucositis grade ≥2 significantly reduced the OS in the CBV group ($p = 0.013$; Fig. 2A), but not in the LEAM group (Figure 2B). In the CBV group, OS in patients with gastrointestinal mucositis was lower than the OS of the CBV patients without gastrointestinal mucositis ($p = 0.050$; Fig. 2C); this trend was not observed in the LEAM group ($p = 0.740$; Fig. 2D). Duration of neutropenia and transplantation, primary disease, status of the disease, previous radiotherapy, and number of previous chemotherapies did not significantly influence OS.

We performed a Cox regression to verify whether the presence of gastrointestinal mucositis, oral mucositis grade ≥2, or conditioning with CBV affected OS. In the second model, after omitting gastrointestinal mucositis (Table 4), oral mucositis grade ≥2 and CBV regimen were found to significantly impact OS.

DISCUSSION

In this retrospective study, our goal was to compare oral and gastrointestinal mucositis between patients having undergone CBV and LEAM regimens. We found that the frequency of oral mucositis with mild severity was significantly higher in the LEAM group than in the CBV group. In addition, oral mucositis grade ≥2 reduced the OS rate in the CBV group,

suggesting that in CBV, the oral toxicity had a high impact.

The conditioning type was the only predictive factor for mucositis in the digestive tract in the present study. None of other factors related to the patient and the transplantation were linked to mucositis. It is important to mention that we failed to find other studies (apart from those of our group) analyzing the severity of mucositis in LEAM and CBV conditionings.

On the other hand, there are studies comparing LEAM with BEAM conditioning, which showed a lower frequency of severe oral mucositis in LEAM; however, these differences were not statistically significant.[6,8,10] Other investigations reported similar trends in oral toxicity between these two regimens.[11] Comparing BEAM and CBV, BEAM toxicity appears to be controversial. For instance, one study showed that the frequency of oral mucositis and diarrhea was higher in BEAM than in CBV,4 but another report found the opposite.[12]

Although we found differences in oral mucositis, this trend was not detected in gastrointestinal mucositis. The present study neglected the impact of gastrointestinal mucositis, addressing only its frequency, and not its severity. Other authors reported a lower rate of gastrointestinal toxicity in LEAM relative to BEAM.[6,10]

Besides high oral toxicity, the CBV regimen also presented longer durations of neutropenia compared to the LEAM regimen. Another study showed that CBV resulted in a longer duration of neutrophil engraftment than did BEAM.[12] We also detected that the length of hospitalization was reduced in the LEAM group, with a median of 18 days; in the literature, the hospitalization period of patients who underwent LEAM conditioning was >20 days.[6,10,11]

Despite the differences between the two conditionings, the oral mucositis was, in general, not severe in the majority of the patients, and the prescription of artificial nutrition was rare. This trend is in accordance with the other study that investigated LEAM and BEAM.[11] The routine oral care protocol may have contributed to this lower toxicity.

Survival in LEAM regimens has been considered similar to that observed in BEAM regimens.6,8,10 However, the follow-up period in these investigations is quite short, which limits the veracity and generalizability of any conclusions drawn. We found a significant improvement in OS in patients who underwent LEAM relative to CBV, but our follow-up period (only one year) was also substantially limited. A previous study from our group reported better OS in LEAM than in CBV, but the analysis was restricted to 100 days post-transplantation.[7] It is important to mention that some patients who were retrospectively included in the present study were analyzed prospectively in our prior study, which restricts any comparisons made between the two studies.

One of the main findings was that, in addition to CBV conditioning, oral mucositis grade ≥2 impacted negatively on OS, suggesting the importance of oral mucositis in relation to other risk factors in the transplantation. Therefore, the oral care protocols to prevent and treat oral mucositis should be emphasized in CBV regimens.

CONCLUSION

In conclusion, the severity of oral mucositis is higher in CBV than in LEAM, impacting negatively on the OS rate. Further studies, with comprehensive follow-up and toxicity analyses must be conducted to clarify the safety of LEAM conditioning for the digestive tract.

Acknowledgments: We thank all the staff of Bone Marrow Transplantation Unit at University Hospital of Federal University of Juiz de Fora, for the clinical support and medical records retrieval.

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TABLE 1 – Characteristics of the patients and the transplantation in CBV and LEAM groups.

	CBV (n=71)		LEAM (n=49)		P value*	All (n=120)	
Sex – n (%)							
Male	44	(61.97)	33	(67.35)	0.546	77	(64.2)
Female	27	(38.03)	16	(32.65)		43	(35.8)
Age (y) – median (range)	33	(8-68)	37	(14-67)	0.088	34	(8-68)
Primary disease – n (%)							
Non-Hodgkin lymphomas	24	(33.8)	23	(46.9)	0.208	47	(39.2)
Diffuse large B-cell	13	(18.3)	6	(12.2)			
High-grade B-cell	0	(0.0)	2	(4.1)			
Follicle center B-cell	0	(0.0)	1	(2.0)			
Burkitt	1	(1.4)	0	(0.0)			
Mantle cell	4	(5.6)	8	(16.3)			
Peripheral T-cell	3	(4.2)	4	(8.2)			
Anaplastic large cell	1	(1.4)	2	(4.1)			
No information	2	(2.8)	0	(0.0)			
Classical Hodgkin lymphomas	47	(66.2)	26	(53.1)		73	(60.8)
Nodular sclerosis	32	(45.1)	20	(40.8)			
Mixed cellularity	10	(14.1)	4	(8.2)			
Lymphocyte-rich	2	(2.8)	2	(4.1)			
No information	3	(4.2)	0	(0.0)			
Previous radiotherapy – n (%)	36	(50.7)	17	(34.7)	0.211	53	(44.6)
Number of previous chemotherapy – median (range)	2	(1-5)	2	(1-4)	<0.001	2	(1-5)
Disease status – n (%)							
Partial remission	34	(47.9)	17	(34.7)	0.754	51	(42.5)
Complete remission	23	(32.4)	25	(51.0)	0.009	48	(40.0)
Refractory	9	(12.7)	5	(10.2)	0.678	14	(11.6)
Without data	5	(7.0)	2	(4.0)	0.496	7	(5.8)
Days of neutropenia + - median (range)	12	(8-26)	8.5	(5-18)	<0.001	10	(5-26)
Days of hospitalization § – median (range)	21	(11-74)	18	(7-70)	0.014	20	(7-79)

CBV – cyclophosphamide, BCNU, and VP-16 conditioning; LEAM – lomustine, etoposide, Ara-C, and melphalan conditioning.
* p value for c2 test and Mann-Whitney test.
+ <500cells/mm3
§ From the first day of conditioning to the discharge of the transplantation center.

TABLE 2 – Frequency of digestive tract, liver, and lung toxicities, and prescription of artificial nutrition in CBV and LEAM groups.

	CBV (n=71)		LEAM (n=49)		P value*	ALL (n=120)	
Grade + of oral mucositis – n (%)							
0	38	(53.2)	19	(38.8)	0.160	57	(47.5)
1	14	(19.7)	18	(36.7)	**0.038**	32	(26.7)
2	9	(12.7)	8	(16.3)	0.766	17	(14.2)
3	10	(14.0)	4	(8.1)	0.481	14	(11.7)
4	0	(0.0)	0	(0.0)	1.000	0	(0.0)
Gastrointestinal mucositis – n (%)	37	(52.1)	31	(63.3)	0.305	68	(56.7)
Veno occlusive disease – n (%)	6	(8.4)	4	(8.1)	1.000	10	(8.3)
Lung toxicity – n (%)	9	(12.7)	6	(12.2)	1.000	15	(12.5)
Artificial nutrition – n (%)	2	(2.8)	1	(2.0)	1.000	3	(2.5)

CBV – cyclophosphamide, BCNU, and VP-16 conditioning; LEAM – lomustine, etoposide, Ara-C, and melphalan conditioning.
* p value for c2 test.

+ In accordance of World Health Organization classification.

TABLE 3 – Univariate analysis for factors associated to oral mucositis grade ≥ 2 and gastrointestinal mucositis in CBV and LEAM groups.

	P values*					
	Oral mucositis grade ≥ 2			Gastrointestinal mucositis		
	CBV	LEAM	All	CBV	LEAM	All
Days of neutropenia ≥ 12	0.187	0.488	0.813	0.438	1.000	0.556
Days of transplantation ≥ 21	0.785	0.173	0.532	0.808	0.127	0.583
Non-Hodgkin lymphoma (yes/no)	0.278	1.000	0.397	0.623	0.390	1.000
Previous radiotherapy (yes/no)	0.424	1.000	1.000	1.000	0.355	1.000
Previous chemotherapies ≥ 2	1.000	0.503	0.678	0.770	0.758	0.754
Partial remission/refractory (yes/no)	0.774	0.083	0.386	0.605	0.771	0.444

CBV – cyclophosphamide, BCNU, and VP-16 conditioning; LEAM – lomustine, etoposide, Ara-C, and melphalan conditioning.

* p value for c2 test.

TABLE 4 – Cox proportioznal harzard regression for overall survival with oral mucositis grade ≥2, gastrointestinal mucositis, and CBV conditioning as explanatory variables.

	HR	**95%CI**	**P value**
Gastrointestinal mucositis	1.65	0.89-3.07	0.110
Oral mucositis grade ≥2	2.17	1.17-4.03	0.013
CBV conditioning	2.98	1.38-6.41	0.005

CBV – cyclophosphamide, BCNU, and VP-16 conditioning.

FIGURE 1 – Kaplan-Meier and log rank test for overall survival in CBV and LEAM groups.

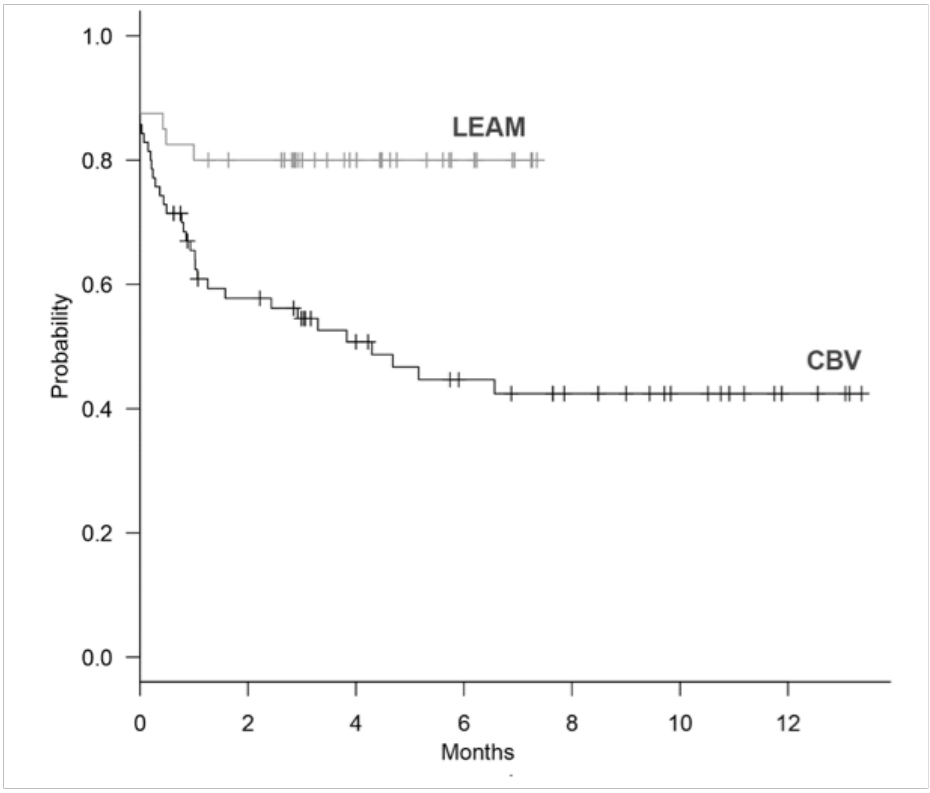
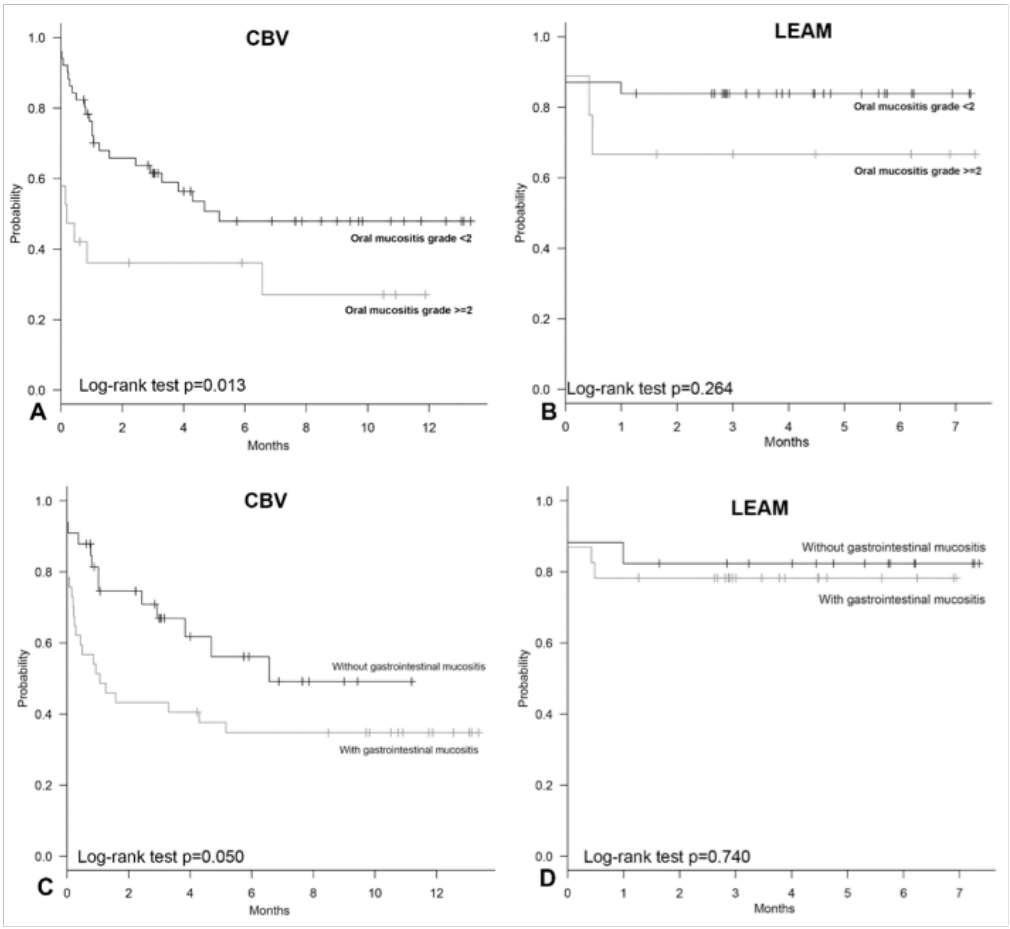


FIGURE 2 - Kaplan-Meier and log rank test for overall survival related to oral mucositis grade ≥2 and gastrointestinal mucositis in CBV (A and C) and LEAM groups (B and D).



DOI: 10.46765/2675-374X.2021v2n2p52

RELEVANCE OF MINIMAL RESIDUAL DISEASE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA: AN OVERVIEW

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Running title: IMPORTANCE OF CD34+ FOR HEMATOPOIETIC

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ABSTRACT

Minimal residual or measurable disease (MRD) can predict relapse in AML patients. Depending on patients` risk stratification, MRD status may indicate that the patient will benefit from autoSCT and alloSCT in first clinical remission. In case of persistent MRD positivity, there is no consensus on whether there are benefits to perform additional consolidation treatments to eradicate MRD before alloSCT. Anyway, the persistence of pre-transplant MRD does not contraindicate alloSCT, but indicates an urgent need for transplantation, in addition to being considered a strong independent predictor of posttransplant outcomes in AML. Currently two approaches can be used to detect MRD in clinical practice, multiparameter flow cytometry (MFC) and real time PCR (RT-qPCR), although more sensitive new technologies are emerging, such as digital droplet PCR and next generation sequencing (NGS). Despite the differences of each distinct methodology available, MRD monitoring is currently part of the standard of care for AML patients.

Key Words: Minimal Residual Disease, Acute Myeloid Leukemia, Stem Cell Transplantation

Minimal residual or measurable disease (MRD) can predict relapse in AML patients, regardless of the variability of results among the currently available methodologies. However, some data are conflicting between different studies, which can be explained by differences both in the evaluation of pre- and post-transplant approaches and in the methods for MRD detection.

MRD persistence in the postinduction phase can predict poor outcomes in AML standard risk patients, indicating that they may benefit from allo-SCT in first clinical remission (CR1).[1]

In intermediate-risk patients, MRD status may indicate consolidation with autoSCT if MRD negative (MRDneg), or allo-SCT in patients with positive MRD (MRD+). In patients with MRD+, alloSCT was able to prolong OS and increase the duration of DFS to the level of favorable risk patients[2-3], suggesting that the transplantation can reverse the adverse prognosis of positive MRD.[2,4]

On the other hand, a study observed that both patients with MRD+ in morphological remission and those with active disease at the time of allo-SCT had similar worse outcomes.[5] However, there is a bias in

this study, which includes both pediatric and adult patients, without differentiating between different molecular risk groups. Currently there is no consensus on whether there are benefits to perform additional consolidation treatments to eradicate MRD before alloSCT.[1,6-7] Furthermore, the ability of alloSCT to overcome MRD positivity, the impact of the conditioning regimen intensity on MRD clearance and the selection of the ideal donor are not fully established.[1] A recent study showed that pre-alloSCT MRD negative (MRDneg) patients, OS and RFS at three years were longer for those who received myeloablative conditioning (MAC) compared to reduced intensity (RIC) and non-myeloablative (NMA) regimens, suggesting that MAC should still be considered for patients with MRDneg AML, if tolerated.[8] It must be taken into account that many patients who are apparently MRDneg, may in fact have occult disease or have pre-leukemic clones responsible for post-transplant relapse. In addition, patients <50 years in CR1 and MRD+ pre-transplant should preferably receive MAC allo-HCT, according to a retrospective study from EBMT.[9]

Anyway, the persistence of pre-transplant MRD does not contraindicate alloSCT1 but in fact indicates an urgent need for transplantation10, in addition to being considered a strong independent predictor of posttransplant outcomes in AML.[11-13] A metanalysis showed a robust association between MRD status, post-SCT relapse and mortality, regardless the method of detection, patients age, conditioning intensity, adverse cytogenetics[13] and donor-recipient HLA-matching.[4]

However, the conversion from MRD positivity pre-transplant to MRD negativity after myeloablative conditioning alloSCT does not substantially improve the relapse rate or overall survival (OS). [11-12]

Pre-SCT MRD is not associated with a significantly increased risk of non-relapse mortality (NRM). The association between pre-SCT MRD and OS in entirely accounted by disease relapse without significant contribution from SCT toxicity.[13]

Some studies have shown that early detection of MRD post-alloSCT (<D + 100) can predict AML patients' progression (relapse or death) over an average of 13 to 94 days from the detection of MRD.[14-16] On the other hand, post-alloSCT MRD status has not been independently associated with OS, RFS and RR in other series.[13,15]

The prevention of disease relapse, mainly for high-risk patients with AML, including those with high-risk cytogenetics or molecular markers, persistent MRD, and those who responded poorly to prior therapy, is the aim of future trials to determine most effective strategies for these patients.[10]

Therefore, post-transplant MRD results allow assessments of the effectiveness of preemptive therapeutic approaches to prevent relapses, such as discontinuation of immunosuppression and donor lymphocyte infusion, as well as the role of post-remission maintenance therapies and potential new drugs under investigation to mitigate the risk of AML recurrence after aloHCT.[17]

Methods for AML MRD detection: Currently two approaches can be used to detect MRD in clinical practice, multiparameter flow cytometry (MFC) and real time PCR (RT-qPCR). Each methodology differs in the applicability and sensitivity to detect MRD.[3,11,18] More sensitive and promising new technologies are emerging, such as digital droplet PCR and next generation sequencing (NGS), which can reach sensitivity superior to RT-qPCR and MFC[18-19], but are not ready for routine application outside of clinical trials.[11,18]

PCR assays have high sensitivity (10^{-5} – 10^{-6}) but a limited applicability to ~40% of AML patients that harbor 1 or more gene abnormalities.[11] It is considered the gold standard method for patients with NPM1 mutations, with fusion genes RUNX1-RUNX1T1, CBFB-MYH11, and PML-RARA. [11,18] Mutations not recommended by European Leukemia Net (ELN) for MRD are FLT3-ITD, FLT3-TKD, NRAS, KRAS, IDH1, IDH2, MLL-PTD, EV1 and WT1 expression, because of frequent losses or gains after treatment and at relapse.[11,18] The persistence of mutations related to clonal hematopoiesis indeterminate potential (CHIP), such as DNMT3A, TET2 and ASXL1, which are detected by NGS, also have no prognostic implications.[11] They may require the acquisition of new mutations to induce relapse, a process that may take longer.[20]

As an advantage, MFC does not require the availability of a previously determined leukemia-associated immunophenotype and is applicable to approximately 90% of AML patients[12,18], but has a limited sensitivity compared with PCR-based methods[12] due to the heterogeneity of approaches and interpretation of tests among the laboratories.[13,18] Two MFC approaches are used to assess MRD: 1) the detection of the leukemia associated immunophenotype (LAIP), which defines LAIPs at diagnosis and tracks these in subsequent samples; and 2) the different-from-normal (DFN) approach, which is based on the identification of aberrant differentiation/maturation profiles at follow up. [11,18-19, 21] Both approaches should be combined to best define MFC MRD burden.[11]

A promising MFC approach is the identification of Leukemic Stem Cells (LSC). The frequency of LCS in patients in remission is an independent prognostic factor for patient outcome[22], including in a post-transplant setting.[14] LSC and conventional MFC or PCR MRD double positivity predicts a very poor outcome in AML patients.[22] Despite this promising result, this approach is still investigational.

An important issue for AML MFC MRD is that immunophenotypic shift may occur and losses and gains of antigens expressions are frequent.[23] In the same way, clonal evolution is a potential obstacle when using somatic mutations as basis for MRD analysis.[23] NGS MRD strategies may overcome these issues as it potentially has more MRD targets than MFC and PCR. [23]

NGS allows millions of DNA fragments to be sequenced simultaneously and can detect mutations with a sensitivity that is superior to RT-qPCR and MFC in some implementations.[19] Despite promising results, measurement of MRD using NGS techniques are under development but are not ready for routine application outside of clinical trials.[11]

Samples for AML MRD detection: MFC MRD should be assessed from bone marrow (BM). ELN recommends 5-10mL BM and to use the first pull for MRD assessment to avoid hemodilution. [11] Molecular MRD should be assessed preferentially from peripheral blood (PB) and requires at least 20mL PB or more, if WBC count below 1000 cells/µL, to assure sensitivity of MRD detection.[11] For patients with a previous PB MRD negative result, subsequent MRD assessments should be from BM.[11]

Threshold for MRD level: The ELN MRD Working Party suggests a threshold of 0.1% to distinguish between MRD positivity and negativity.[11] However, even patients with MRD below this threshold may have significant residual leukemia and are still at risk of relapse.[19] MRD levels below 0.1% showed prognostic significance and some studies. Cutoff levels below 0.1% (eg,,0.01%) may define patients with particularly good outcome.[11] Some studies that measured MRD by MFC used lower detection thresholds, for example, from 0.01% to 1.0%, but the thresholds depend on the presence of informative LAIPs in the study.[24]

To reach the minimum sensitivity level of 0.1%, at least 500,000 to 1 million cells must be analyzed in a flow cytometry setting, with recommended panels of ≥ 8 colors, laboratories must have complete pre, post and standardization and analytical processes, and the MRD assessment must be performed by experienced analysts.[11]

MRD timepoints: For patients undergoing allo-SCT, MRD should be assessed not earlier than 4 weeks before conditioning treatment. [11] The exact time points for post-alloSCT MRD assessments are not well established. According the recommendations of ELN, MRD should be assessed every 3 months in bone marrow during the first two years after the end of treatment.[11] Alternatively, RTqPCR MRD can be assessed in peripheral blood every 4 to 6 weeks.[11]Monitoring beyond this period of follow up should be based on the relapse risk of the patient and decided individually. [11] The definition of molecular progression is the increase ≥ 1 log10 in MRD copy numbers between two positive samples.[11] A positive MRD molecular result should be confirmed after 4 weeks.[11]

CONCLUSIONS

Despite the differences of each distinct methodology available, MRD monitoring is currently part of the standard of care for AML patients.[10-11]

For molecular MRD this is limited to APL, CBF AML, and NPM1-mutated AML. For other AML patients, MRD should be assessed using MFC. [11]

The ELN 2017 recommendations for diagnosis and treatment of AML highlight that MRD testing should be performed in experienced, centralized diagnostic laboratories.[11]

Pre alloSCT MRD in AML is an irrefutable predictor of post-transplant relapse. [2-4,11-13]

In the post alloSCT setting, regular MRD assessments can be effective tools to identify patients at increased risk of relapse and assist with therapeutic decisions.[10,17]

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DOI: 10.46765/2675-374X.2021v2n2p88

ALLOGENEIC TRANSPLANTATION IN AUTOIMMUNE DISEASE AND BONE MARROW APLASIA - CASE REPORT

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Running title: APLASIA AND ALLOGENEIC TRANSPLANTATION

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ABSTRACT

Ulcerative rectocolitis (UC) is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Anemia is the most common hematological disorder in patients with UC and may be due to multiple causes such as blood loss, malabsorption, chronic illness and infection. We present a case report, in which UC and severe aplastic anemia (ASA) occur concomitantly, suggesting a common immune compromise between such pathologies.

Key words: Transplantation, Homologous. Transplantation, Haploidentical. Bone marrow aplasia. Proctocolitis.

INTRODUCTION

Ulcerative retocolitis (UC) is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Anemia is the most common hematological disorder in patients with UC and may be due to multiple causes such as blood loss, malabsorption, chronic disease and infection[1]. Other rare hematological manifestations associated with UC include myelodysplastic syndromes (MDS) and leukemia[2].

Bone marrow aplasia is considered a rare disorder, with an estimated incidence of 2 per 1,000,000 inhabitants per year in Western countries. In Asia, this rate is about 2 to 3 times higher[1,2.] Half of the cases of aplastic anemia occur in the first three decades of life.

Several researchers suggest a clinical association between inflammatory bowel disease and MDS, since they share an immune dysfunction that impairs the activity of T lymphocytes[2,3] Some few case reports suggest an association between UC and severe aplastic anemia[4,5].

Aplastic anemia is a disease of bone marrow stem cells characterized by ineffective hematopoiesis, leading to pancytopenia. Although aplastic anemia is often idiopathic, immune-mediated suppression of hematopoiesis can occur in at least 50% of patients, since more than half of them achieve hematological remission in response to immunosuppressive therapy[6].

We report here a case of UC associated with pancytopenia requiring blood transfusion in a young patient whose bone marrow examination was compatible with aplastic anemia. A common pathogenic association between UC and aplastic anemia is suggested in this patient and can be explained based on an underlying immune compromise shared in both diseases.

LITERATURE REVIEW

Bone marrow aplasia is defined as pancytopenia, associated with aplasia or spinal hypoplasia, with a

consequent significant decrease in hematopoietic and progenitor stem cells[7].

Severe aplastic anemia (SAA) evolved from a disease with a high lethality rate in the 1960s to one in which long-term survival can be achieved in most patients after diagnosis. Current clinical and laboratory evidence defines an immunological pathophysiology in which effector cells and related cytokines recognize and destroy bone marrow precursor elements[8]. Among the associated immune diseases, most cases do not have a clear cause and are defined as idiopathic[8].

Aplastic anemia is also associated with histocompatibility antigens. The presence of "escape clones" (granulocytes with loss of chromosome 6 region that includes HLA alleles) in 10 to 15% of patients is impressive; selected cells due to the absence of HLA, acquired by 6p loss of heterozygosity (LOH) or somatic mutations support hematopoiesis by means of clonal expansion[9].

The HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms may be associated with an increased risk of SAA in Asians. Immunosuppressive therapy may be more effective in Asian patients with HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms than in Asian patients without such polymorphisms[10].

The immunosuppressive therapy of choice in AAS is with horse thymoglobulin associated with cyclosporine, which produces hematological recovery in 60 to 70% of cases and very good long-term survival, particularly among responders. However, hematological recurrence occurs in 30 to 40% of responders and clonal evolution to myelodysplasia in 10 to 15%. In Brazil, there is still a limitation regarding immunosuppressive therapy, since rabbit thymoglobulin is not available[9].

The immunosuppressive therapy of choice in AAS is with horse thymoglobulin associated with cyclosporine, which produces hematological recovery in 60 to 70% of cases and very good long-term survival, particularly among responders. However, hematological recurrence occurs in 30 to 40% of responders and clonal evolution to myelodysplasia in 10 to 15%. In Brazil, there is still a limitation regarding immunosuppressive therapy, since rabbit thymoglobulin is not available[9].

For aplastic immune anemia in a young patient, transplantation is always the treatment of choice. When performed immediately after diagnosis, using a graft from a histocompatible donor brother, the results are excellent, with an estimated long-term survival rate of more than 90% among children and greater than 80% among adolescents, with a low rate of short- and long-term complications[8].

Haploidentical transplantation has been advocated in China as first-line treatment for children. In Europe, with an average 1-year survival rate of around 74%, haploidentical transplantation is recommended as second-line therapy. The current results are promising, but due to the relatively limited number of reported cases and the unknown long-term effects of complicated regimes and an incompatible immune system, haploidentical transplantation is considered experimental in the United States and Europe[8].

Ulcerative Retocolitis is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Immunological mechanisms play an important role in UC, and immunogenetic factors are related to the development of the disease.

In this patient, the justification for the coexistence of ulcerative colitis and aplastic anemia is suggested based on an underlying immune compromise shared in both diseases[11].

CASE REPORT

A 23-year-old patient presents in September 2019 with abdominal pain associated with diarrhea. He had a colonoscopy performed and showing a diagnosis of ulcerative colitis. It was prescribed Mesalazine therapy (3.2 g / day) and dietary guidelines were started.

He developed headache and intermittent fever. Clinical and laboratory investigation of the condition showed severe pancytopenia.

In December 2019, he was referred for hematological investigation. Bone marrow biopsy was performed, showing hypoplasia, with a diagnosis of marrow aplasia. PNH research (02/2020) with the presence of a clone in 3% of red blood cells // 94.8% of granulocytes // 91% of monocytes. Negative DEB test.

At that time, he also had abdominal pain and severe diarrhea, despite the use of Mesalazine. An investigation was carried out with a new colonoscopy showing descending colitis, affecting the descending and sigmoid colon; in addition to an active ileum ulcer.

He was maintained n supportive therapy with platelet transfusions and red blood cell concentrates. Using Danazol.

After three months, despite dose adjustments of Danazol, due to the lack of response he started immunosuppressive therapy with Ciclosporin 200mg / day.

In this context, he already had partial improvement in diarrhea and abdominal pain.

Control colonoscopy was performed in July 2020, which maintained diagnostic characteristics, with edema and enantematous rectal mucosa, from the distal segment to the anal mucosa. Erosions, friabil-

ity, edema and enanthema even in the anal canal. There was no longer an ileal ulcer.

Search for bone marrow donor started, considering young patient, with adequate performance status. It was not found any unrelated compatible donor.

At that time, he remained with red blood cells and platelets transfusions, presenting different kinds of reactions, with the need for washed components.

He was referred to the Bone Marrow Transplant service, maintaining severe pancytopenia (Hb 7.9g / dL; Neutrophils: 740; Platelets 35,000).

The patient was submitted to an allogeneic transplant, with haploidentical donor. Female donor, 25 years old, ABO compatible, CMV status discordant (IgG + donor / IgG receptor -). Anti HLA negative.

Conditioning protocol was used with Cyclophosphamide (14.5mg / kg), Fludarabine (30mg / m^2) and Total Body Irradiation (TBI - 400cGy dose), associated with the dose of Cyclophosphamide (50mg / kg) in D + 3 and D + 4 for prophylaxis of GVHD. He received hematopoietic stem cells from the bone marrow (mononuclear cells 4.5 x 10 ^ 8 / kg).

Neutrophil and platelet uptake occurred on September 9th (D + 18). Transplantation underwent without major complications, he was discharged at D + 20 for outpatient follow-up, without acute GVHD.

Currently, 4 months after transplantation, using Tacrolimus, in an immunosuppressive dose, controlled by weekly dosage of the serum level of the drug. Hematimetric indices within normal values (Hb 12g / dL; leukometry 3030; neutrophils 1970; platelets 143,000), with no signs of chronic GVHD. He denies any gastrointestinal complaints.

DISCUSSION

The case in question reports a young patient, with a recent diagnosis of severe bone marrow aplasia, associated with Ulcerative Colitis.

It is known that allogeneic transplantation is indicated as the initial strategy to approach ASA in young patients, with a related donor available.

However, currently, there are no robust data in the literature regarding haploidentical transplantation in severe aplastic anemia. Despite that, this type of transplantation has been widely used, considering the advantage of having a related donor available immediately. In addition, recent studies have shown response rates similar to transplants from related and unrelated donors.

Another issue to be considered for allogeneic pre-transplant evaluation is the response to thymoglobulin. In Brazil, difficulties are encountered in the treatment of marrow aplasia, since rabbit thymoglobulin is not available. Such medication is not marketed in the country, only horse thymoglobulin, which is known to have much lower efficacy results.

In addition, most of the Hematology services, related to the public health care system (SUS), do not have anti-thymocytic therapy.

In the reported case, a young patient with a high transfusion need and consequent exposure to various pathologies has been admitted to a transplant service, including a positive HBsAg antibody dosage during treatment. In addition, he already had indication to use only washed hemoconcentrates, due to the high incidence of transfusion reactions.

No 10/10 compatible donor, related or unrelated, had been found, despite extensive search on REDOME (National Registry of Bone Marrow Donors).

It was also known that the patient has HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms that may be associated with increased risk of AA; while the haploidentical donor did not have it.

Thus, it was considered a young patient, with very severe marrow aplasia, without the availability of adequate immunosuppressive therapy, in need of frequent hospitalizations, due to infection or transfusion reaction. A few months after the diagnosis of AAS, the COVID-19 pandemic began, which made it even more difficult for the patient to have immediate access to health service.

Despite limited data involving haploidentical transplantation in AAS, we opted for such alternative since the patient's imminent risks at that time justified our choice.

With bone marrow transplantation, it was possible to treat both ongoing diseases: Ulcerative Colitis and Severe Bone Marrow Aplasia.

It is known that currently in Brazil, the transplantation of hematopoietic stem cells is very little used in the approach of autoimmune pathologies, despite presenting quite satisfactory results in international studies. With the development of new techniques and improvements in care, such therapy is increasingly safe and is the only one that can offer an improvement in the quality of life of young patients, who would naturally be exposed to various immunosuppressive therapies, and their respective risks, to the throughout life.

FINAL CONSIDERATIONS

The aim of this report was to discuss the curative approach to both bone marrow aplasia and ulcerative colitis, through allogeneic transplantation in a young patient. In addition, the modality of haploidentical transplantation is also addressed, which has been increasingly used, considering greater chances of finding a compatible donor.

It was not possible to compare our results with other studies, since there is little data in the literature evaluating patients whose incidence of such pathologies already considered rare, occurring in concomitance, becomes even more limited.

Thus, we exhibit a case of cell therapy, with haploidentical bone marrow transplantation, capable of achieving remission of AAS and UC. The patient in question is being followed up on an outpatient basis. At the present moment, immunosuppressive therapy has been suspended, the patient does not present any gastrointestinal symptoms or cytopenias, with hematimetric indices within normal values.

Cases like this one encourage both hematologists and gastroenterologists to consider bone marrow transplantation as a curative therapeutic possibility for their patients.

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DOI: 10.46765/2675-374X.2021v2n2p89

MAINTENANCE TREATMENT POST-TRANSPLANT

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Disease recurrence is the most common cause of HCT failure in patients with AML,ALL and SMD and factors such as the presence of measurable residual disease before and after transplantation, stage of the disease before transplantation and the cytogenetic and molecular risk profile are factors associated with increased risk of recurrence.

The development of treatments with less toxicity for acute leukemias and high-risk MDS has resulted in the emergence of several agents potentially useful in this context. This issue has a greater relevance in patients who receive reduced intensity conditioning (CIR), due to the high and early recurrence rates observed in these patients[1]. The emergence of maintenance treatment options has raised several issues in addition to their effectiveness, including the duration and time of initiation of treatment, their interactions with the clinical sequelae of graft versus host disease (GVHD), grafting, hematopoietic toxicity and potential impacts on the effects of the donor graft. Nowadays, HCT is performed early in the course of the disease and improvements in supportive care, the use of conditioning regimes with less toxicity make patients more able to receive post-transplant treatments and several anti-neoplastic agents are available for the preemptive prevention treatment or treatment (in those patients who already have positive DRM) of relapses, including tyrosine kinase inhibitors, epigenetic modifiers, checkpoint inhibitors, bcl-2 inhibitors, drug-monoclonal antibody conjugates, monoclonal antibodies specific products, in addition to cellular engineering products.

The choice of agents for maintenance treatment must take into account the toxicity of the same (mainly myelotoxicity), their interaction with the patient's post-transplant medications, as well as their interference with the development of GVHD and the graft response against leukemia.

If a mutation is present, it may be tempting to use approved agents for the treatment of active disease, such as BCR-ABL inhibitors, FLT3, IDH1 and IDH2. Registry studies have shown that AML patients with FLT3 ITD mutations have a higher risk of relapse after allogeneic HCT than patients who do not have the mutation[2].

Several FLT3 inhibitors have been studied in the post-TCH maintenance scenario with superior results reported with sorafenib when compared with historical controls[3-6]. A small prospective randomized study (total of 83 patients) reported superior developments in patients in complete hematological remission receiving sorafenib, when compared to placebo6, however the lack of information provided on the frequency of FLT3 alleles at diagnosis, pre-HCT DRM and persistence or recurrence of DRM in post-HCT did not clarify which subpopulation of these patients may benefit from this treatment.

Midostaurin was the first FLT3 inhibitor drug approved to treat AML patients with the gene mutation. The approval was based on a randomized study that demonstrated a better overall survival rate (OS) in patients who received midostaurine in combination with induction and consolidation chemotherapy[7]. Patients recruited in this study discontinued the drug before HCT because it was not intended to assess the role of midostaurin in post-transplant maintenance, but a continued benefit in OS in the post HCT period was observed in those patients who received the drug before transplantation. The RADIUS study randomized 60 patients to receive midostaurine after HCT or standard treatment[8]. There were no significant differences in relapse-free survival(RFS) rates between the two arms of the study; the estimated two-year RFS and OS was 85% for midostaurine and 76% for standard treatment. There was a 40% reduction in the risk of recurrence and 42% in the risk of death in the midostaurine arm. Both studies excluded patients who had received previous treatment with FLT3 inhibitors and those who had morphological evidence of post-HCT relapses.

Other preliminary studies have evaluated the use of FLT3 inhibitors to prevent recurrences after HCT4,6. More recently, two randomized phase 2 studies have been completed in patients with AML and mutated

FLT3. The SORMAIN study randomized 83 patients to receive sorafenib (n = 43) or placebo (n = 40)9. There was a significant improvement in the RFS rate but without a significant improvement in the OS rate.

Nevertheless, this and other single-arm studies are the basis for some groups to indicate the use of other FLT3 inhibitors only partially studied, after allogeneic HCT. A randomized phase 3 maintenance study with gliteritinib is ongoing and includes the determination of DRM by PCR of the FLT3-ITD mutation and should result in important information to identify which patients could have benefit.

Azacitidine can induce remissions in patients who relapse after HCT[10]. A series of small studies using azacitidine preemptively or prophylactically in patients with decreased CD 34 + cell chimerism suggested a delay in these patients' relapse, by inducing an anti-leukemic cellular response by CD 8 + [11,12]T lymphocytes. . In another study, azacitidine was combined with donor[13] lymphocyte infusion. Although at the expense of a higher incidence of acute and chronic GVHD, recurrence rates were low and that of SG promising. These are uncontrolled studies, given the difficulties of conducting a study of controlled cases in this scenario. In a recent prospective, randomized study of azacitidine (N = 93) versus observation (N = 94) after allogeneic HCT, there were no differences in disease recurrence: the recurrence-free survival curves were virtually overlapping[14]. The development of oral azacitidine formulations has shown benefit in a randomized study as maintenance after induction chemotherapy in AML, therefore maintenance studies after HCT should be reviewed with these new agents[15,16].

Several studies at an early stage suggest that the use of hypomethylating agents (HMA) can prevent the occurrence of recurrence[10,17] by inducing an anti-leukemic cellular response by CD 8 + T lymphocytes and treating early recurrences after TCH[11]. In another study, azacitidine was combined with donor lymphocyte infusion[12]. Although at the expense of a higher incidence of acute and chronic GVHD, recurrence rates were low and that of OS promising. These are uncontrolled studies, given the difficulties of conducting a controlled case study in this scenario. The combination of these results with the low toxicity of HMA and its potential role in improving the effect of the graft against leukemia in the post HCT[13] resulted in the development of post-HCT maintenance protocols with HMA. A randomized study from the MD Anderson Cancer Center compared azacitidine (n = 93) to standard treatment (n = 94) in patients with MDS and AML[18]. There was no significant difference in RFS at 1 year, which was 2.07 years (azacitidine) versus 1.28 years (standard treatment). The dose of azacitidine was 32 mg / m2 daily for five consecutive days, and although the planned duration of maintenance treatment was one year, only 29% of patients completed treatment. Among the causes of discontinuation of treatment with azacitidine are: relapse (47%), toxicity (18%), patient preference (15%) and infection (11%). There was a trend towards better RFS in patients who received at least nine post-HCT maintenance cycles. The oral formulation of azacitidine can improve its effectiveness, treatment adherence and tolerability, with better outcomes[14,18].

There is currently interest in studying hypomethylating agentes combined with a variety of other agentes such as venetoclax,checkpoint inhibitors and monoclonal antibodies, although the evidence for these strategies has not yet been established.

Probably the greatest risk for AML recurrences after HCT is the presence of a mutation of the p53 gene[15]. APR-246 is being developed specifically for patients with myeloid neoplasms and mutated p53. The results of the initial studies seem promising, with a complete remission rate (CR) of around 80% in patients with AML and SMD15. There is an ongoing phase 2 study evaluating the combination of azacitidine combined with APR-246 in the post-HCT period for patients with AML and MDS with a p53 mutation. The primary endpoint of the study is SLR at 1 year.

Ivosidenib and enasidenib are recently approved agents that target IDH 1 and IDH 2, respectively[16,19]. They are well tolerated and could, theoretically, be used as a maintenance treatment after allogeneic HCT in patients with AML with these mutations. Studies with these agents are underway and will allow us to first understand the relevance of these mutations in the dynamics of post-HCT relapses and to assess their tolerance in this scenario. There is currently no evidence to support the use of these agents in maintenance.

An ideal maintenance treatment should not only reduce the risk of relapse but also the incidence of GVHD. Donor lymphocyte infusions (DLI) have been used for several years in this scenario. A multicenter study suggested that donor lymphocyte administrations in patients with post-HCT AML were able to convert mixed chimerisms into complete[20]. In another study, DLI after the first month after HCT in a total of three administrations in patients with AML and SMD resulted in high rates, lower incidence of relapses and high rates of chimerism conversion, but at the expense of a higher incidence of GVHD[21]. Subse-

quent studies found higher survival rates in patients with myeloid neoplasms who received prophylactic or preemptively DLI[22-24]. A study conducted by EBMT (n = 343) demonstrated that the use of DLI is associated with a reduction in the rate of relapse (28%) in five years when administered preemptively to reverse mixed chimerism or when used prophylactically in patients with high-risk diseases. However, the cohort of patients with positive MRD who received preemptive DLI had a recurrence rate of 43% [25].

In conclusion, due to the complexity of the HCT, the risks of GVHD and infections, the high costs involved and the patients' own adherence to maintenance treatments, studies in this area are difficult to carry out. In myeloid neoplasms, we will have more and more treatment "targets" that can be studied in this scenario. It should also be noted that any maintenance treatment after HCT must be started early, since a significant rate of recurrence occurs in the first 3 to 6 months after HCT, as well as the duration of treatment must take into account that the greatest risks of relapse occur in the first and second years after HCT. The decision to initiate maintenance treatment after HCT will depend on the judgment of the transplant team and the assessment of parameters such as risk factors for the disease, the patient's "performance status", genetic and molecular profile of the disease and the accessibility and cost of the chosen agent. So far, maintenance treatment for AML is considered experimental and should preferably be carried out in a clinical study context.

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DOI: 10.46765/2675-374X.2021v2n2p92

ANALYSIS OF THE PROFILE AND OVERALL SURVIVAL OF PATIENTS SUBMITTED TO TOTAL BODY IRRADIATION AS A FORM OF CONDITIONING FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (RADIOTHERAPY SERVICE OF HOSPITAL DE CLÍNICAS DE PORTO ALEGRE)

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Running title: PROFILE OF TOTAL BODY IRRADIATION FOR HSCT

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ABSTRACT

Since the beginning of the use of ionizing radiation in the treatment of neoplasms, hematological diseases have been shown to be radiosensitive, which caused them to be the focus of the work from great researchers of the time, initially with palliative intent and, later, as part of the conditioning for hematopoietic stem cell transplants. (HSCT). Total body irradiation (TBI) is a radiotherapy technique used in the treatment of several benign and malignant diseases since the beginning of the last century. It remains, today, as one of the central parts of allogeneic transplants, with special emphasis on cases of acute leukemia. It perfectly fulfills the cytotoxic role of eradicating possible residual disease, even in places with low penetration of chemotherapeutic drugs, such as the CNS and testicles and it participates in the immunosuppression necessary to decrease graft rejection. Although being a relatively simple technique, widely used in various conditioning schemes for HSCT, TBI is a potentially fatal procedure that should be used in tertiary centers with experienced multidisciplinary teams. This work sought to evaluate the number of patients undergoing this procedure at the Hospital de Clínicas de Porto Alegre, emphasizing the overall survival of patients, particularly the ones diagnosed with Acute Lymphoid Leukemia (ALL) - neoplasia, in which the TBI proved to have a fundamental role - and the ones who underwent haploidentical HSCT, a revolutionary, cheaper and quicker technique that provided a chance of cure for patients with a reserved prognosis, who did not have potential bone marrow donors. We also report acute and delayed effects that can be attributed to ionizing radiation over these 15 years. Data that allow the comparison with other services and a better management of the patients of our institution, highlighting the concern about the toxicity of the treatment.

Key Words: Whole-Body Irradiation. Hematopoietic Stem Cell Transplantation. Graft vs host disease.

1. INTRODUCTION

The discovery of X-rays by Roentgen at the end of 1895, and, later, the manipulation of elements capable of spontaneously emitting particles and/or electromagnetic radiation due to the instability of their nuclei were an important basis for the birth of madame Curie's concept of radioactivity in 1897 [1].

The concept of Total Body Irradiation (TBI) in the treatment of leukemias and generalized diseases sensitive to radiation was developed by Friedrich

Dessauer. Paying attention to how cell types of body parts of different thicknesses reacted to radiation and impacted on the homogeneity of the dose distribution, giving rise to important concepts of Radiobiology and Medical Physics, Friedrich Dessauer started to devote himself to develop the necessary devices to carry out the procedures and listed his findings in his book "Dessauer's laws of homogeneous irradiation".

In 1907, Adalar Eifer described the first clinical data of a treatment used in three patients diagnosed with leukemia [2]. In 1923, Chaoul & Lange described 12 patients treated at the University of Munich who were diagnosed with Hodgkin's Disease, eight of whom responded to treatment for seven months, something extraordinary at the time.

In 1925, Werner Teschendorf started a program arguing that, in patients with advanced hematological diseases, TBI would not only have a palliative role, taking to Europe the concept of "X-ray bath", in which patients were subjected to low doses of TBI in order to eliminate systemic disease cells. This practice was abandoned due to the acute, potentially fatal toxicity that many patients experienced [3].

In May 1931, Gioacchino Failla and Arthur Heublein installed special equipment at Memorial Hospital in New York, featuring the first TBI unit in North America. In an article, they described that by delivering an energy of 185 kV from X-rays, with a dose rate between 0.67 to 1.26 cGy per hour, at an average distance of 5.5-7.5 meters, it was possible to notice encouraging improvements in three out of 10 patients. They also concluded that the safety rate for the procedure would be 25% of the erythema dose (7.5 Gy measured in the air) [4].

The "Manhattan Project" contributed to the understanding of human biological behavior in the face of different forms of radiation exposure, including under the TBI technique, even allowing the application of the technique previously to HSCT [5]. It was found that the dose of body irradiation made in animals (rodents, dogs and monkeys) between 500 to 700 rads compromised the bone marrow; 1,200 to 10,000 rads caused intestinal damage and 12,000 to 1,000,000 rads caused brain damage. One noted that animals subjected to large doses of radiation died immediately or a few days after exposure; others, with intermediate doses, evolved with diarrhea due to severe intestinal lesions and died within the first 10 days. Finally, those submitted to lower doses succumbed to infections and/or hemorrhages many days later, due to the probable spinal failure [6].

In 1949, Jacobson and his team submitted mice to the TBI with myeloablative doses. The ones which used lead protection in their spleens recovered more quickly, while the others frequently died, showing that, even after undergoing ablative doses, these animals were able to produce cells from their bone marrow again [7]. In 1951, Lorenz and colleagues achieved similar results in India, but with the difference that they subsequently had cells infused with their own marrow, which were removed before irradiation [8].

Although the knowledge acquired in this period is undeniable, it should be noted that concepts such as medical ethics and awareness of the use of radiation were the consequences of negligent experiments in the name of science.

TBI was used in malignant diseases but also in the process of immunosuppression in benign diseases and solid organ transplants. In 1959, the first successful transplant through dizygotic twins used TBI at the dose of 450 Roentgen in the recipient [9].

Due to a greater understanding of the toxicity resulting from the procedure, several protocols have been developed, aiming to compensate for the damage caused by radiation exposure, especially in patients with hematological diseases with poor prognosis, such as leukemia. In 1957, Donnal Thomas described for the first time a successful bone marrow transplant carried out on humans after undergoing TBI (600 Roentgen), which earned him the 1990 Nobel Prize for Medicine [10].

In the last century, different types of fractionation and doses have been used and, despite the difficulty of establishing a pattern, what we have been proposing are schemes ranging from 12 to 15 Gy divided into six to eight fractions carried out over three to four days, respecting the dose rate <0.2 Gy per minute [11].

Patients may experience well-documented acute effects in relation to exposure to high doses of radiation, such as nausea, vomiting, mumps, headache, dehydration, mucositis, diarrhea and inappetence. These symptoms can also be attributed to chemotherapy regimens, making it difficult to achieve a real definition of etiology, easily treated with hyperhydration and symptomatic medications. As late effects, we have described pneumopathies, veno-occlusive diseases (mainly liver), renal dysfunction, early cataract, hypothyroidism, infertility, cognitive impairment and secondary neoplasms [6, 12].

Through this work, we analyzed the overall survival of patients diagnosed with ALL who underwent HSCT at the Hospital de Clínicas de Porto Alegre (which provided their first bone marrow transplant

with TBI in their conditioning on November 12, 2001), as well as potential late effects of ionizing radiation over these 15 years. These data allow us not only to compare our data to those of other services, but also, a better understanding related to the management of patients in our institution.

2. OBJECTIVES

2.1 Primary

To outline the profile of patients undergoing TBI as a form of conditioning for HSCT, analyzing the overall survival of benign and malignant diseases.

2.2 Secondaries

Analysis of acute and late toxicity, with emphasis on changes that interfere with quality of life, such as the index of secondary neoplasms, infertility and cognitive deficits resulting from total body irradiation.

3. MATERIAL AND METHODS

3.1 Outline

Sampling consisted of 139 patients who received TBI as part of the conditioning for HSCT and were treated at the hematology service of HCPA (Hospital de Clínicas de Porto Alegre) during the period between January 2001 and December 2016.

3.2 Statistical analysis

The statistical analysis used the IBM SPSS Statistics software, version 20.0. The categorical variables were described using frequencies and percentages, while quantitative variables were described using medians and interquartile ranges.

The Kaplan Meier curve was prepared to analyze the patients' survival and relapse and the Log-Rank test for the established comparisons, considering a significance level of $p < 0.05$.

For statistical analysis, we entered the data into a table in Excel and later exported to the SPSS v. 20.0. program. We described categorical variables by frequencies and percentages and quantitative variables by median and interquartile range. The Kaplan Meier curve was prepared to analyze the patients' survival and relapse and the Log-Rank test for the established comparisons, considering a significance level of $p < 0.05$.

3.3 Approval by the Research Ethics Committee

The study design was submitted to the HCPA research ethics committee, registered and approved in accordance with Brazilian legislation and respect Helsink declarations.

3. RESULTS

3.1 Sampling Characterization

139 pacientes were submitted to allogeneic stem cell transplantation using TBI as a part condition regiment from 2001 until 2016. The majority 92 (66%) were male and the median age was 8,2 years old. The regiment was myeloablative in 112 (81%) patients , The diagnoses more frequently was acute lymphoblastic Leukemia(ALL) in 102 patients (73.4%) and most them 102 (70%) was advanced stage (second or more remissions) at transplantation time. Six patients (4,3%) had benign hematologic disorders . Table 1 shows patients characteristics.

Regarding the type of HSCT, 88 cases (63.3%) were related and, as of 2013, Unrelated transplants began to be performed in our institution in 2006, being instituted in 46 patients (33.1%) and autologous, with more restricted indications, in only five (3.6%). A subgroup composed of 17 patients who underwent haploidentical HSCT after 2013 was also defined, 10 of whom were male (58.8%) with an average age of 17.5.

The intention of conditioning was myeloablative in 114 patients (82%) and non-myeloablative in 25 (18%). The prescription of the dose of TBI directly related to the intention of conditioning, subjected 112 patients to the myeloablative scheme, with a dose of 12Gy fractionated in minimum daily interval of six hours, with the addition of a 4Gy booster dose in the scrotum in male patients. Two patients received a dose of 9.9Gy in three daily fractions, a protocol recently adopted for conditioning of haploidentical HSCT, aiming at decreasing acute toxicity, since these patients are submitted to high doses of cyclophosphamide after transplantation (in vivo depletion). In non-myeloablative conditioning, three patients underwent 4Gy TBI: two in a single dose and one in two fractions, and 22 patients underwent 2Gy TBI in a single dose, without the need for lung protections due to the low dose prescribed.

TABLE 1 - Patient characteristics, frequency of diagnoses and types of HSCT

		Descriptive Measures	n	%
Characteristics	Males, n (%)	92	139	66,2
	Age to HSCT, medium (minimum-maximum)	8,2 (2,0-58,8)	138	
	Conditioning, n (%)			
	Myeloablative	112	138	81,2
	Non Myeloablative	26		18,8
Frequency of Diagnoses	ALL		102	73,4
	AML		12	8,6
	CML		6	4,3
	NHL		6	4,3
	Benign		6	4,3
	HL		4	2,9
	CLL		1	0,7
	Multiple Myeloma		1	0,7
	MDS		1	0,7
Frequency of types of HSCT				
	Related Haploidentical		71 17	51,1 12,2
	Unrelated		46	33,1
	Autologous		5	3,6

HSCT: Hematopoietic stem cell transplantation; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; NHL: Non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; CLL: Chronic lymphocytic leukemia; MDS: Myelodysplastic syndrome.

TABLE 2 – TBI Haploidentical Prescribed Dose

Radiation Dose (Gy)	n	%
2	11	64,7
4	1	5,9
9,9	2	11,8
12	3	17,6

TBI: Total body irradiation; Gy: Grey.

Regarding diagnosis, the most common diseases were ALL and AML, each of these entities with five patients (29.5%).

TABLE 3 - Frequencies of Haploidentical HSCT Diagnoses

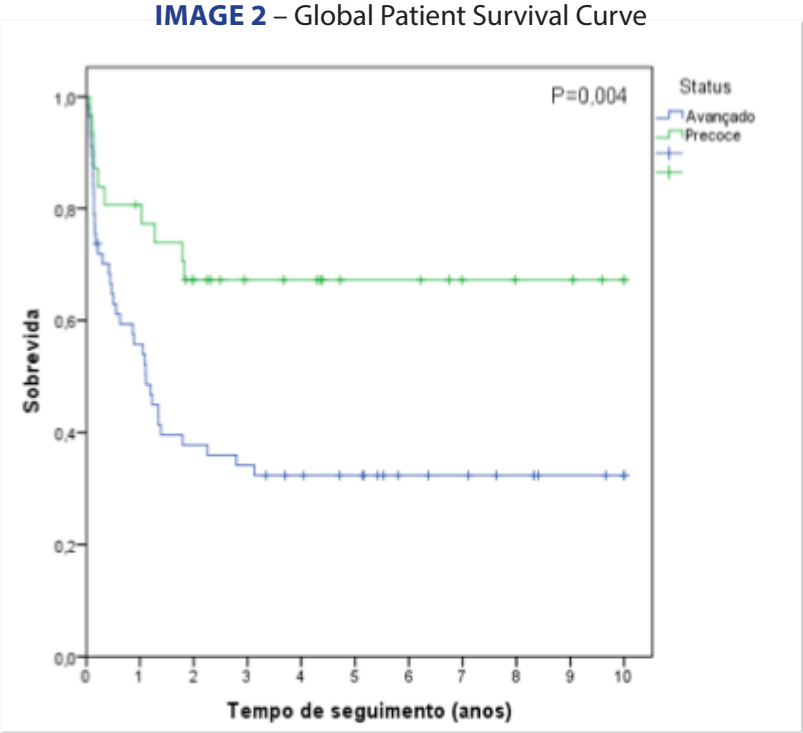
Diagnoses	**n**	**%**
ALL	5	29,5
AML	5	29,5
HL	3	17,6
Severe bone marrow aplasia	3	17,6
Leukocyte deficiency syndrome	1	5,8

The treatment was performed using a linear accelerator (Mevatron or 23EX) with 6MV energy with 40x40cm fields and 45º angled gantry. The patient was positioned in lateral decubitus and the treatment was performed with AP/PA fields. The DAP differences were compensated with saline bags and the calculations were performed in SSD, with the patient's umbilical scar as the center definition. The average dose rate was 0.08cGy/me.

3.2 Results analysis

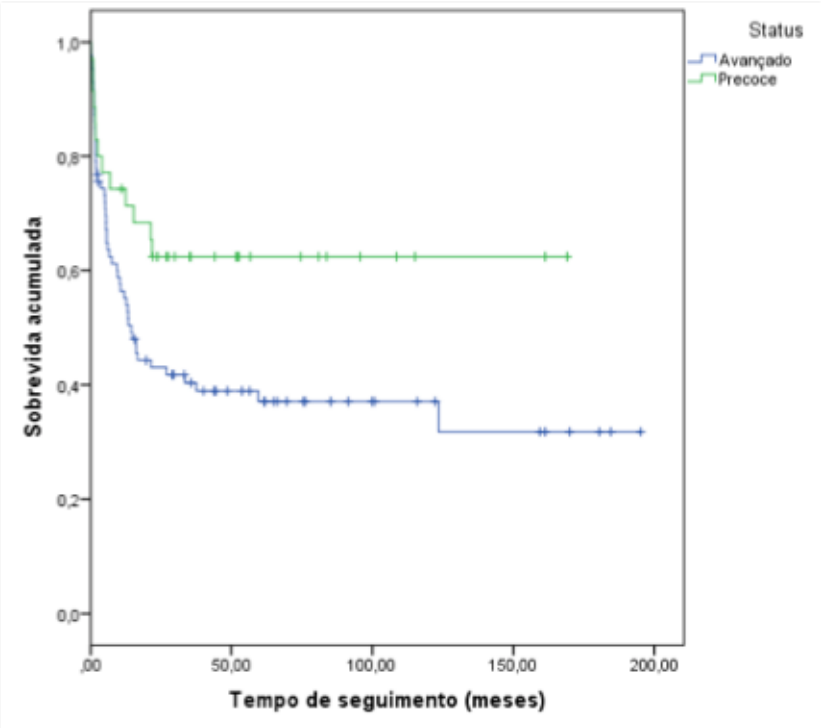
The mean time follow-up of patients was 28 months, with a death rate related to HSCT of 36.7% and disease related to 34.6%. The average overall survival time for patients was 87.2 months (95% confidence interval, 69.7 to 104.8 months). At the end of the follow-up, 38.9% of the patients survived.

IMAGE 2 – Global Patient Survival Curve



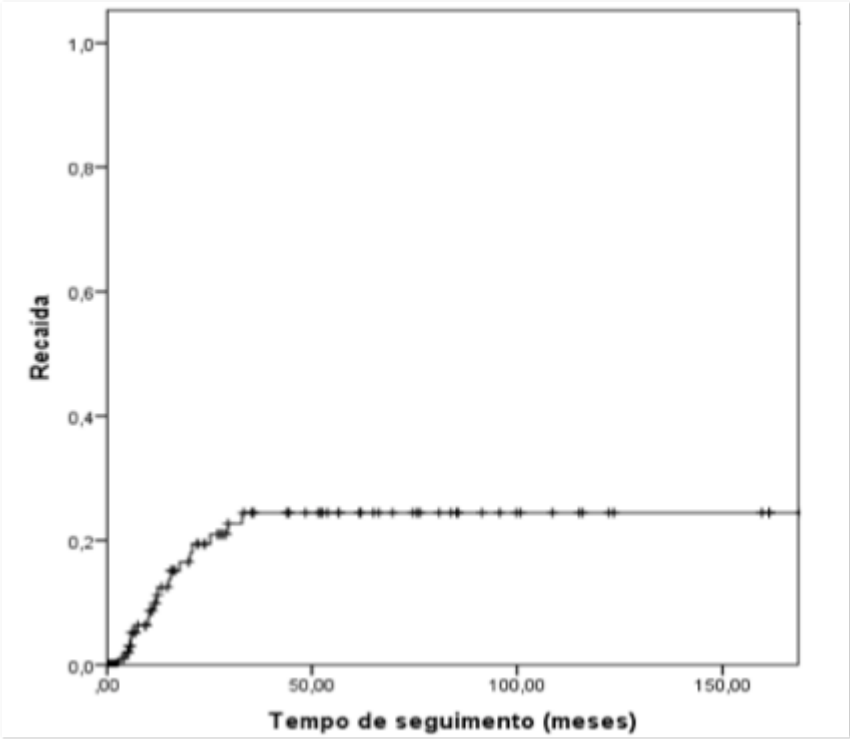
The percentage of living patients with advanced disease at the end of the follow-up was 31.8%, with an average survival time of 74.6 months (CI: 54.7 to 94.4 months). For patients with a disease classified as early, the percentage was 62.4% and the average survival time was of 108.2 months (CI: 81.9 to 134.4 months). There was a statistically significant difference, with patients with early disease having a longer survival time (P = 0.032).

IMAGE 3 – Global survival curve of patients with advanced and early disease.



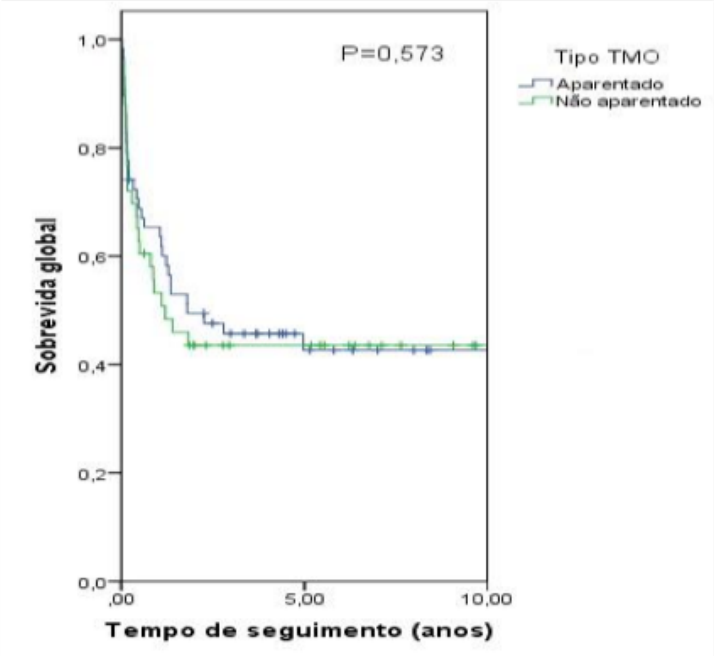
The relapse mortality was 38.8%, with an average time of 148.4 months (95% CI: 130.8 to 166.0 months).

IMAGE 4 – Curve of patients' relapse.



Due to the quantitative difference between patients diagnosed with ALL who underwent related and unrelated HSCT, the difficulty in comparing the impact of this variable was assessed. We then restricted the follow-up time to 10 years, with 88 patients assessed remaining more evenly distributed in each type of HSCT, 64.8% classified as advanced and 35.2% as early. In patients with advanced status, the percentage of patients alive at the end of the follow-up was 32.3% and the median survival time was 44.6 months (CI: 30.9 to 58.5 months). In patients with early status, the percentage of patients alive was 67.2%, with an average survival time of 83.4 months (CI: 64.7 to 102 months). It was also possible to find a significant difference in relation to the disease status.

IMAGE 5 - Survival curve in relation to the type of HSCT in patients diagnosed with ALL.



Fifty patients received previous radiotherapy treatment (36%), most of them through total brain treatment, applied to 37 patients (74%), followed by skull and neuro-axis (14%) and mediastinum (6%).

TABLE 4 – Previous Radiotherapy

Description	n	%
Yes	50	35,7
No	81	57,9
Uncharted	9	6,4
Total	140	

Regarding acute toxicity, febrile neutropenia (60.4%) was the prevalent, followed by mucositis grade three in 23% of patients and grade four 18%. The 4.3% who presented hemorrhagic alveolitis, died, two with probable CMV infection (clinical picture without a diagnosis confirmed by serology) and the other four without an apparent infectious cause, possibly related to exposure to ionizing radiation, although this is an exclusion diagnosis.

Regarding late toxicity, endocrinological changes were the most common, contributing 17.3%. We emphasize that severe cognitive changes were present in four 2.9% of the patients, with three patients having undergone previous radiotherapy of the brain before the TBI.

TABLE 5 – Frequency of Acute and Late Effects – Previous Radiotherapy

	Description	n	%
Acute Effect	Febrile Neutropenia	84	60,4
	G3 Mucositis	32	23,0
	G4 Mucositis	25	18,0
	G1 Mucositis	24	17,3
	G2 Mucositis	19	13,7
	Parotitis	10	7,2
	Hemorrhagic Alveolitis	6	4,3
	Hemorrhagic Cystitis	3	2,2
Late Effect	Infertility	8	5,8
	Short Stature	7	5,0
	Hypothyroidism	6	4,3
	Osteonecrosis	5	3,6
	Cognitive Impairment	4	2,9
	Hypogonadism	3	2,2
	Cataract	2	1,4
	Hemorrhagic Cystitis	2	1,4
	Interstitial Pneumonitis	1	0,7

Only two patients showed second neoplasms, one of them developed a squamous cell carcinoma of the right ear two years after HSCT treated with radiotherapy and the other with a follicular thyroid carcinoma, 12 years after exposure to ionizing radiation, submitted to radical surgery. It remains alive without evidence of recurrences, both of hematological and thyroid neoplasms.

Analyzing the rate of GVHD, 34.5% of patients had an acute condition, with cutaneous involvement seen in 45%, followed by TGI, 33%. 25.2% of the patients had chronic GVHD, the cutaneous also being the most common, with 49%, followed by GIT and hepatic impairment, with 9 patients each (8.4%).

TABLE 6 – Acute GVHD and Chronic GVHD.

	Place	n	%
Acute	Skin	30	62,5
	Liver	8	16,7
	Ocular	2	4,15
	GI tract	22	45,8
	Unknown	5	10,4
	Total	48	
Chronic	Mouth	3	8,57
	Skin	24	68,5
	TGI	9	25,7
	Liver	9	25,7
	Lung	1	2,86
	Ocular	3	8,57
	Total	35	

GVHD: Graft-versus-host disease; GI tract: Gastrointestinal tract.

During the study period, 17 haploidentical HSCTs were performed, and one of the patients had already undergone a previous HSCT, with graft failure. The graft's neutrophilic grip could be evaluated in the 17 patients, having been successful in 100% of the sample. The median days of neutrophilic uptake was 20 days.

In this sample of patients, the most common acute toxicity was febrile neutropenia, reported in 11 patients (64.7%), followed by GVHD manifestations. In patients with mucositis, milder degrees of the condition prevailed, an expected outcome, considering the use of non-myeloablative conditions.

As for late effects, the highest percentage was attributed to GVHD, with cutaneous involvement being the most frequent (17.6%). By the end of the study, three patients had not yet presented any type of late toxicity (17.6%).

TABLE 7 – Frequency of Acute and Late Effects - Haploidentical HSCT

	Description	n	%
Acute Effect	Febrile Neutropenia	11	64,7
	Skin GVHD	5	29,4
	GI tract GVHD	4	23,5
	Hepatic GVHD	1	5,8
	G1 Mucositis	5	29,4
	G2 Mucositis	2	11,8
	G3 Mucositis	1	5,8
	G4 Mucositis	1	5,8
Late Effect	Short Stature	1	5,9
	Hemorrhagic Cystitis	1	5,9
	Hepatic GVHD	1	5,9
	Oral cavity GVHD	1	5,9
	GI tract GVHD	1	5,9
	Skin GVHD	3	17,6
	Does not show	3	17,6
	Not Applicable (death)	6	35,3

47.1% of the patients died, five with death related to HSCT, four of infectious origin and one of acute GVHD in GIT. Death due to early disease-related relapse was observed in three patients.

4. DISCUSSION

Although TBI is a relatively simple and old technique, it is still used in several myeloablation schemes for conditioning HSCT. Its role is fundamental for the success of the therapy, since it encompasses all the patient's tissues without differentiating potential "sanctuaries", such as testicles and central nervous system, allowing, based on medical analysis, to attenuate or intensify doses in places of greater or lesser risk, without the need to pay attention to detoxification or excretion of any medication.

Our results are similar in international literature .Our study is the first report of knowledge about results of the TBI regiment in Brazilhan population , considering long time survival, relapsed e acute e late effects.

With the technological revolution that Radiotherapy has undergone in recent years, different techniques are being pursued for the realization of TBI, through which ways are sought for the target of treatment to receive the prescribed dose without reaching healthy tissues, aiming at reducing the toxicity, both acute and late effects

Other new Technologies like use of beam modulation with Intensity Modulated Radiation Therapy whit dose escalation in the bone marrow, sparing critical normal tissues such as lungs, liver and kidneys can improve the results. Beside that's facilitate concomitant reinforcements in places with a higher risk of recurrence, such as the brain.

5. CONCLUSION

During the last century, the evolution in the treatment of hematological diseases has been dizzying. HSCT has an important role in controlling and improving the life expectancy of patients who are even considered incurable. In this context, radiotherapy proved to be a complementary technique of great value, which role was often questioned, due to its potential toxicity. Our results are similar to international literature .The development of new, more precise protocols and techniques reinforces the centennial importance of this specialty as a therapeutic resource. Studies reporting the results of the new techniques for the TBI realization are still in progress, leaving us with the future perspective that, through the learning acquired over several years, coupled with technological development, it is possible to merge the past and the future into a treatment that is finally ideal [13, 14].

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DOI:10.46765/2675-374X.2021v2n2p93

REVACCINATION PROGRAM POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION AND COVID-19 VACCINE: CURRENT CHALLENGES

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Hematopoietic stem cell transplantation (HSCT) is a therapeutic modality that has been used for the treatment of various diseases and hematological neoplasms for decades. HSCT is a long, individualized, and highly complex process that requires multidisciplinary skills. HSCT starts much earlier and extends far beyond the infusion of the hematopoietic stem cells. Regardless of the type of transplant to be performed, autologous or allogeneic, before graft infusion, total or partial ablation of the bone marrow's immunohematopoietic elements is necessary, a procedure known as conditioning regimen.

After conditioning, HSCT recipients lose immune memory to infectious agents and vaccines accumulated throughout life. Post-HSCT immune reconstitution is slow and may be affected by other pre- and post-HSCT events, such as the drugs used to treat the underlying disease, the source of progenitor cells, the prophylaxis or treatment of graft-versus-host disease (GVHD), among others [(1)].

After HSCT, antibodies against vaccine-preventable diseases gradually wane over time, leaving the recipient susceptible to these diseases, if not revaccinated. One year after HSCT, about 60% of patients lose antibodies against diphtheria, 50% against tetanus, 35% against measles, 33% against polio and 24 % against hepatitis A, with slight variations between published studies [(2–7)].

Although the response to vaccines is usually inferior in this population, post-HSCT revaccination is necessary to enable the reconstitution of lost immunity, protection against infections that are potentially lethal in these patients and to ensure the same protection offered to the general population.

Since 1995, revaccination protocols post-HSCT have been proposed through international consensus and revised by experts [(8–11)]. Such programs must be adapted regionally, taking into account the local epidemiological situation. The most recent international guideline on this topic was published in 2019 by the working group of the European Conference on Infections in Leukemia (ECIL) [(12)].

In Brazil, the first recommendations on HSCT revaccination program emerged in 1992, at the initiative of a few transplant centers. At that moment, there were no agencies with specific infrastructure and logistics to care for individuals with special clinical conditions. In 1993, the National Immunization Program (PNI) created the Reference Centers for Special Immunobiologicals (CRIE), following the basic principles of universality and equity of the Unified Health System (SUS). A recent publication of the CRIE Manual describes a proposal for a revaccination program for the HSCT recipient, offering through the country and free of charge, most of the vaccines recently proposed by the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO) [(13,14)].

Despite the spectacular vaccine program made available by the Ministry of Health through PNI and CRIE, HSCT recipients have difficulties in complying with the revaccination schedule, which invariably result in delays and failure to complete the proposed scheme.

The revaccination program is complex since it involves 12 to 14 different vaccines, with multiple doses (except for the inactivated vaccine against influenza in those over 9 years old), different intervals between doses and restrictions of attenuated vaccines in certain circumstances. To achieve the expected outcome, the program involves three phases that must act synergistically, namely: 1) the correct referral for vaccination by the HSCT center; 2) patient or guardian's adherence to the orientation of the transplant center; and 3) compliance with the schedule proposed by those responsible for the reg-

istration and application of the vaccines, in private clinics, CRIE, basic health units (UBS) or vaccination rooms [15].

Unfortunately, the perfect coordination of these actions has not yet been achieved. According to a national study, delays in the revaccination program were observed in about 80% of the participants, the majority due to failures by the transplant center in referring the patient for vaccination or in the application of vaccines in the vaccination sites. The lack of compliance by the patient or guardian was observed in a small frequency (15). Therefore, it is clear that efforts to ensure the success of the revaccination program must focus mainly on educational activities at HSCT centers and on greater integration of HSCT centers with CRIE and vaccination sites.

In view of the pandemic and the prospect of starting COVID-19 vaccination for groups with comorbidities, which include transplant recipients, the reported problems anticipate the challenges to come, which are added to the difficulties already inherent to the revaccination program.

So far, we have more questions than answers: Which vaccine against COVID-19 is the safest, the most effective, the best time to vaccinate, how many doses will be needed, when to vaccinate recipients with graft versus host disease (GVHD), how often the vaccine will be introduced into the revaccination calendar, among others. However, these questions need time to be answered.

Despite the scarcity of studies in immunocompromised patients, a few publications indicate that these patients should be monitored carefully after vaccination.

A recent study in solid organ transplant (SOT) recipients showed that at a median of 20 (17-24) days after the first dose of vaccine, SARS CoV-2 antibodies were detectable in 76 of 436 SOT recipients (17%; 95% CI, 14%-21%) who received mRNA BNT162b2 vaccine (Pfizer-BioNTech) or mRNA-1273 vaccine (Moderna). After the first dose, significantly better response was observed in younger patients, in those receiving Moderna in comparison with Pfizer-BioNTech vaccine (69% vs 31%, respectively), and in those not receiving anti-metabolite immunosuppression (63% vs 37%), respectively [16].

Del Bello et al., reported a case of acute rejection in a kidney transplant recipient 8 days after the second dose of Pfizer-BioNTech vaccine and suggest careful monitoring of organ rejection in SOT recipients undergoing anti-SARS-CoV-2 vaccination [17].

At the moment, the vaccines approved by ANVISA for use in Brazil (Coronavac, Oxford-Astrazeneca, Pfizer-BioNtech and Janssen) are considered safe and can be used in HSCT recipients. Inactivated vaccines such as the Coronavac have been used for decades in HSCT recipients (e.g. influenza vaccine). However, non-replicating viral vector vaccines (Oxford-Astrazeneca and Janssen) and mRNA vaccines (Pfizer-BioNtech) have never been used in this population. Therefore, careful and close monitoring of vaccinated patients is recommended.

Due to the high transmission rates still observed in Brazil and the greatest severity and lethality of COVID-19 in HSCT recipients, the SBTMO recommends vaccinating patients with any available vaccine, ideally after the 6th month of HSCT when a better response to vaccine is expected. However, in regions with accelerated rates of transmission, vaccination may be anticipated from the 3rd month of transplantation. A summary of the SBTMO recommendations can be seen in figure 1.

It is important to note that the studies conducted with the available COVID-19 vaccines have not included immunocompromised populations, and therefore, the efficacy is unknown in these patients. HSCT recipients should be aware of this and be encouraged to maintain the preventive measures, even after vaccination. The greatest risk of transmission of COVID-19 is at home and even vaccinated, HSCT recipients may have a weaker antibody response. Therefore, household contacts should also receive COVID-19 vaccine. However, due to the lack of vaccines, only household contacts with comorbidities are eligible to receive the vaccine and should be encouraged to do so.

The Ministry of Health is in charge of COVID-19 vaccine distribution to the states. Therefore, once vaccination dates for HSCT recipients have been announced, transplant centers should refer patients to receive the vaccine. Despite the unassertive attempts to recover the vaccination delay caused by the disastrous management of the pandemic in Brazil, the vaccination campaign against COVID-19 remains slow, with numerous challenges to be overcome, such as the interruptions due to lack of vaccines, fraud in the administration or exchange of vaccines, lack of the second dose, among others.

The long-awaited time for COVID-19 vaccination of HSCT recipients has arrived. We hope that the lack of a central and unique vaccination guidance for this large group of people with comorbidities does not hinder the ultimate goal of protecting these patients at high risk of COVID-19 complications.

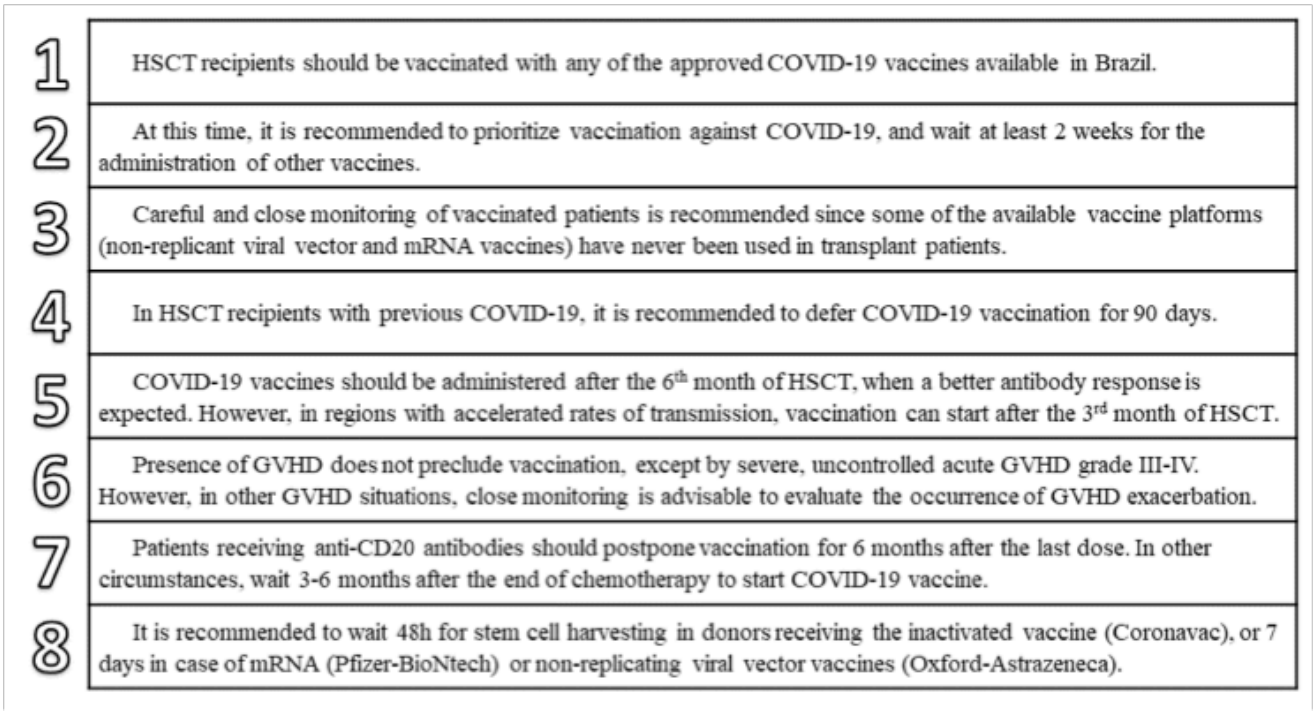

FIGURE 1 – SBTMO recommendations for COVID-19 vaccination of HSCT recipients and information concerning donors vaccinated before donation [18].

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DOI:10.46765/2675-374X.2021v2n2p94

THE IMPORTANCE OF CD34 POSITIVE CELL QUANTIFICATION FOR HEMATOPOIETIC STEM CELL MOBILIZATION

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Running title: IMPORTANCE OF CD34+ FOR HEMATOPOIETIC

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ABSTRACT

Objective: The success of autologus hematopoietic stem cell transplantation relies on CD34+ cells' availability in peripheral blood (PB), which is affected by several factors as age, sex, type of the disease, treatments, and others. In that regard, this prospective study aimed to evaluate the influence of these factors, correlating them with the pre-apheresis CD34+ cell count.

Method: Before autologous hematopoietic stem cell transplantation, CD34+ cells were quantified in the pre-apheresis PB and the final product. Then, after the determination of minimum CD34+ value, clinical and laboratory parameters were compared between patients with higher and lower CD34+ cells count.

Results: Out of the 34 patients, 29 presented more than 20,000 leukocytes/µl. Patients who failed in the mobilization presented <20,000 leukocytes/µl. There was a significant difference between the groups with different pre-apheresis CD34+ cells status regarding age (p=0.025), leukocyte count (p<0.001) and mononuclear cells (p=0.001) in PB. In addition, the pre-apheresis CD34+ ≥14 cells/µl group was related to a better yield of these cells in the final product and with the requirement of a single collection to obtain the minimum yield, of 2x106 CD34+/kg.

Conclusion: This study demonstrates age and leukocyte count relate to CD34+ count in PB, and that CD34+ cells yield in the collection, can be predicted by CD34+ cells frequency in PB.

Keywords: Stem Cells. CD34 positive cells. Autologous Hematopoietic stem cell transplantation. flow cytometry.

INTRODUCTION

Peripheral blood stem cell transplantation is highly indicated as a therapeutic strategy for patients who have undergone high doses of chemotherapy for malignant hematological or solid neoplasms. Furthermore, the success of stem cell transplantation and grafting depends on the infusion of an adequate number of progenitor cells [1-3].

Hematopoietic stem cells (HSC) have the capacity for self-renewal and present proliferative potential, allowing them to differentiate into progenitor cells of all blood lineages and the reconstitute the hematopoietic population [4-5]. These cells express CD34 on their cytoplasmatic membrane, which can be used as a marker to assess this population[5].

In unstimulated healthy donors, HSC constitutes 0.01 to 0.1% of peripheral blood cells (PB) and1 to 3% of all bone marrow (BM) cells [6]. However, for autologous transplantation of hematopoietic progenitor cells (AHSCT), it is recommended a minimum dose of 2 x 106 CD34+ cells/kg [7], making it necessary

to mobilize those cells from the BM. In that sense, the most commonly used forms of HSC mobilization from BM to PB is the isolated use of growth factors, or their combination with chemotherapeutic agents. Among the available growth factors, the most commonly used is the recombinant granulocyte colony-stimulating factor (G-CSF) [8-9]. Another approach is the use of plerixafor, which inhibits CXCR4 present in CD34 + cells, associated with G-CSF [10].

Several factors have been reported to affect HSC mobilization, such as age, sex, type of disease, bone marrow conditions, prior chemotherapy and radiotherapy, and stability of peripheral blood CD34 + cell counts [11-14]. Hence, the present study aimed to evaluate the influence of the above-mentioned factors on HSC mobilization, in patients treated with G-CSF before AHSCT.

Material and Methods

A prospective, non-probabilistic evaluation was performed on 34 patients undergoing HSC mobilization in the Bone Marrow Transplantation services of the University Hospital (UFJF) and the Monte Sinai Hospital and Maternity, from February 2016 to July 2017. This study was approved by the Ethics Committee on Research in Human Beings of HU-UFJF (CEP HU-UFJF), embodied report no. 1,419,207 and CAAE 53105615.9.0000.5133.

Patients

Patients undergoing HSC mobilization with G-CSF were included irrespective of gender, age, or underlying diseases. All patients, who accepted to participate in the study, signed the informed consent form (ICF). Patients subjected to G-CSF mobilization protocol while in chemotherapy, or who did not have the clinical criteria to perform the AHSCT were excluded.

CD34+ cells quantification

The CD34+ count was performed on the fourth mobilization day, however, the CD34+ value of the first day of collection was included for data analysis. The collection started when the CD34 + cell count was ≥ 10 cells µL in the PB. Nevertheless, when patients did not reach this value, after 5 days of G-CSF treatment, it was considered a mobilization failure. Quantification of CD34+ cells was performed on a double platform. The cytometry was carried out on the flow cytometer Fluorescence-Activated Cell Analyzer, FACSCalibur, Becton Dickinson (BD), and its analysis performed on the Cell Quest analysis software according to the International Society of Hematology and Graft Engineering ISHAGEprotocol[15], and the hemogram was obtained in the Mindray hematological counter (BC-2800).

For CD34+ cells quantification, the following antibodies were used: CD45 monoclonal antibody conjugated with fluorescein (FITC), monoclonal antibody CD34 conjugated with phycoerythrin (PE), monoclonal antibody isotype IgG1-PE (negative control). 2 × 106 cells were platted in an adjusted volume of 50 µl to 100 µl. Two tubes were identified, one as "control" and another as "patient", in each 10µl of anti-CD45 antibody were added; in the control tube 10µl of anti-IgG1 were added, and in the patient tube 10µl of anti-CD34 were added. The tubes were homogenized in vortex and incubated for 20 minutes at room temperature, protected from light. After the incubation time, 2 ml of lysing solution were added, followed by homogenization and 10 minutes incubation, at room temperature, protected from light. After the incubation period, the cytometer analysis was performed.

Data analysis

The collected data were gathered for descriptive and inferential analysis, frequency, median, minimum and maximum distributions, average, and standard deviation, presented in tables.

After determining the minimum value of CD34+ cells in the PB, for a sensitivity of 100% by the Receiver Operating Characteristic(ROC) curve (Figure 1), related to the lower number of collections to obtain the minimum value for AHSCT (14 CD34 + cells/µl in PB), two groups were created. Patients with CD34+ cells counting <14 cells/µl and patients with CD34 + cells ≥ 14 cells/µl were compared regarding the averages of age, global leukocytes count, mononuclear cells, platelet count, as well as the yield of CD34 + cells in the final product, statistical significance was checked through unpaired Student's t test. However, a previous assessment of normality was performed through the Shapiro-Wilk test and the Levene variance homogeneity test.

The chi-square test was used in order to associate categorical variables (CD34+ cells and sex, number of collections, disease, radiotherapy, chemotherapy cycles, disease status during mobilization, protocol number and BM infiltration). The test was chosen according to the assumptions of any box in the table of expected values smaller than 1 and greater than or equal to 5, in at least 80% of the samples. The association with myelotoxic drugs was not tested, as only

one patient was using such medication. Additionally, it was also not possible to test the infiltration of BM, since none of the patients with lymphoma presented BM involvement.

The analyzes were performed in the software Statistical Package for Social Science® (SPSS) version 17.0. For the statistically significant values, the p value ≤ 0.05 was considered for rejection of the null hypothesis.

Results

From 34 evaluated patients, only 2 non-Hodgkin lymphoma patients, aged 38 and 47, have failed mobilization. The characteristics of the 34 patients, among which 32 managed to reach a minimum of 2 × 106, are shown in Table 1. The average dose of G-CSF was 11.4 µg / kg/day.

Among the tested variables (sex, disease, disease status, whether the patient was in complete remission or not, platelet count, previous radiotherapy, previous chemotherapy protocols, whether the patient had one or more protocols, number of cycles, mobilization, amount of G-CSF / kg/day) there was no significant difference between the proposed groups based on CD34 + cells population. However, the ≥14 cells/µlvalue was associated withthe need for a single collection to reach the aim of 2×10^6 CD34+/kg, for the AHSCT.

Twenty-nine (85%) patients presented more than 20,000 leukocytes/µl, among which 95% had CD34+ cells count ≥ 14, while only 4,2% of them displayed lower values. Moreover, the two patients who failed in the mobilization presented less than 20,000 leukocytes / µl. In addition, patients with CD34+ ≥14 cells / µl were younger, presenting a difference in the average of leukocytes and pre-leukapheresis mononuclear cells. (Table 2).

Except for the patients who failed in the mobilization, the CD34 + ≥14 cells / µl was related to the need for only one collection and a better yield in the final product (Table 3), with a significant difference (p = 0.002) between those which required one collection, compared to the those who needed two or more. FurthermoreThe number of CD34 + cells in the final product of apheresis collections was higher in patients presenting CD34+ ≥14 cells/µL in PB, when compared to those with CD34+ < 14 cells/µl, respectively 4.98 × 10 6 and 2.87 × 10 6 CD34+ / kg (p = 0.002). (Table 4)

Discussion

Among the 34 patients, only 2 (5.88%) patients failed in the mobilization, while no MM patient failed it. This finding is consistent with others describing the failure of 5 to 40% of patients [7,16]. Although, underlying diseases were not related to mobilization failure, it is noteworthy that the two failing patients had NHL. On that way, the percentage of failures within this diagnosis were similar to another Brazilian center [17]. According to Stiff et al [18], prior chemotherapy and radiotherapy impair HSC mobilization, however, in our study, those factors did not affect the number of CD34+ cells in post-mobilization PB.

Consistent with the literature, younger patients demonstrated higher mobilization capacity, with the average ages of 55 and. 45 years, for the patients with CD34+<14cells/µl and ≥14cells/µl respectively. As described, it may indicate that older people would be more likely to present mobilization failure than younger people, this probably relates to the lower marrow reserve, in the older group [17,19]. Although young patients have been correlated with a higher number of CD34+ cells, guide mobilization, based only on clinical datamay lead to an overtreatment of patients who may be good mobilizers, as well as to undertreatment of those who fail in the mobilization.

The average global leukocyte count among individuals with CD34+cell ≥14 cells/µl was higher than in those with a <14 cells/µl count, showing an association between global leukocyte and CD34+cells counts (p <0.001). In that regard, studies show there is little correlation between leukocytes count in PB and the number of CD34+ cells in PB, and our findings allow us to conjecture that the initial dosage of CD34 associated with less than 20,000 leukocytes/mm3 would be unproductive, and would end up making the process more expensive [3,20].

Among the leukocytes, the PB mononuclear population was higher in the CD34+ cells≥14 cells/µl group (p = 0.001). However, there are no reports of this correlation, and it can be important to guide a pre-selection of patients to undergo CD34 count, optimizing the mobilization process [21].

According to the consensus of the American Society for Blood and Marrow Transplantation (ASBMT), the minimum cell value for performing AHSCT is $2x10^6$ CD34 + cells/kg, however the decision to perform the AHSCT between 1x 0^6 and $2x10^6$ CD34 + cells/

kg can be taken according to the patient, still there is aim for3x106 [10]. In that way, higher CD34+ yield in the final apheresis product associatiated with CD34+ ≥ 14 cells/μL cells in peripheral blood (p = 0.002), demonstrating the importance of the CD34+ cells count during mobilization for a suitable final product, as demonstrated in other studies [13,16,22].

Sixty-seven percent of patients with CD34+ ≥ 14 cells/μL in PB achieved the minimum counts required for AHSCT with a single collection, while all patients with less than 14 CD34 + cells/μL cells performed two or more collections. This data reinforces the importance of CD34+ cells count on mobilization, as a success predictor in the collection of hematopoietic stem cells from peripheral blood (HSCPB).

Based on our findings and the literature, the use of CD34+ cells counts to guide interventions, to avoid mobilization failures and improve the yield of the final product, should be encouraged. Nevertheless the two patients who failed mobilization were subjected to one collection which enabled the AHSCT, after a second mobilization with cyclophosphamide and G-CSF, however t the use of chemotherapy increases the infectious risks and leads to new costs. Anyway, that the measure of CD34 + cells on the fourth day, can be used to optimize the mobilization [9,23].

Although the rate of mobilization failureis compatible with the literature, early intervention based on CD34 + cells may be able to reverse the results on patients who could not reach the minimum number of cells for leukapheresis.

Conclusion

We conclude that the CD34+ cell count in the peripheral blood is related to age and number of leukocytes, being the only factor with a significant association with the number of collections and the yield of the final product.

Acknowledgements

We would like to thank the whole transplantation team from the Centro de Transplante de Medula Óssea from the Monte Sinai Hospital and Maternity (Juiz de Fora – MG – Brazil), mainly Dr. Angelo Atalla.

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TABLE 1 – Socio-demographic, clinical and laboratory data of patients subject to G-CSF mobilization protocol, in order to achieve optimum CD34+ countings in PB.

VARIABLES	TOTAL N=34	MOBILIZED N=32
Age	49,5 (14 - 69)	52,5 (14 -69)
Average		
Sex		
Male	18 (52,9%)	18 (56,3%)
Female	16 (47,15%)	14 (43,7%)
Transplant Center		
University Hospital – UFJF	22 (64,7%)	20 (62,5%)
Monte Sinal Hospital	12 (35,3%)	12 (37,5%)
Disease		
MultipleMyeloma	23 (67,6%)	23 (71,9%)
Lymphomas	11 (32,4%)	9 (28,1%)
Disease Status in Mobilization		
Complete remission	15 (44,1%)	14 (43,8%)
Without complete remission	19 (55,9%)	18 (56,2%)
Number of prior chemotherapy regimens		
1	25 (73,5%)	25 (78,1%)
≥2	9 (26,5%)	7 (21,9%)
Number of Cycles	6 (3 - 15)	5 (3 - 15)
Average		
Radiotherapy		
Yes	12 (35,3%)	11 (34,4%)
No	22 (64,7%)	21 (65,6%)
G-CSF/Kg/day	11,3 (10 - 19,6)	11,3 (10 - 14)
Average		
Interval between start of mob. CD34+ peak (days)	4 (3 - 6)	4 (3 - 6)
Average		
Apheresis number		
1 collection	16 (50%)	16 (50%)
≥2 collections	16 (50%)	16 (50%)
Nº of leukocytes in PB pre-leukoapheresis (µL)	30.750 (4.900 - 70.600)	32.600 (5.300 - 70.600)
Average		
Nº CD34+ cells in PB pre-leukoapheresis (µL)	22 (2 - 98)	22,5 (9 - 98)
Average		
Nº of mononuclear cells in PB pre-leukoapheresis (µL)	3.900 (1300 - 16.600)	4.200 (1.700 - 16.600)
Average		
Nº of platelets in PB pre-leukoapheresis (µL)	182.000 (29.000 - 335.000)	182.000 (29.000 - 335.000)
Average		
Nº of CD34+ in final product	4,07 (1,51 - 12,41)	4,07 (1,51 - 12,41)
Average		

TABLE2 – Comparison between the designated groups according to their amount of CD34+ cells in PB (< 14 cells/µl and ≥ 14 cells /µl), regarding the factors which can influence the quantity of recovered cells.

Variable	CD34 in peripherial blood	N	Average	Standard deviation	p-value
Age	< 14 cells/µl	10	55,3	9,0	0,025*
	≥ 14 cells /µl	24	45,2	15,7	
Global LeucocyteCount	< 14 cells /µl	10	17860,0	7486,6	<0,001*
	≥ 14 cells /µl	24	38033,3	13807,2	
Mononuclear cells	< 14 cells /µl	10	2922	1032,64	0,001*
	≥ 14 cells / µl	23	5898	3730,05	

*p-value obtained via T Student´s Test.

TABLE3 - Comparison between the designated groups according to their amount of CD34+ cells in PB (< 14 cells/µl and ≥ 14 cells /µl) and association with the number of apheresis required to achieve optimal CD34+ cells counting.

< 14cells/µl ≥14 cells/µl			CD34		Total	*p value
Number of collections performed	**1 apheresis**	Counting	0	16	16	0,002
		% inside CD34	0,0%	100,0%	100,0%	
	≥ 2 apheresis	Counting	8	8	16	
		% inside CD34	50,0%	50,0%	100,0%	

*p-value obtained via Chi-Square test

TABLE 4 – Association between the amount of CD34+ cells in PB and the quantity of these cells recovered in the FP.

	CD34	N	Average (CD34 x 106/Kg)	Standard deviation	*p value
CD34 Final Product	<14 CD34+/µL	8	2,87	1,03	0,002
	≥14 CD34+/µL	24	4,98	2,41	

*p-value obtained via T Student´s test

DOI: 10.46765/2675-374X.2021v2n2p95

OVERALL SURVIVAL IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH CALGB 8811 PROTOCOL IN LOW INCOME COUNTRY

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ABSTRACT

Introduction: ALL is known to have a lower survival rate in adults and this can be attributed, among other aspects, to intolerance to intensive regimens. As the treatment of ALL is very complex, with many protocols available, this study proposes an analysis regarding the CALGB 8811 protocol in a tertiary health unit in Ceará.

Methods: In this retrospective study, 50 patients with a recent diagnosis of ALL who underwent the CALGB8811 protocol were evaluated. Disease risk criteria were based on the CALGB8811 protocol.

Results: CR was obtained in 86% of patients. 12% of patients died during induction due to infectious complications. 30% of patients underwent alloSCT, 60% were on CR1.

The median overall survival (OS) was 21.5 months (8.1-38.7). The 5 years OS was 25% in the transplanted patients versus 60% in the transplanted group. Achieving complete remission after induction chemotherapy and allogeneic hematopoietic stem cell transplantation were the factors associated with better long-term survival rates in uni and multivariate analysis.

Conclusion: Risk factors classically associated with worse adult ALL outcome and post-induction MRD status were not outcome predictors, in addition, post-induction remission and alloSCT were factors associated with a favorable outcome.

Keywords: acute lymphoblastic leukemia. CALGB 8811 protocol. hematopoietic stem-cell transplantation.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematological malignancy with high survival rates among children through protocols with multiagents intensive chemotherapy [1]. Adults patients have an inferior overall survival (OS) mainly due intolerance to intensive regimens and because an adverse disease biology [2].

Treatment of adult ALL is complex with many available protocols [3-4] based on corticosteroids, anthracyclines, alkylating agents, methotrexate and L-asparaginase. Complete remission (CR) rates after induction are high, but many patients relapse during or after chemotherapy leading to a low long term OS. In this context, disease risk stratification is important because it defines patients who should be referred to allogeneic hematopoietic stem-cell transplantation (HSCT) in first remission [5].

The CALGB 8811 protocol has a multidrug design, consisting of an induction, intensification, central nervous system (CNS) prophylaxis and maintenance phases. It was initially evaluated in a phase II mul-

ticenter trial with high rates of CR, especially in patients under 30 years with prolonged leukemia free survival [2].

Treating adults ALL is challenging in the context of the Brazilian public health system because it requires a tertiary healthcare facility with an onco-hematological ward, a day hospital structure to provide sequential outpatient chemotherapy, and a HSCT unit.

Previous studies in Brazil demonstrated particular points that interfere in clinical outcomes in ALL patients, such, difficulties in the treatment of infections, absence of, clinical trials and, the lack of High Efficiency Particulate Arresters (HEPA) filters in induction and allogeneic HSCT phases [6].

There are few studies evaluating different protocols in low income countries[7]. In this retrospective study we report the outcomes of adult ALL patients treated with CALGCB 8111 protocol in a public tertiary single center located in northeast Brazil.

METHODS

Study Design and Patients:

This was a retrospective study conducted from March 2011 to December 2018 at Hospital Universitário Walter Cantídio of Federal University of Ceará. Patients with newly diagnosis ALL who underwent CALGB8811 protocol during the proposed period were evaluated. Patients younger than 18 years, with a diagnosis of biphenotypic or mixed lineage leukemia and with a previous diagnosis of chronic myeloid leukemia were excluded from the analysis.

Disease risk criteria were based on the CALGB8811 protocol. High risk patients were those with WBC more than 30 000/mm^3 in B-ALL; more than 100 000/mm^3 in T-ALL; more than 35 years aged; BCR-ABL1 positivo B-ALL; complex karyotype (more than 3 chromosomal alterations).

The indications to allogeneic HSCT were High risk ALL; relapsed ou refractory ALL. We defined relapsed ALL in patients that had a recurrence after 6 months of response. We defined refractory ALL in patients that do not achieve CR in first induction or patients who relapsed before 6 months.

Disease assessment

We defined ALL based on 2008 WHO classification. The phenotypic definition was based in flow cytometry analysis. Karyotype was made by classical cytogenetic analysis in Giemsa and BCR-ABL1 analysis was made by PCR.

CR was defined by less than 5% of blasts in bone marrow aspirate at the end of induction. Treatment related mortality (TRM) was defined as death for any cause, except in the setting of relapsed disease.

Minimal residual disease (MRD) was made at the end of induction and before the alloSCT. Patients with BCR-ABL1 negative ALL, analysis of MRD was made by flow cytometry. Patients with BCR-ABL1 positive ALL, MRD was investigated by flow cytometry and PCR.

Statistics

Data analysis was performed using the R program., Results with p-value < 0,05 were considered statistically significant. Survival curves were performed by the Kaplan-Meier method, and the groups were compared using the log-rank test. The univariate and multivariate analysis was made with R program. Data from patients undergoing allogeneic HCT were also recorded, and patients were not censored at the time of transplantation.

Results

During the study period 50 patients with de novo ALL were admitted. The male / female ratio was 1.4 (29/21) and the mean age was 34.4 (18-74, SD=16.1 years). Most patients (62.0%) analyzed at diagnosis had high-risk criteria. The demographic characteristics are in Table 1.

CR was obtained in 86 % patients . 12% of patients died during induction by infection complications. 30% patients underwent alloSCT, 60% were in CR1.

The median overall survival (OS) was 21.5 months (8.1-38.7) (Figure1). The 5 years OS was 25% in no transplanted patients versus 60% in the transplanted group (Figure 2). OS was not statistically different according to age, immunophenotype (B versus T ALL) or risk groups.

There was a statistically difference on Cox regression model between patients who underwent allogeneic HSCT, independently of time of remission (HR=1.34; p-value = 0.01) and patients who achieved CR1 (HR=4.6; p-value<0.001) (Table 2).

The overall survival of patients with ALL who underwent the CALGB8811 protocol had no influence by gender, age over 35 years, risk stratification, immunophenotype and MRD scores in uni and multivariate (logistic regression) analysis. Although achieving complete remission after induction chemotherapy and allogeneic hematopoietic stem cell transplantation were the factors associated with better long-term survival rates in uni and multivariate analysis.

Discussion

ALL is a more common haematological malignancy in children than in adults [8]. In pediatric patients, cure rates with intensive chemotherapy regimens may reach up to 90-95% [7]. In adults, cure rates are lower, with a high relapse rate after induction, especially in patients at unfavorable risk.

Classically, the main risk factors are leukocytes above 30000 / mm^3 in B-ALL and 100000 / mm^3 in T-ALL; age over 35 years; unfavorable cytogenetics (BCR-ABL1 positive ALL;t(4;11); Ph-like kinase profile; hypodiploid and complex karyotype) [9-10].

Modernly other risk factors are being added to the analysis, especially post-induction MRD which has been shown to be a good predictor of long-term response and surrogate of favorable outcome after alloSCT [10].

These risk factors have not been studied in the Brazilian population although many centers use these variables to define indication for allogeneic hematopoietic stem cell transplantation (alloSCT) in first remission [11].

Some studies have shown that patients with standard risk ALL and post-induction negative DRM would not benefit from first remission alloSCT. In the present study, however, the risk factors classically used in the CALGB8811 protocol and negative post-induction DRM were not good predictors of favorable outcome in univariate analysis, nor were they associated with longer survival.

The two main factors that were associated with better outcome and higher median overall survival were post-induction morphological remission (data not shown) and alloSCT. The present study did not evaluate the reasons why the risk factors established in international studies were not predictors of better outcomes in the northeast Brazil reality; however, possible reasons for non-reproducibility are the relatively small patient sample, difficulties in stratifying patients better by flow cytometry and MRD analysis, hospital infrastructure in the single health system, low human development index of patients treated and delayed arrival of acute leukemia patients in specialized services[11].

Conclusions

Risk factors classically associated with worse adult ALL outcome and post-induction DRM status were not predictors of outcome in the northeast Brazilian reality. Post-induction remission and alloSCT were factors associated with a favorable outcome. In this context, the need for further studies evaluating such risk factors in Brazilian context is reinforced.

FIGURE1 - Overall survival of patients with ALL treated with GALGB8511

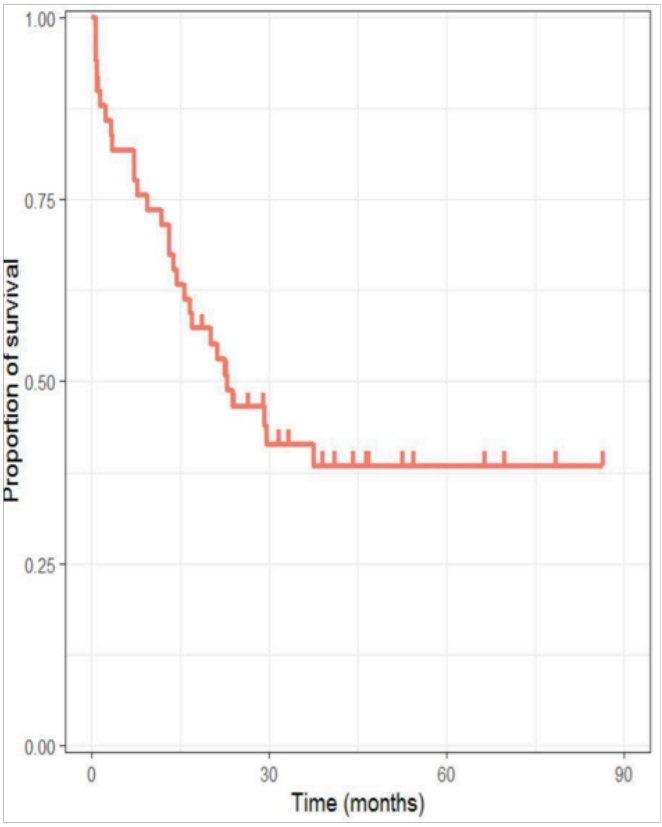

FIGURE2 - Overall survival according hematopoietic stem cell transplantation

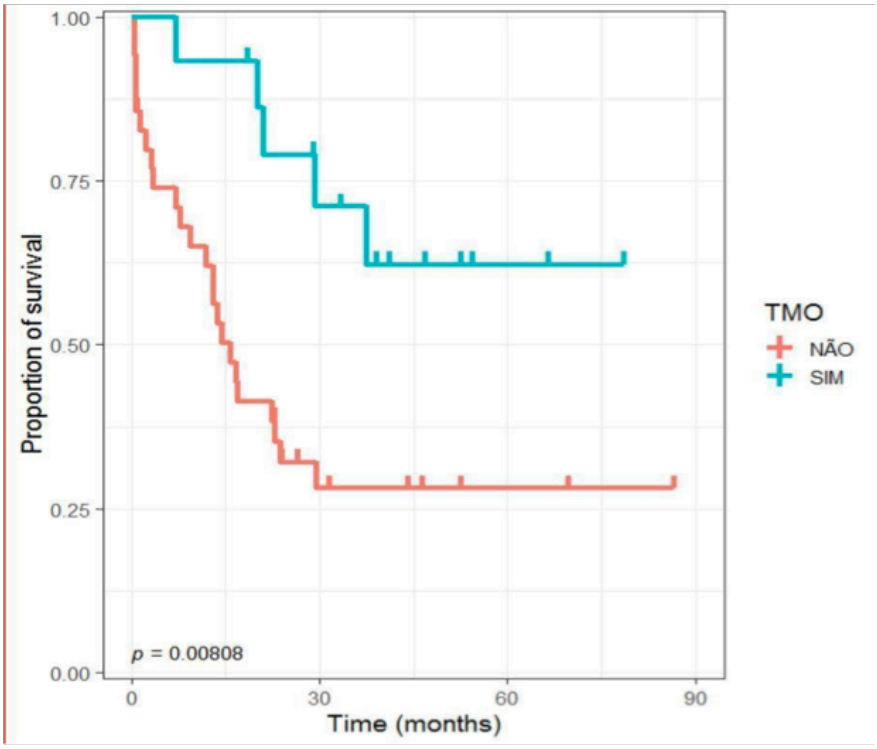

TABLE 1 - patients demographics

Variables	N(%)
Sex	
Female	21 (42)
Male	29 (58)
Age	
Below 35 years	30 (60)
Above 35 years	20 (40)
Immunophenotype	
B-ALL	40 (80)
T-ALL	10 (20)
GALB 8811 risk stratification	
Standard	31 (62)
High	19 (38)
CR1	
Achieved	43 (86)
Not achieved	7 (14)
alloSCT	
Yes	15 (30)
No	35 (70)

TABLE 2: Cox regression model analysis. Age was analyzed as continuous indepedent variable; sex was analyzed in dichotomous independent variable (1 as male); CALGB risk stratification was analyszed as dichotomous independent variabel (1 as high risk), also CR1 and alloSCT.

Variables	HR	p-value
Age	0.01	0.3
Sex	0.78	0.1
GALGB 8811 risk stratification	0.6	0.2
CR1	4.6	<0.001
alloSCT	1.34	0.01

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DOI: 10.46765/2675-374X.2021v2n2p99

CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: THE FIRST BRAZILIAN SUMMARY SLIDES

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ABSTRACT

Understanding the HSCT scenario in Brazil is challenging due to the lack of a national registry that allows the analysis of results. The partnership between the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) and the Center for International Blood and Marrow Research (CIBMTR) allowed the return of Brazilian data registered in the CIBMTR, through the Data Back to Center (DBtC), in a standardized and organized way. With this database it was possible to know the demographic data and the outcomes of transplants performed in Brazil. The spreadsheet was imported into the Power BI desktop, and functions and charts were created. Between 2008 and 2019, 7,264 transplants were reported to the CIBMTR from 24 Brazilian transplant centers. The partnership between SBTMO and CIBMTR, made the Brazilian registry possible and allowed the development of the first Brazilian Summary slides. Despite the difference in the number of cases and of follow-up time, the results in this study were similar to those presented in the US Summary Slides.

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

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a therapy that can be the only option for curing many malignant and non-malignant hematological diseases, as well as extending the survival of many patients[1]. Brazil has a large HSCT program, with 126 teams in 86 transplant centers recognized by the Brazilian Ministry of Health. The results of these transplants are not organized and available for public awareness.

The only current source of information is the Brazilian Association of Organ Transplants (ABTO), which discloses the number of procedures performed each year. According to ABTO, in 2019, 3,805 transplants were performed: 1,428 allogeneic and 2,377 autologous[2]. According to the Center for International Blood and Marrow Transplant Research (CIBMTR), a total of 269,203 autologous and 280,299 related and unrelated allogeneic transplants were reported around the world between 1970 and 2020.[3]

Understanding the HSCT scenario in Brazil is challenging due to the lack of a national registry that allows the analysis of results and provides greater scientific production and national benchmarking. Therefore, over the years, through a working group composed of physicians and data managers (DM) and with the collaboration of the CIBMTR and the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation (SBTMO), strategies such as continuing education in data management and communication channels were developed. These actions increased the number of registered and active Brazilian centers in the CIBMTR.[4]

The partnership between SBTMO and CIBMTR allowed access through the tools available in the registry, such as the Data Back to Center (DBtC), which allows the return of the data sent to the transplant center. Part of the data inserted can return to the centers registered in a standardized and codified way, allowing the analysis of the outcomes of transplants performed in the country. Accessibility to these data is fundamental for health and public administration.

OBJECTIVE

Our objective is to understand the demographic data and the outcomes of transplants performed in Brazil using the DBtC tool to retrieve the data registered in the CIBMTR in a standardized and organized way.

METHODS

Make the data available to HSCT centers and maintain a routine to update the results.

Data from transplants performed between 2008 and 2019 were extracted from the CIBMTR portal using the DBtC, with information from transplanted patients in 24 Brazilian centers that sent their data to the CIBMTR. The records that had completed HSCT data were selected for analysis, totalizing 7,264 transplants. The spreadsheet was imported into Power BI Desktop (PBI). Functions were created to count the number of transplants performed and the number of participating centers, to translate some columns into Portuguese, to categorize disease classification, to group variables, and for calculating global survival analyses, and sheet relationships.

Patients were classified in pediatric (0-17 years of age) and adults (≥ 18 years of age). Allogeneic transplants were categorized as matched related donor, mismatch related donor, 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 early disease for patients transplanted in 1st remission, intermediate disease for patients in 2nd or further remission and advanced for patients who underwent HSCT with active disease.

Patients with Myelodysplastic Syndrome (MDS) were divided into Early Stage, which is subdivided into refractory anemia (RA); refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia (RCMD); and with 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 HSCT.

The classification of conditioning 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/m2 as a single agent or in combination with other drugs. The other conditionings that did not fill the criteria for MAC were classified as Reduced Intensity/Non-Myeloablative (RIC/NMA).[5-6] The causes of death were classified using the standard classification from DBtC. The main causes of death between 2015-2019 were

separated between deaths 0-100 days and deaths >100 days up to 3 years after HSCT. For the analysis of overall survival (OS), patients who underwent 1st HSCT were selected, and those who were without follow-up update after transplantation or had error in survival time were excluded (table 1).

The charts were generated in the PBI and exported to PowerPoint for publication. Global survival analyses were performed by the Kaplan Meier method (Comparison between groups by long-rank test) using the R program (Version 4.0.3).

RESULTS

Between 2008 and 2019, 7,264 transplants were reported from 24 transplant centers in Brazil (table 2), 14 (58%) located in the state of São Paulo; 2 in Rio de Janeiro; 2 in Rio Grande do Sul; and 1 center in each state: Ceará, Distrito Federal, Minas Gerais, Paraná, Rio Grande do Norte, and Santa Catarina.

An increase in the number of active centers was observed in recent years, reaching 23 active centers in 2019 (figure 1). This increase in the number of participating and active centers contributed to the increase in the total number of transplants registered in the CIBMTR since 2016, reaching 1,073 transplants in 2019 (figure 2). The increase in registered cases was observed both in allogeneic and autologous transplants.

Half of the allogeneic transplants performed in Brazil used a matched related donor (49.7%), followed by an unrelated donor (BM/PBSC) (28.9%), and a mismatch related donor (15.8%).

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

Mismatched related donors were used to treat non-malignant diseases (30.1%), followed by acute myelogenous leukemia (AML; 29.4%) and acute lymphoblastic leukemia (ALL; 21.1%); half of them used MAC (50.5%) and 49.5% used RIC/NMA.

The number of autologous and allogeneic transplants have increased in recent years in recipients over 60 years of age.

The main indications for HSCT in Brazil between 2017-2019 were Multiple Myeloma (25%), followed by AML (16%), ALL (13%), non Hodgkin lymphoma (NHL; 12%) and Hodgkin disease (HD; 9%) (figure 3). In pediatric allogeneic HSCT, the main diseases were ALL (32%), other Non-Malignant (25%) and AML (18%). In adults, the main indications for allogeneic transplants were AML (33%), ALL (19%) and MDS (14%).

Acute leukemias continue to be the main indication for allogeneic transplantation, but from 2016 on, there was an increase in indications for MDS/MPN and Lymphomas. The main indications for autologous HSCT remain Multiple Myeloma and Lymphomas.

In patients with acute leukemias, half of the patients with AML were in the early phase of the disease (50.4%), but for ALL 45.9% were in the intermediate phase. Most HSCT were from matched related donor in both AML (55.1%), as well as in ALL (44.9%) (table 4).

Adults and children having an allogeneic HSCT in early phase of the disease had a higher OS ($p<0.001$ and $p=0.008$, respectively; table 5).

Infections were the leading cause of death in the first 100 days after all transplants: autologous (60%), matched related donor (38%), unrelated donor (40%), and mismatch related donor (54%). The most common cause of death more than 100 days after HSCT was the primary disease: autologous (76%), matched related donor (39%), unrelated donor (44%) and mismatch related donor (48%).

For the analysis of OS, the median follow-up was 25 months in allogeneic and 23 months in autologous HSCT. Patients who underwent transplantation with advanced stage had lower survival rates compared to the other stages.

Adults had a significantly better survival after HSCT from matched sibling donors when having HSCT for AML ($p=0.047$; figure 4) and ALL ($p=0.027$; figure 5), but donor source had no impact in pediatric patients with acute leukemias.

The 2-year survival for MDS was similar despite disease risk and donor source (figure 6). Patients with CML a 2-year OS of 60.1% with a matched related donor and 55.0% with an unrelated donor ($p=0.314$) (figure 7). Patients with Myelofibrosis had a survival of 59.0% in 2 years (figure 8). Donor source had no impact in adults and children with Aplastic Anemia (figure 9).

Patients undergoing autologous HSCT to treat chemosensitive Lymphomas had a significantly better 2-year OS than chemoresistant disease: 89.2% versus 64.9% in HD ($p=0.005$) and 79.7% versus 58.6%

in NHL (p=0.019) (figure 10). In Multiple Myeloma, the 2-year OS was 83.4% (figure 11).

DISCUSSION

Our study, using DBtC data, demonstrated a greater number of allogeneic than autologous transplants reported to the CIBMTR, but according to ABTO there is a greater number of autologous transplants in the country. The explanation for this difference is due to the larger number of affiliated centers in the CIBMTR that perform allogeneic transplants.

We observed an increase in the number of transplants with mismatch related donor since 2012, and a decrease in unrelated CB transplants in the same period, probably due to the use haploidentical donors with cyclophosphamide after transplantation.

Comparing our data with the American summary slides published in the CIBMTR website,[7] the matched related donor is the main type of transplants performed in Brazil, while in the United States (USA), it is unrelated BM/PBSC.

In pediatric patients, the main source was BM in Brazil, following the same trend in the USA; in adult, while in Brazil the use of PBSC has been increased over the years and has become the main source used since 2018, in the three modalities of allogeneic donors, in the USA the main source was PBSC since 2000.

In Brazil, in recent years, the main indications for HSCT were MM, AML, ALL, NHL, and HD, while in the USA in 2019 were MM, NHL, AML, MDS/MPN and ALL.

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 and matched related donor transplants, while in the USA, it was the primary disease; in transplants with mismatch related and unrelated donors, in Brazil the main cause of death was infections, while in the USA, organ failure was classified as the leading cause.

Comparing the 2-year OS in our study with the 3-year OS in the US Summary Slides, the Brazilian data is similar to the survival reported by American centers (table 6) despite the socioeconomical differences.

CONCLUSION

The partnership between SBTMO and CIBMTR made the Brazilian registry possible through the DBtC. The analysis of the data from Brazil, allowing us to develop Brazilian Summary slides to know the outcomes of transplants, making them available to centers as a national and international benchmarking. The Brazilian Summary slide will be updated twice a year and published at the SBTMO website. Despite the difference in the number of cases and follow-up time, the results in this study were similar to those presented in the US Summary Slides.

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TABLE 1. Exclusion criteria for overall survival

Exclusion criteria	n
Patients without follow-up update	1,014
Error in survival time	4
2nd HSCT or more	626

TABLE 2. HSCT centers

Participants Centers
Associação Hospitalar Moinhos de Vento
Bio Sana's São Camilo
Centro de Pesquisas Oncológicas Dr. Alfredo Daura Jorge (CEPON)
Complexo Hospitalar de Niterói
Fundação Pio XII - Hospital de Amor
Hospital Amaral Carvalho
Hospital das Clínicas da Faculdade de Medicina da USP
Hospital de Clínicas da Universidade Federal do Paraná
Hospital de Clínicas de Porto Alegre
Hospital Israelita Albert Einstein
Hospital Leforte Liberdade
Hospital Samaritano
Hospital Sírio Libanês
Hospital Universitário Walter Cantídio da Universidade Federal do Ceará / HUWC-UFC
IBCC - Instituto Brasileiro de Controle do Câncer
Instituto da Criança - Hospital de 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 Cancêr - INCA
Natal Hospital Center
Real e Benemérita Sociedade de Beneficência Portuguesa de São Paulo
Universidade Estatual de Campinas (UNICAMP)
Hospital das Clínicas da Universidade Federal de Minas Gerais
Universidade Federal de São Paulo - Hospital São Paulo

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

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Patients <18 Years												
Matched Related Donor												
PBSC	2.9%	1.8%	5.1%	1.8%	2.0%	5.0%	2.5%	3.4%	11.1%	5.6%	6.9%	9.1%
BM	94.1%	92.7%	94.9%	92.7%	96.0%	95.0%	97.5%	93.1%	88.9%	91.7%	89.7%	88.6%
CB	2.9%	5.5%	0.0%	5.5%	2.0%	0.0%	0.0%	3.4%	0.0%	2.8%	3.4%	2.3%
Unrelated Donor												
PBSC	0.0%	7.7%	7.7%	8.2%	5.3%	3.5%	14.5%	13.3%	8.1%	8.3%	14.0%	4.6%
BM	43.2%	42.3%	56.9%	58.9%	56.0%	75.4%	79.0%	73.4%	83.8%	85.0%	79.0%	90.8%
CB	56.8%	50.0%	35.4%	32.9%	38.7%	21.1%	6.5%	13.3%	8.1%	6.7%	7.0%	4.6%
Mismatch Related Donor												
PBSC	0.0%	0.0%	0.0%	25.0%	26.1%	10.3%	28.0%	10.7%	27.3%	21.3%	33.3%	31.0%
BM	100.0%	100.0%	100.0%	75.0%	73.9%	89.7%	72.0%	89.3%	72.7%	78.7%	66.7%	69.0%
Patients ≥18 Years												
Matched Related Donor												
PBSC	49.0%	50.9%	55.2%	49.4%	48.3%	47.4%	43.1%	52.5%	43.5%	53.9%	53.6%	60.7%
BM	51,0%	49.1%	44.8%	50.6%	51.7%	52.6%	56.9%	47.5%	56.5%	46.1%	46.4%	39.3%
CB	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Unrelated Donor												
PBSC	8.3%	17.6%	20.0%	24.5%	39.4%	29.1%	36.1%	54.2%	52.1%	48.2%	64.1%	57.3%
BM	75.0%	70.6%	53.3%	54.7%	43.9%	63.6%	63.9%	44.1%	47.9%	51.8%	35.9%	41.7%
CB	16.7%	11.8%	26.7%	20.8%	16.7%	7.3%	0.0%	1.7%	0.0%	0.0%	0.0%	1.0%
Mismatch Related Donor												
PBSC	0.0%	0.0%	50.0%	0.0%	13.3%	29.4%	36.8%	34.5%	41.9%	42.3%	60.5%	67.7%
BM	100.0%	100.0%	50.0%	100.0%	86.7%	70.6%	63.2%	65.5%	58.1%	57.7%	39.5%	32.3%

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

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
AML												
Disease Stage												
Early	55.6%	53.7%	45.8%	44.4%	42.6%	53.3%	47.8%	45.3%	59.8%	50.0%	53.3%	53.9%
Intermediate	14.8%	26.8%	31.3%	30.9%	31.5%	22.7%	37.7%	41.9%	30.9%	29.8%	27.4%	25.1%
Advanced	29.6%	19.4%	22.9%	24.7%	25.9%	24.0%	14.5%	12.8%	9.3%	20.2%	19.3%	21.0%
Donor Type												
Matched Related Donor	77.8%	78.5%	74.0%	62.5%	52.8%	58.7%	68.1%	47.1%	49.5%	48.7%	46.7%	41.3%
Mismatch Related Donor	0.0%	1.5%	2.1%	2.5%	13.9%	6.7%	7.2%	18.4%	22.7%	25.6%	30.4%	32.3%
Unrelated Donor (BM/PBSC)	3.7%	10.8%	17.7%	22.5%	28.7%	25.3%	20.3%	33.3%	27.8%	25.6%	22.2%	26.3%
Unrelated Donor (CB)	18.5%	9.2%	6.3%	12.5%	4.6%	9.3%	4.3%	1.1%	0.0%	0.0%	0.7%	0.0%
ALL												
Disease Stage												
Early	26.5%	38.3%	34.6%	47.0%	44.8%	43.3%	55.4%	58.9%	50.6%	42.6%	52.2%	37.4%
Intermediate	64.7%	55.0%	52.6%	45.5%	51.0%	50.0%	36.5%	40.0%	39.1%	48.5%	34.8%	49.6%
Advanced	8.8%	6.7%	12.8%	7.6%	4.2%	6.7%	8.1%	1.1%	10.3%	8.9%	13.0%	13.0%
Donor Type												
Matched Related Donor	52.9%	63.3%	61.0%	50.0%	43.8%	56.7%	51.4%	44.2%	38.8%	37.0%	40.0%	29.0%
Mismatch Related Donor	0.0%	1.7%	3.9%	1.5%	6.3%	1.7%	2.7%	8.4%	18.8%	28.0%	27.0%	31.3%
Unrelated Donor (BM/PBSC)	23.5%	23.3%	20.8%	31.8%	32.3%	35.0%	44.6%	42.1%	41.2%	34.0%	32.2%	36.6%
Unrelated Donor (CB)	23.5%	11.7%	14.3%	16.7%	17.7%	6.7%	1.4%	5.3%	1.2%	1.0%	0.9%	3.1%

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	77	57.2%	
Unrelated Donor	87	54.9%	0.874
Mismatch Related Donor	40	62.5%	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	462	56.3%	
Unrelated Donor	176	52.0%	0.047
Mismatch Related Donor	104	47.6%	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	40	58.6%	
Intermediate	24	65.3%	0.011
Advanced	13	38.5%	
Patients Age ≥18 Years			
Disease Stage			
Early	312	65.0%	
Intermediate	79	43.0%	<0.001
Advanced	71	30.6%	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	34	61.2%	
Intermediate	37	62.4%	0.013
Advanced	16	26.4%	
Patients Age ≥18 Years			
Disease Stage			
Early	64	69.7%	
Intermediate	74	52.5%	<0.001
Advanced	38	22.3%	

	N	OS in 2 years (%)	p
ALL			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	131	56.5%	
Unrelated Donor	221	59.9%	0.232
Mismatch Related Donor	55	37.2%	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	266	51.6%	
Unrelated Donor	139	45.4%	0.027
Mismatch Related Donor	57	46.6%	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	36	71.1%	
Intermediate	81	47.6%	0.131
Advanced	14	67.5%	
Patients Age ≥18 Years			
Disease Stage			
Early	195	61.5%	
Intermediate	57	24.1%	<0.001
Advanced	14	15.3%	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	61	73.7%	
Intermediate	145	56.8%	0.008
Advanced	15	38.1%	
Patients Age ≥18 Years			
Disease Stage			
Early	80	57.1%	
Intermediate	45	33.4%	<0.001
Advanced	14	14.3%	

TABLE 6. Comparison overall survival – Brazil and USA

	Brazilian Registry		US Summary Slides 2020	
	N	OS in 2 years (%)	N	OS in 3 years (%)
AML				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	40	58.6%	406	70.0%
Intermediate	24	65.3%	136	67.0%
Advanced	13	38.5%	84	33.0%
Patients Age ≥18 Years				
Disease Stage				
Early	312	65.0%	5,228	57.0%
Intermediate	79	43.0%	1,275	53.0%
Advanced	71	30.6%	1,838	31.0%
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	34	61.2%	509	61.0%
Intermediate	37	62.4%	302	61.0%
Advanced	16	26.4%	166	34.0%
Patients Age ≥18 Years				
Disease Stage				
Early	64	69.7%	8,101	55.0%
Intermediate	74	52.5%	2,467	50.0%
Advanced	38	22.3%	3,091	30.0%
ALL				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	36	71.1%	332	81.0%
Intermediate	81	47.6%	472	68.0%
Advanced	14	67.5%	42	52.0%
Patients Age ≥18 Years				
Disease Stage				
Early	195	61.5%	2,258	62.0%
Intermediate	57	24.1%	621	43.0%
Advanced	14	15.3%	279	34.0%
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	61	73.7%	450	74.0%
Intermediate	145	56.8%	611	62.0%
Advanced	15	38.1%	64	58.0%
Patients Age ≥18 Years				
Disease Stage				
Early	80	57.1%	2,707	61.0%
Intermediate	45	33.4%	1,006	42.0%
Advanced	14	14.3%	350	32.0%
MDS				
Matched Related Donor				
Disease Stage				
Early	99	63.2%	704	51.0%
Advanced	99	56.8%	1,645	46.0%
Unrelated Donor				
Disease Stage				
Early	68	59.3%	1,265	44.0%
Advanced	43	59.2%	3,166	43.0%
Aplastic Anemia				
Patients Age 0-17 Years				
Donor type				
Matched Related Donor	95	86.7%	503	97.0%
Unrelated Donor	85	85.4%	450	85.0%
Patients Age ≥18 Years				
Donor type				
Matched Related Donor	162	79.2%	653	81.0%
Unrelated Donor	69	64.2%	711	74.0%

FIGURE 1. Brazilian active centers in the CIBMTR by year

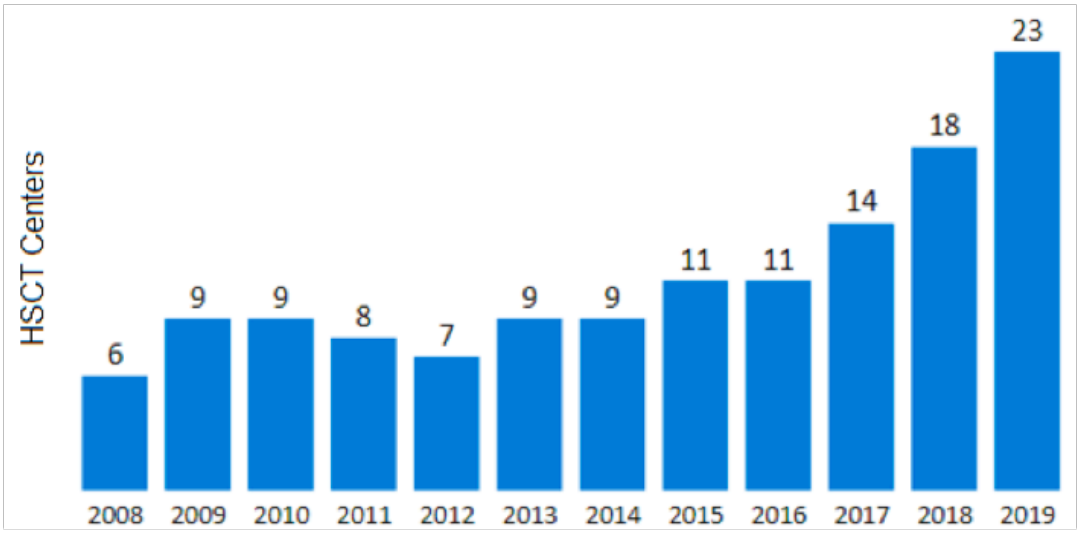


FIGURE 2. Tranplants performed in Brazil and reported in the CIBMTR

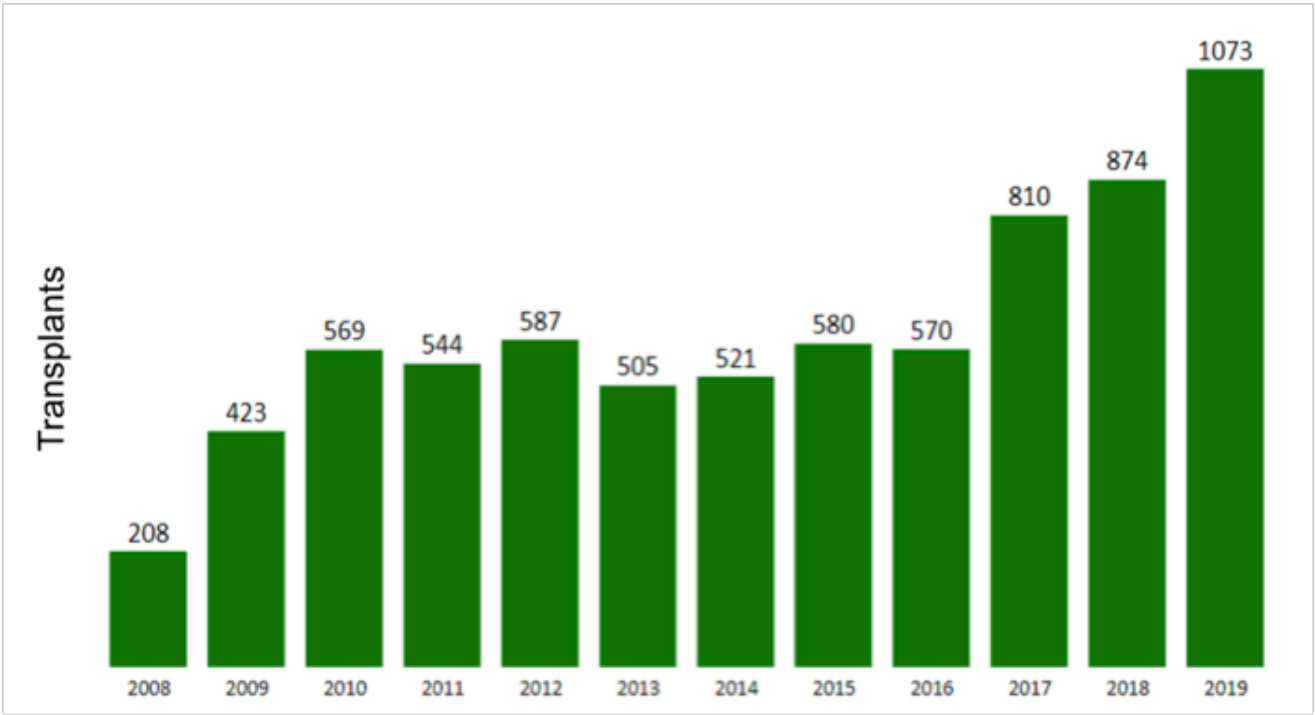


FIGURE 3. Indications for HSCT in Brazil, 2017-2019

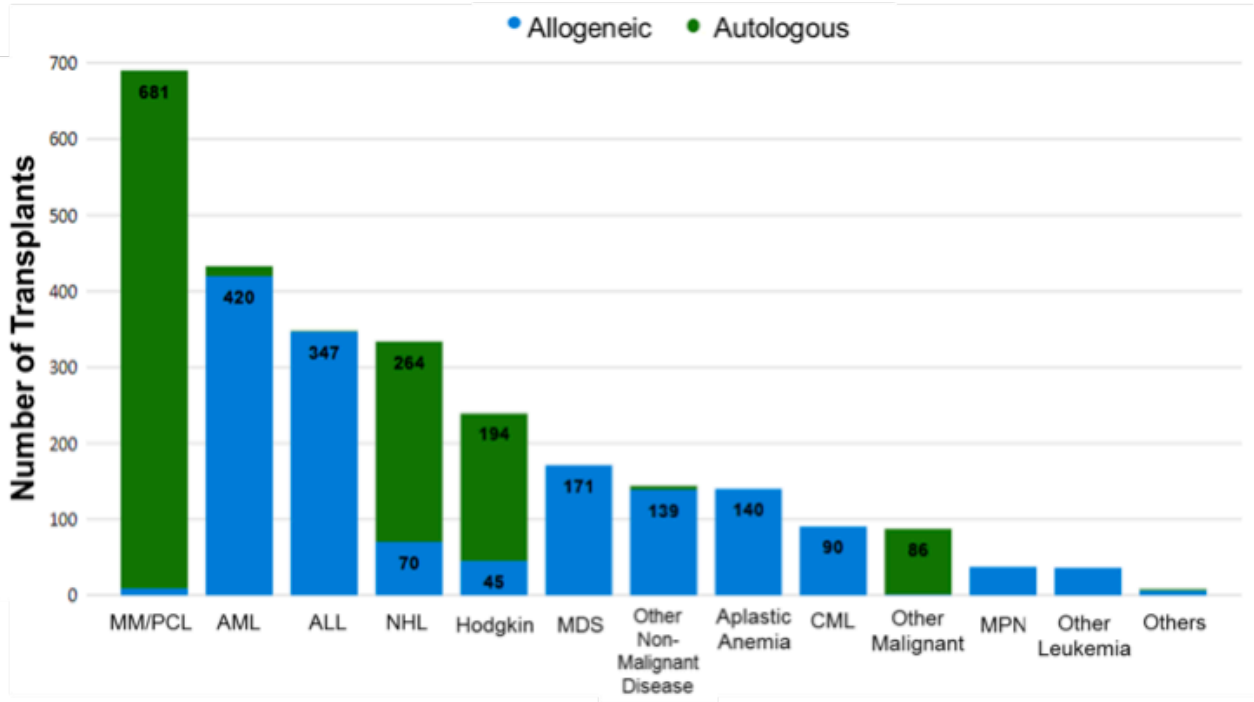


FIGURE 4. AML, overall survival after 1st allogeneic HSCT by donor type

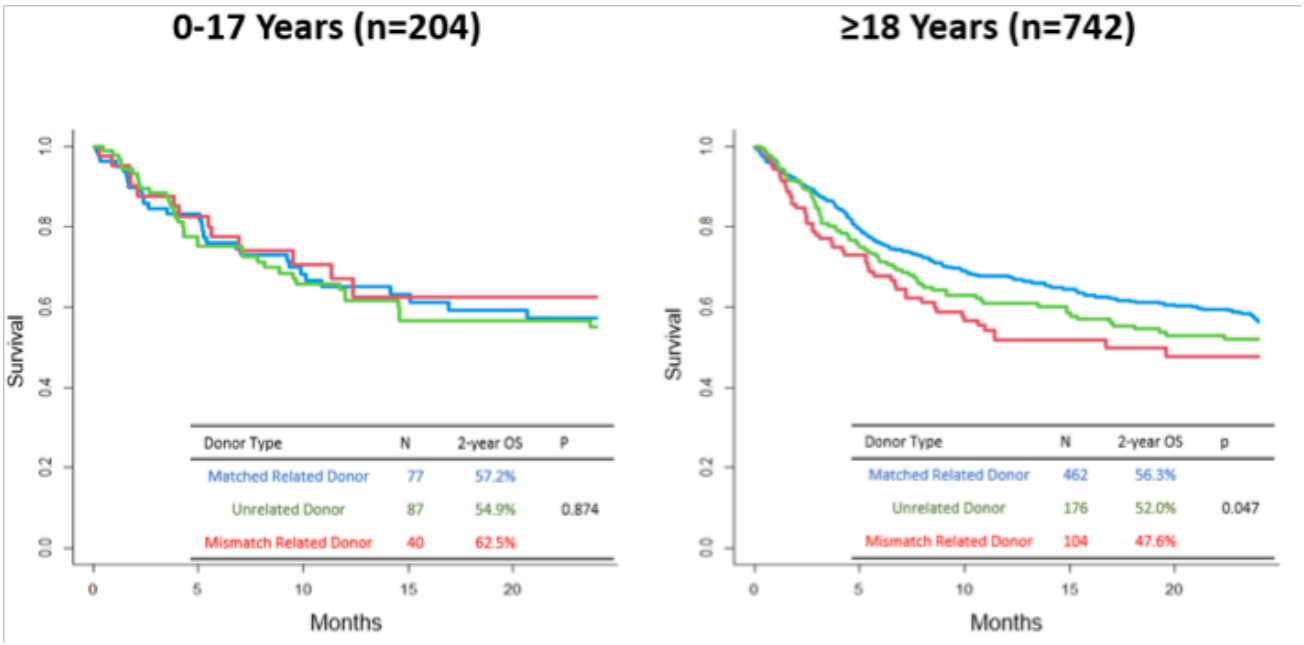


FIGURE 5. ALL, overall survival after 1st allogeneic HSCT by donor type

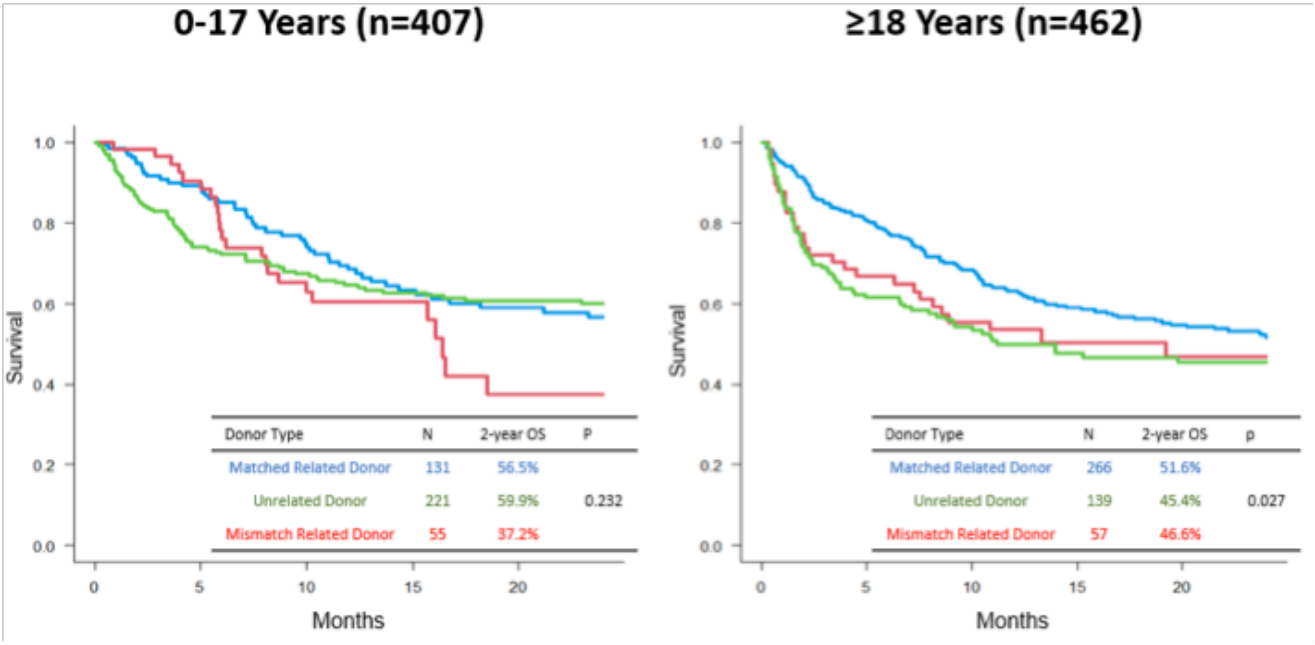


FIGURE 6. MDS, overall survival after 1st allogeneic HSCT by disease stage

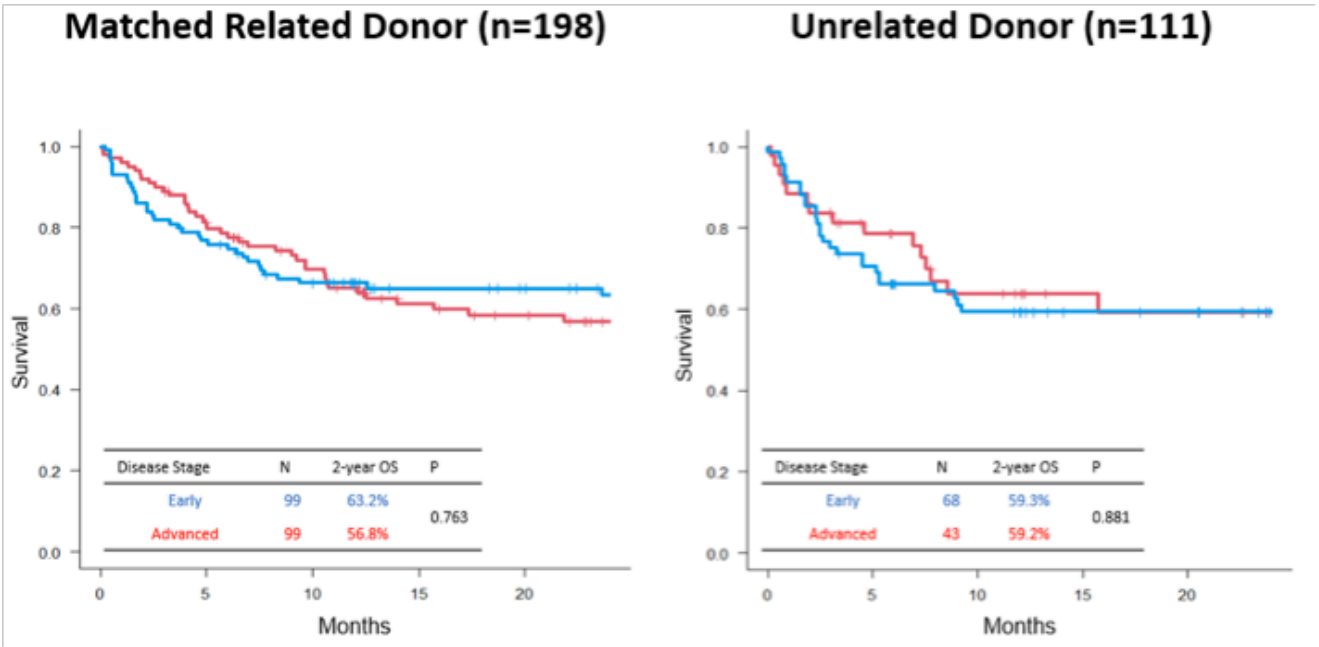


FIGURE 7. CML, overall survival after 1st allogeneic HSCT by donor type

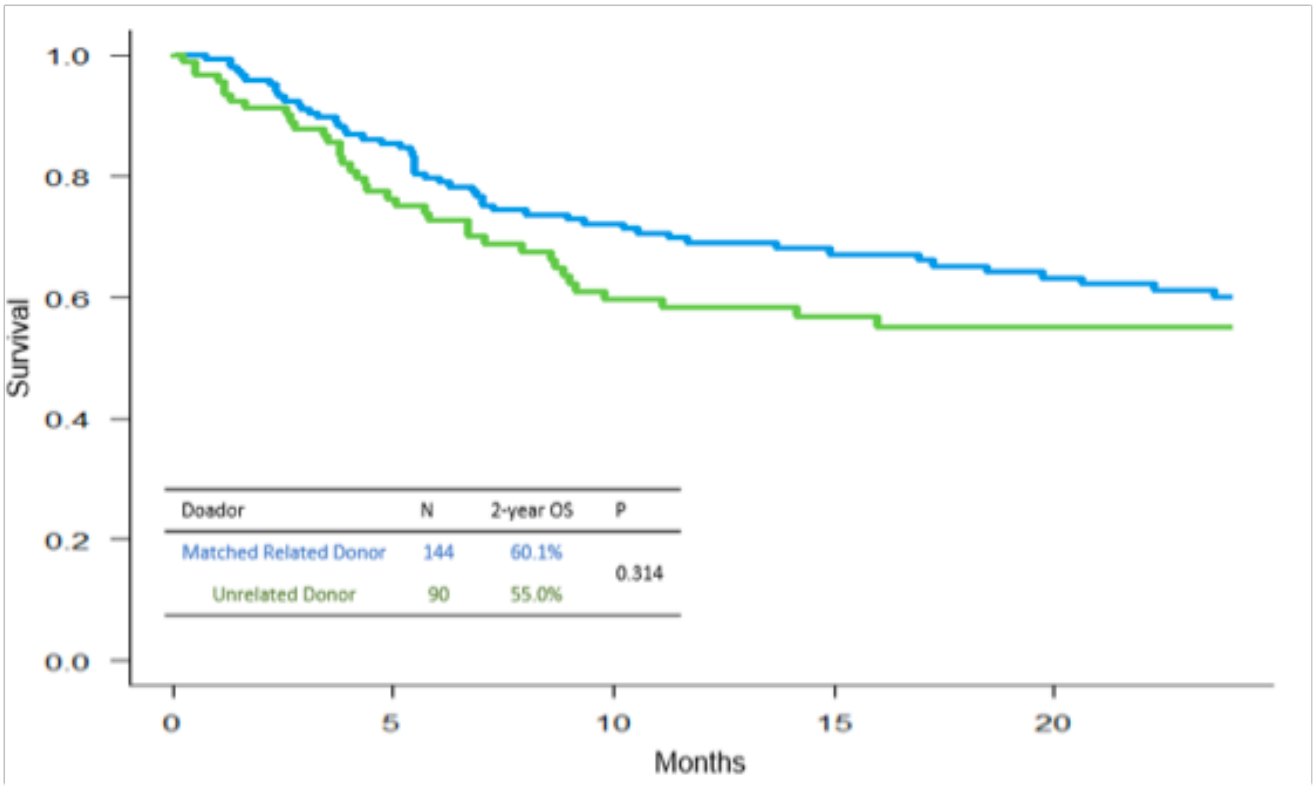


FIGURE 8. Myelofibrosis, overall survival after 1st allogeneic HSCT

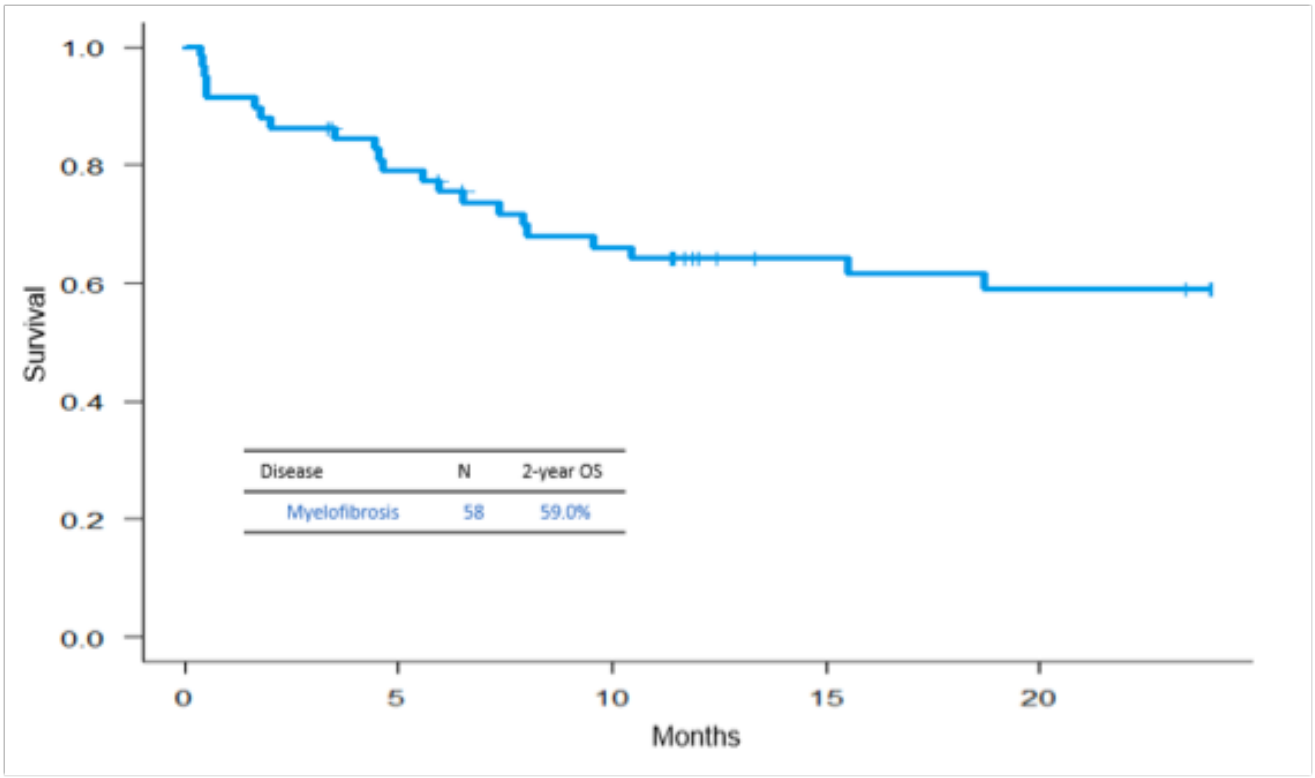


FIGURE 9. Aplastic Anemia, overall survival after 1st allogeneic HSCT by donor type

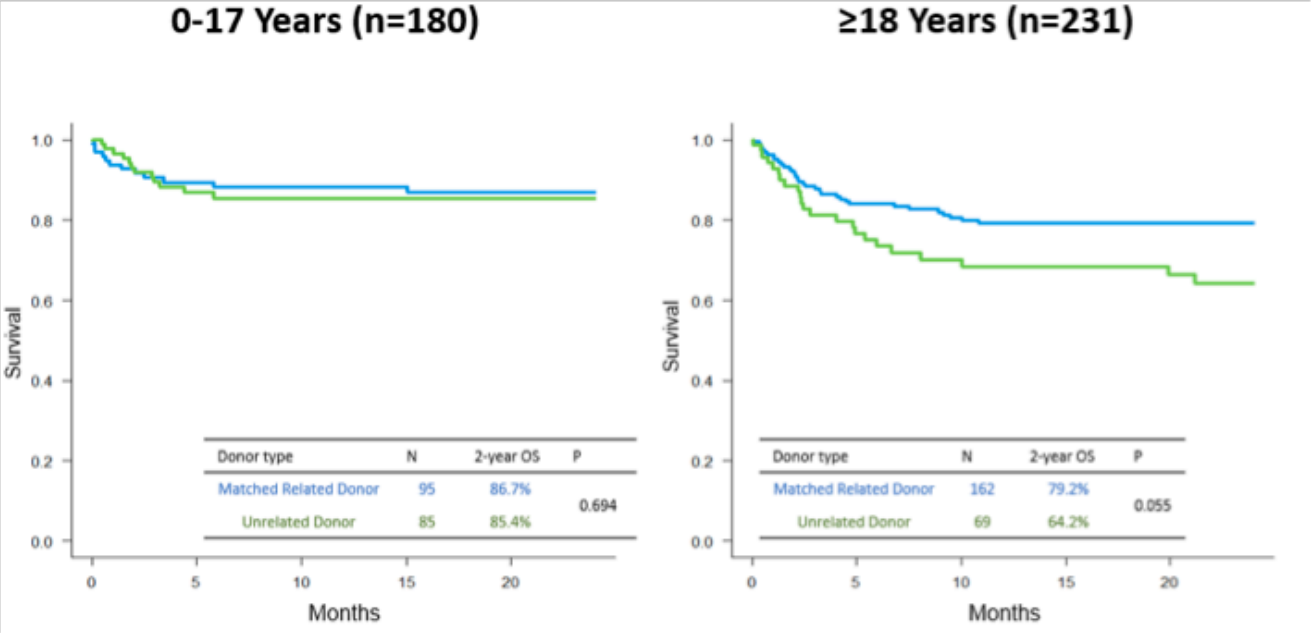


FIGURE 10. Lymphomas, overall survival after 1st autologous HSCT

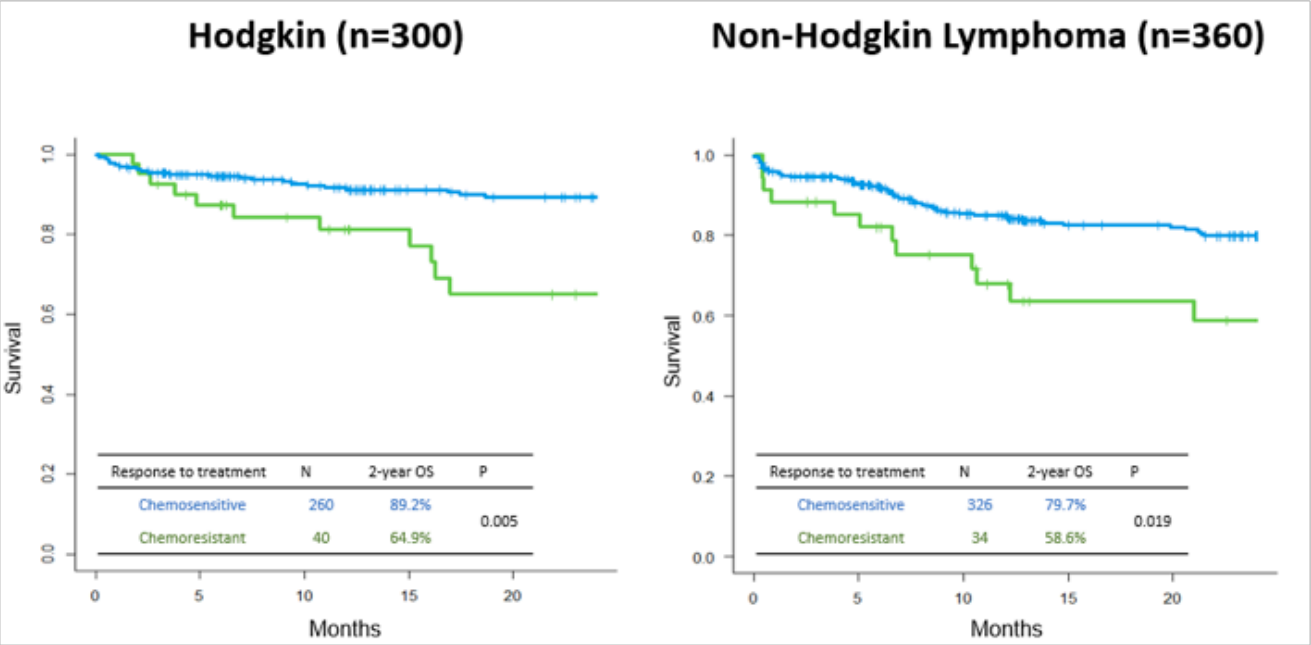
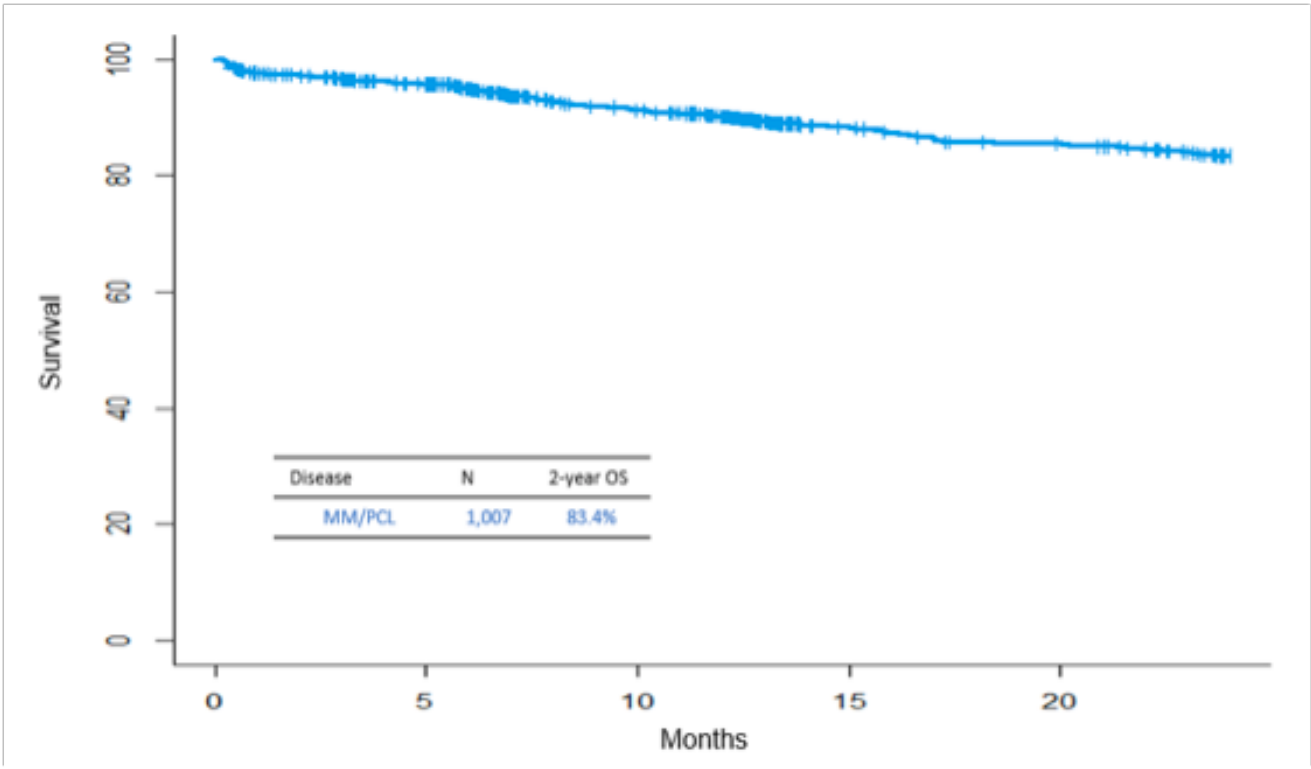


FIGURE 11. Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HSCT



DOI: 10.46765/2675-374X.2021v2n2p100

ESTABLISHMENT OF THE BRAZILIAN REGISTRY OF HEMATOPOIETIC STEM CELL TRANSPLANTATION, USING THE DATABASE THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH

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Running title: BRAZILIAN REGISTRY OF HSCT

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ABSTRACT

The number of hematopoietic stem cell transplantation (HSCT) in Brazil is growing rapidly. To better understand the outcomes of HSCT in Brazil, strategies have been developed with the Center for International Blood and Marrow Transplant Research (CIBMTR), using its standardized registry structure and data sharing application. The methods adopted to establish the registry were through efforts to increase the Brazilian centers that report to CIBMTR included training courses for HSCT data managers, the officialization of a multicenter HSCT study using the CIBMTR structure and the partnership between Brazilian Society of Bone Marrow Transplantation (SBTMO) and the CIBMTR. Here we describe the history for establishing the HSCT Brazilian database using the CIBMTR back to center data and present the aggregated results since 2016. We found a significant increase in the numbers of active centers reporting to CIBMTR from 11 in 2016 to 21 in 2020 corresponding to higher numbers of transplants reported to the CIBMTR from 574 to 921 in that period. The model used to generate this national database was effective as it leverages existing infrastructure to assess the activity and outcomes of HSCT in Brazil.

Keywords: Hematopoietic Stem Cell Transplantation, CIBMTR, Data manager, Database, Outcomes, Information system and Brazil.

Hematopoietic stem cell transplantation (HSCT) is a treatment that can cure or improve the quality of life of patients with malignant and non-malignant hematologic diseases[1]. HSCT began in Brazil in 1979 with the physicians Ricardo Pasquini and Eurípides Ferreira at the Federal University of Paraná (Universidade Federal do Paraná, UFPR)[2]. Since then, there has been a geometric growth in the number of transplant centers. In addition, the Brazilian volunteer unrelated blood and marrow donor registry (REDOME) has increased substantially, currently being the third largest donor registry, and with the increased popularity of haploidentical HSCT with post-transplant cyclophosphamide (PTCy) strategy, has greatly expanded the donor pool for Brazilian population. In 2010, 1,581 (916 autologous and 665 allogeneic) transplants were reported to the Brazilian Association of Organ Transplantation (ABTO) by 44 groups from 12 Brazilian states[3]. In 2020, the numbers of HSCT was 51% higher, with a total of 3,195 transplants (1,927 autologous and 1,268 allogeneic) reported by 93 groups[4]. However, it would

be extremely important to know quantitative indicators and outcomes after HSCT in Brazil. Although some articles have been published by the GVHD and Others Study Group (Grupo de estudos de doença do enxerto contra o hospedeiro - DECH (GEDECO), a research group within the SBTMO)[5-11], greater scientific production is somewhat hindered by the lack of a consistent database and standardized data collection. Moreover, national benchmarking that would enable analysis-based improvements in the quality of the procedure can be quite challenging without a national registry, not to say hampered.

The establishment of a structure to manage HSCT data is complex, as it requires planning, investment, infrastructure, time, professional training, awareness of transplant teams and support from government entities[12]. Thus, the model proposed by the SBTMO in cooperation with the Center for International Blood and Marrow Transplant Research (CIBMTR) uses the North-American registry infrastructure to allow centers to share the data, which is then processed and returned to the centers. The model here is to aggregate the data from a country and return to a central location to allow an assessment of transplant activity and outcomes in the region. This model has been successful in Canada and Japan. The data is then available in a tool called enhanced Data Back to Centers (eDBtC) which uses QlickView, a Business Intelligence application that extracts the data from the CIBMTR data warehouse in a format that is consumable and analyzable, additionally is includes data visualization tools and data download in different formats. (Figure 1). The importance of this cooperation came from the idea that duplicating the CIBMTR structure would be laborious, costly and redundant, combined with the guidelines of the research regulation in the country (resolution 466/2012)[13], as well as the regulation that ensures the protection of patient's personal data, according to the General Data Protection Law (GDPL 13.709/1018) 14 in force in Brazil.

Many Brazilian centers already had a long standing relationship with the CIBMTR even before this possibility was suggested. Some Brazilian centers, such as the UFPR and the Brazilian National Cancer Institute (Instituto Nacional de Cancer, INCA) had been affiliated to CIBMTR since the 1980's. Other Brazilian centers became members of the CIBMTR after that, with variation over time. Additionally, Brazilian centers with capabilities and certification to perform unrelated donor hematopoietic cell transplant from international donors, were require to report data when performing a transplant with a graft acquisition facilitated by the National Marrow Donor transplant. The CIBMTR is a research affiliation between the Medical College of Wisconsin and the NMDP, and the data for unrelated donor HSCT is done using the CIBMTR systems.

According to the first results of aggregate data from Brazil via CIBMTR[15], in 2008 there were 8 active centers in the registry, with 208 transplants reported to the CIBMTR. From 2008 to 2016, there was a cumulative increase of 28% in the number of active centers (N=11), although there was a large fluctuation from 2010 to 2012. In that period, we had a decrease of 22% in the number of active centers, probably due to the lack of local infrastructure or availability of a professional to perform the data manager position compounded by an increase the amount of data collected in the CIBMTR forms, which required a dedicated professional. As for the number of records, there was a growth of 174% from 2008 to 2016, but from 2010 to 2016 the average was 554 transplants per year, with a fluctuation of less than 10% (Figures 2 and 3).

With the lack of an HSCT data registry that could support the scientific community, public health, medical decision making, and also increase the number of active centers in the CIBMTR registry, a working group of physicians and data managers (DMs), starting in 2016 and in partnership with the CIBMTR and the SBTMO. This was a grass roots initiative to train the trainers, i.e. train data managers that would then serve as reference for other center data managers professionals with the objectives to further establish this profession in Brazil, increase the number of reporting centers, improve the quality of the reported data and to continue data collection to capture long term follow up. (Figure 4)[16].

Between 2016 and 2017, the first free online distance learning (ODL) course was offered in Portuguese and Spanish on filling out the pre and post HSCT Transplant Essential Data (TED) forms of the CIBMTR[17]. This first course joined the data managers from UFPR, Hospital Amaral Carvalho and Hospital Israelita Albert Einstein, which began to perform joint actions to support the establishment of the Brazilian registry. In 2018, the SBTMO board of directors for the 2018 to 2021 triennium established among their priorities of its strategic planning the development of the Brazilian transplant registry and support to DMs. For greater capacity building for DMs, in 2018 the Bone Marrow Association of the State of São Paulo (Associação da Medula Óssea, AMEO) promoted, through a PRONON funding from the Brazilian Ministry of Health, an in-person and online training for data managers with focus on centers of greater complexity and that

are dedicated to allogeneic transplants[18]. This fostered the consolidation of the group of DMs in the country and through SBTMO there was the recognition of the Data Managers Working Group (DMWG) in 2019[19]. The DMWG has promoted activities and fluid and effective communication among the DMs, through monthly meetings on specific HSCT and statistical topics, organization of the DMs meetings at the SBTMO Meeting webinars and group interaction via WhatsApp, with more than 20 interested professionals. Throughout the history of the DMs' scientific production has been awarded as best abstract in the session of the DMs in TCT Meeting in 2017 and 2018, and the Ricardo Pasquini Young Scientist prize at the SBTMO Meeting in 2019 and 2020. Currently there are more than [20] professionals active in the role.

With greater mobilization of the centers to become active in the registry, a multicenter study was proposed to formalize the submission of Brazilian data to the CIBMTR. It was approved in March 2017 by the Institutional Review Board (IRB) of the proposing center representing the SBTMO and by the Central IRB in 2019. The Brazilian Registry of Bone Marrow Transplantation was then formalized with the CIBMTR. Later this year the study was approved by the GEDECO. Currently, this scientific study, which regularizes the sending of data to the CIBMTR, contains 33 participating centers and 24 are waiting for the approval of the Central IRB to make this practice official in the institutions, (N=57).

Reporting the number and type of transplants to the Brazilian National System of Transplants (Sistema Nacional de Transplants, SNT) is mandatory, and this data is compiled by ABTO and made publicly available. No follow-up report is required. Therefore, we found that approximately 30% of the HSCT performed in Brazil in 2020 were reported to the CIBMTR, showing there is room for improvement and a long road until 100%-reporting to the CIBMTR.

As a result of the project, the first report done in the country of 7 participating centers was generated, using Brazilian aggregated data from the CIBMTR through the eDBtC. This study was selected for oral presentation at the Transplantation & Cellular Therapy Meetings in 201920. In 2020 there was the publication of the first article coming out from that study, with the 7 centers cited above, in the Journal of Bone Marrow Transplantation and Cellular Therapy. In 2021, the 1st Brazilian summary slides[21] was made available, which is a contemporary compilation of the transplant activity and general outcomes of HSCT performed in Brazil based on the summary slides annually reported by CIBMTR, with data from 24 institutions participating in the project, covering the period from 2008 to 2020. In recognition, these institutions were certified for being active in the CIBMTR by the National Transplant System (NTS) and SBTMO (figure 5).

Another important step was the formalization of the partnership between the SBTMO and the CIBMTR for our country, through a contract signed in 2019[22] that triggered the creation of the Brazilian dashboard on the CIBMTR portal (figures 5 and 6), with aggregated data from all centers active in the registry. The centers active in the CIBMTR, have access to a tool called eDBtC, which allows the return of data sent to their own transplant center in a standardized way, favoring the analysis of some outcomes. The accessibility to this data is fundamental for health and public administration.

With all the actions described above and some consolidated results of these strategies, an increase of active centers in the CIBMTR was noticed, with an average increased rate of 27%, from 2016 to 2019 and a growth of 88% in the number of Brazilian transplants reported to the CIBMTR. Referring to the last two years, in 2019, 23 centers registered data in the North American data registries with a total N of 1,073 transplants and in 2020, due to COVID-19 pandemic, there was a decrease in active centers to 21 and the number of transplants registered to 931 (Figures 2 and 3). According to the CIBMTR report of April 30, 2021, there are 33 active Brazilian centers in the CIBMTR, 12 in the process of contractual regularization with the CIBMTR, and 10 inactive, with 4 in the process of reactivation to the CIBMTR. It is important to emphasize that the inclusion of data from the centers when they become affiliated is not immediate, because there is an infrastructure preparation in the transplant center, awareness of the medical team on how to record the data in the patient's medical record, and the training of the DM with both the CIBMTR platform and the HSCT area, if this is not the area.

In conclusion, the process of creating an HSCT registry, associated with the affiliation of the CIBMTR was the result of actions of the partnership between the SBTMO, CIBMTR and Brazilian professionals who embraced the cause on behalf of the project. It was possible to obtain feasible data for the analysis of outcome and quantitative indicators in Brazil, which is directly linked to the increase in the number of affiliated centers in the North-American/Brazilian registry. Through the last results that generated the Brazilian summary slides and the direct communication of the SBTMO with the NST, the NTS recognized the CIBMTR, as the HSCT registry of the country, accred-

iting 26 centers affiliated to the CIBMTR, through the issuing of a certificate approving the efforts of the HSCT centers. The efforts from multiple stake holders described here demonstrated that implementation of a Brazilian Transplant Registry is feasible. As the data accumulates there is need to continue promoting this activity to reach close to 100% of centers to have a more representative assessment of transplant activity and results. Additionally, it allows for regional specific research and benchmarking to improve the outcomes of patients and the quality of care for Brazilian patients.

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FIGURE 1: Brazilian Registry Model using the CIBMTR

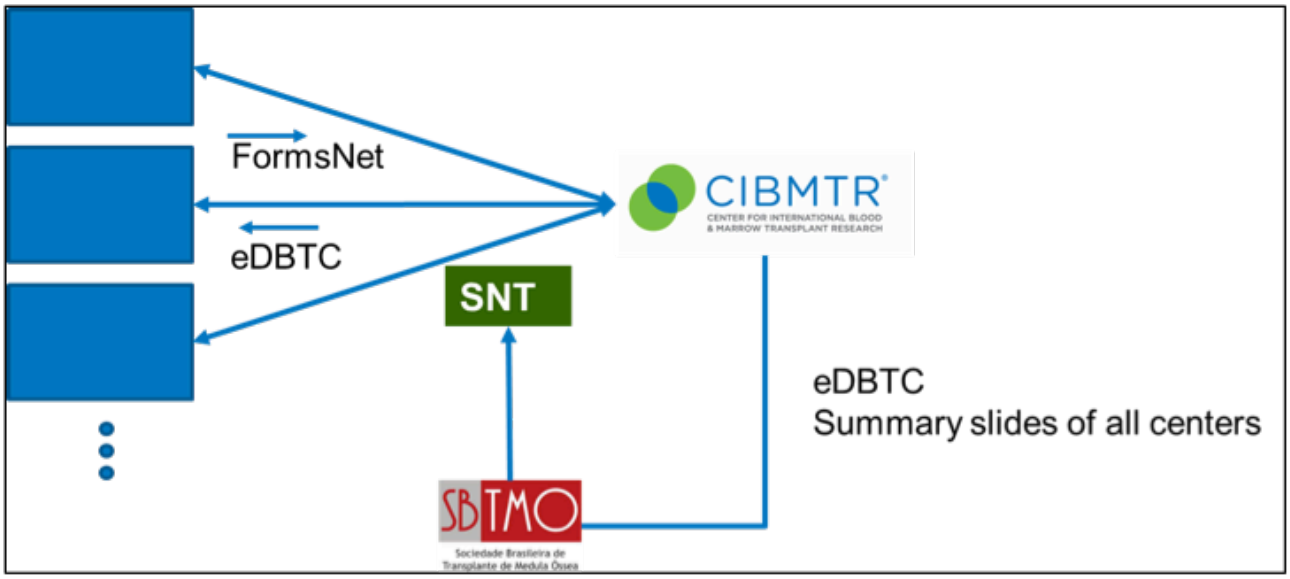

FIGURE 2: Active centers in the CIBMTR registry

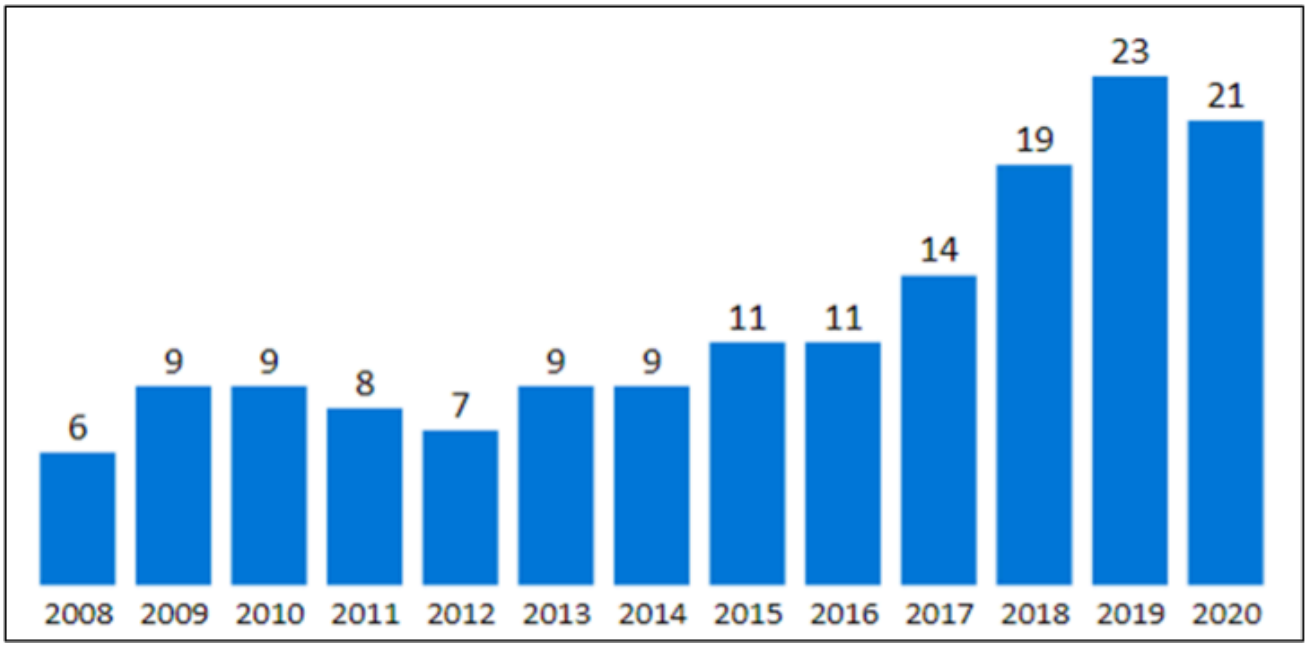

FIGURE 3: Number of transplants registered in the CIBMTR database

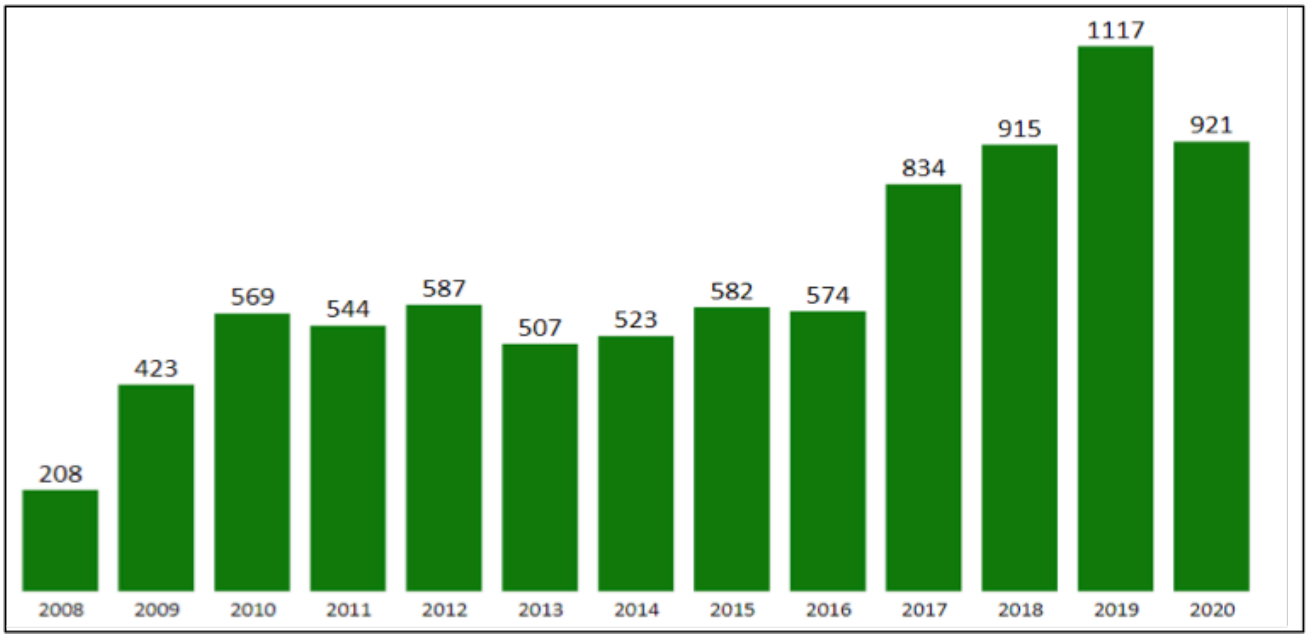

FIGURE 4: Actions timeline

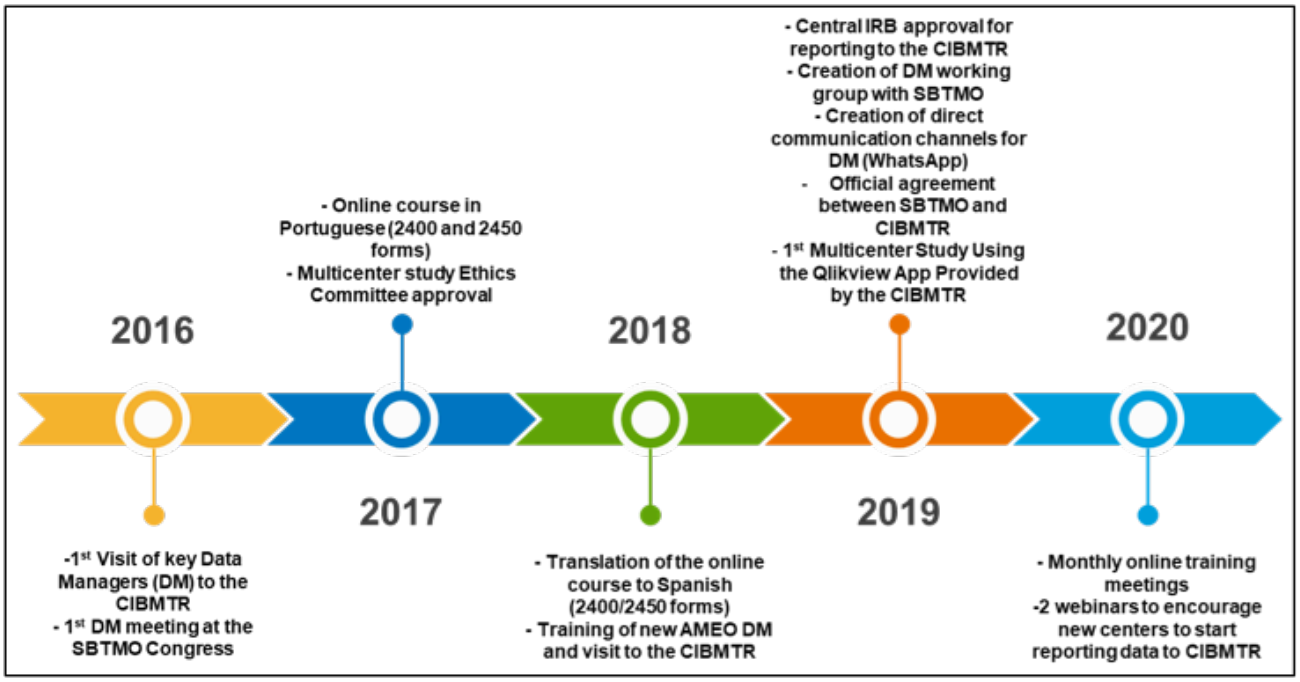

FIGURE 5: Certificate issued by SBTMO and TNS

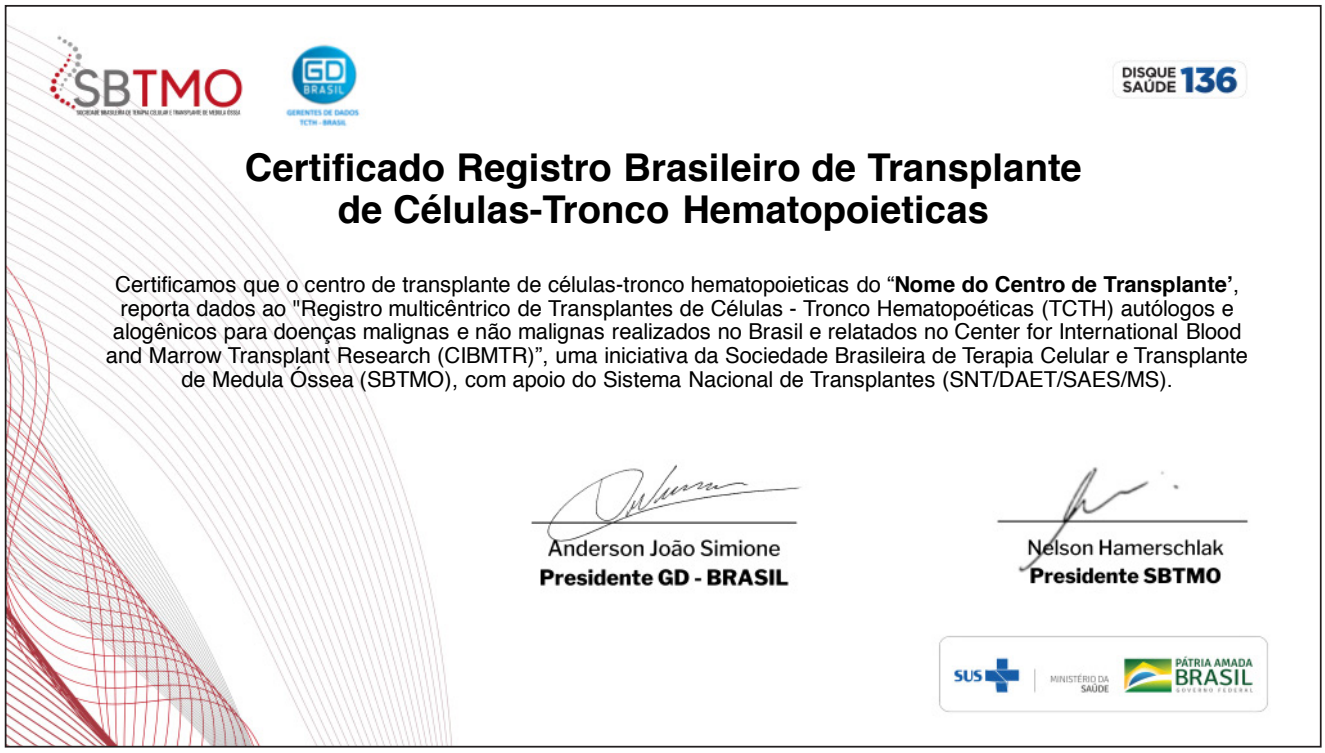

FIGURE 6: Data Back to Centers (DBtC-Consented) - Patient

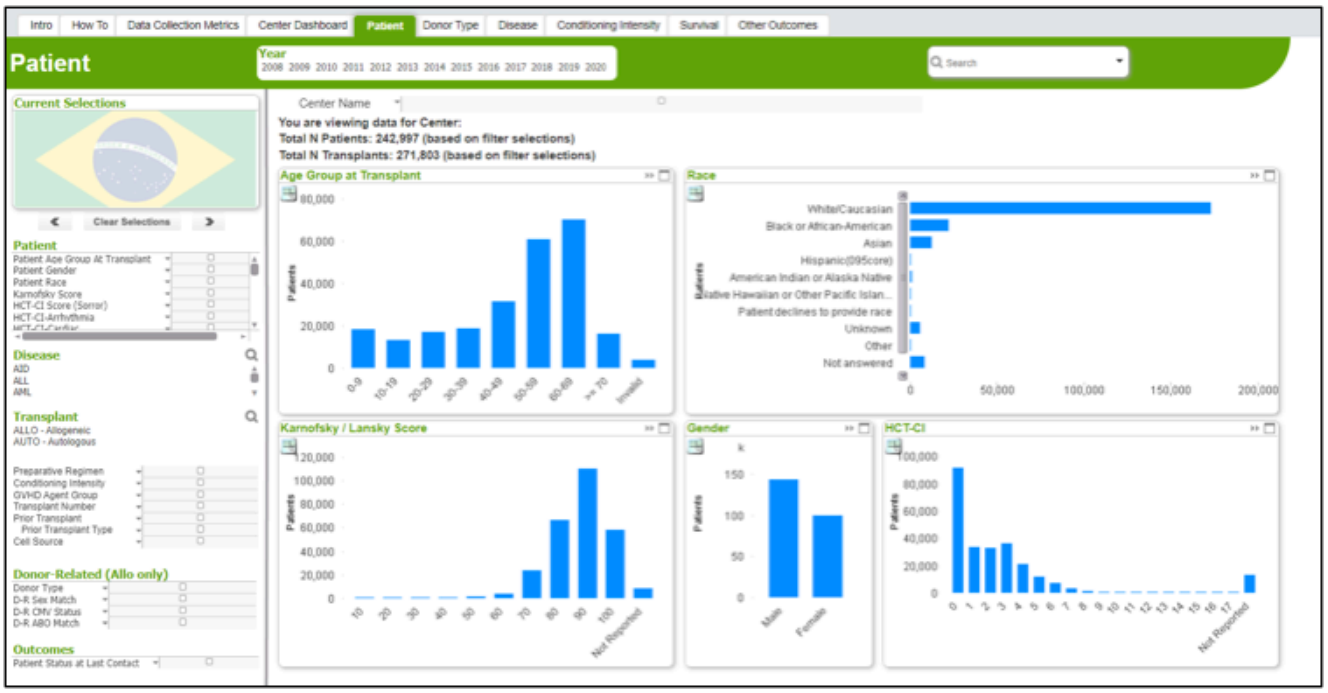

FIGURE 7: Data Back to Center (DBtC-Consented) - Other Outcomes

DOI: 10.46765/2675-374X.2021v2n2p101

THE MAP OF BMT IN BRAZIL: A PUBLIC ACCESS PANEL TO HEMATOPOIETIC STEM CELL TRANSPLANTATION DATA

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ABSTRACT

Brazil has a vast Hematopoietic Stem Cell Transplantation (HSCT) program with 126 teams and 86 Centers recognized by the Ministry of Health. Outcomes of these transplants are unknown. The objective of this work is to create a public database to help the public and health care professionals to find information on allogenic HSCT performed in Brazil. Methods: The team chose indicators, outcomes, and developed tools to accept secure data input using e-DBtC, Access, RedCap and excel spreadsheet. All data was inserted into the Virtual Analytics platform after careful validation and then presented as tables and graphics in separate portals for healthcare professionals and general public. Results: 29 HSCT centers participating in the project sent data on all consecutive allogeneic transplants performed between August 2019-2020. We gathered data from 943 transplants, with results arranged in graphs and tables, with the possibility of using various filters, so users can customize their search. In conclusion, more than 60% of all allogenic transplants performed in the country are now included in the Map of BMT, in an easy and accessible way to be searched. We hope to continue this initiative and extend it to other services, emphasizing great accomplishment of the Brazilian transplant community.

Keywords: Allografts. Data Collection. Disease-Free Survival. Hematopoietic Stem Cell Transplantation. Information Technology. Patient Access to Records. Registries. Survival Rate.

Thousands of patients undergo hematopoietic stem cell transplants (HSCT) in Brazil every year in public and private centers. [ABTO] Patients are usually treated according to international trials and guidelines published in peer reviewed journals and adapted to conditions and medications that are available in the country.

Two articles in this same volume of the Journal of Bone Marrow Transplantation and Cellular Therapy describe the beginning of the Brazilian BMT Registry using data reported to the Center of International Blood and Marrow Transplant Research (CIBMTR) and then reported back to the Brazilian Bone Marrow Transplant Society (Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea – SBTMO) as a consolidated unidentified Data Back to Center file. We are thrilled that the Brazilian summary slides are being published for the first time. This is an outstanding initiative to understand our results and to build up a solid database to develop several registry-based trials.

Another pioneer initiative was launched in 2020: the public and free website the "Map of Bone Marrow Transplantation" where primary physicians, transplant centers and the public can access the Brazilian HSCT activity in Portuguese and apply filters to look for the information of interest.[1]

The objective of this paper is to present this new website as an excellent tool to understand the Brazilian transplant activity.

METHODS

Training new data managers

Between 2019 and 2020, the Sao Paulo State Bone Marrow Association (Associação da Medula Óssea do Estado de São Paulo – Ameo), with funding from the Brazilian government (Programa Nacional de Apoio à Atenção Oncológica – Pronon - NUP 25000.001178/2017-55) and Ministry of Health, developed a program to provide online training for new data managers to understand the complex HSCT-related data and to be able to report it to the CIBMTR, as detailed elsewhere.[2,3] All centers already performing HSCT from unrelated donors were invited to participate.

The Brazilian Central Ethics Committee (Comitê Nacional de Ética em Pesquisa - Conep) was consulted and the Map of Transplants was interpreted as a registry as defined by Resolution CNS number 510 from 2016, Article 1 and the Brazilian Law number 12.527, of November 18, 2011, because patients cannot be identified and there is public access of the results so, neither a specific research project, nor specific consent form are needed. Likewise, lawyer consultants reassured that the portal is compliant with the Brazilian General Personal Data Protection Law (Lei Geral de Proteção de Dados Pessoais) and that no specific consent was needed.

One professional was appointed by each transplant center director to receive a scholarship, but the participation of other professionals was open and free. Public centers also received a laptop to work.

Building up the Center dataset

Each data manager, as part of their training, had to organize the information about all patients undergoing allogeneic transplants between August 2019 and August 2020 in the institutional to be reported. Centers were encouraged to use a surrogate institutional dataset to organize the patients' data and to have the items already translated into Portuguese in the same format they are entered in the CIBMTR portal. Centers were offered an Access and/or RedCAP database ready to be used. Transplant centers already reporting to the CIBMTR could use their "Data Back to Center" file to avoid duplicate work. Other centers chose to use a simple Excel file. Patient identifiers were coded by the institution never shared with AMEO and, once in the Virtual Analytics Platform, all data was encrypted. The variables initially collected are shown in Table 1

Importing data to the Virtual Analytics Platform

Unidentified but individualized patient data was sent from the transplant centers in four different formats: CIBMTR-Data Back to Center files, Access, RedCap and structured excel files. These was carefully checked for consistency before being entered into the Virtual Analytics platform, as shown in Figure 1.

Building the Map of Bone Marrow Transplantation PortaL

Three separate Portals were designed: Public, Professionals and a password protected Center Portal. The data selected to be presented in the portal is shown in Table 2. The portal "Map of BMT" was built as a free and reliable tool for the public to understand the number of transplants performed in each region, being able to filter it according to the age group, disease, donor source, and for professionals to access HSCT results shown as a Kaplan Meier graphic format. Centers can use the password protected access to check their own data within the portal.

Results

The training program for the new Brazilian Data Managers happened over 14 months, with 200 hours of online teaching, time to practice, in person teaching and audit of every center, later changed to online audit due to the Covid pandemic[2,4] A total of 66 data managers from 31 hospitals completed the training (Table 3).

Thirty centers sent the data of all consecutive allogeneic transplants performed between August 2019 and August 2020. Seventeen of the centers are public. Most centers are located in the Southeast region (23), followed by South (4) and Northeast (3). A total of 943 transplants were performed in 929 patients, 870 of them were the first allogeneic transplant.

The Map of BMT, hosted at the AMEO website (www.ameo.org.br) has three portals: Patients, Professionals and a password protected Transplant Center access (Figure 2).

Graphics included in the portal are number of allogeneic transplants according to age, gender, schooling, donor, underlying disease, graft source, number of participating public and private centers in the region. Results include number of allogeneic transplants in each region, time between diagnosis and transplant and the first appointment and transplant, overall survival, disease free survival and primary cause of death (Figure 3).

The majority of the transplants were performed in patients older than 18 years (605 in adults vs. 338 in children), as shown in Figure 4. However, there are profound differences in the age groups transplanted in the country: children (less than 18 years of age) are 20% of the patients undergoing HSCT in the Northeast, versus 35% in the Southeast and 56% in the South.

Information on education was specifically collected for the project and show that 25% of the patients had not completed all school years, as opposed to 36% who had already graduated from university (Figure 5)

The most common underlying diagnoses were acute leukemias, followed by non-malignant disease in pediatrics (Figure 6) and by myelodysplastic syndrome and lymphomas in adults (Figure 7).

The number of allogeneic transplants from matched sibling donors (MSD) is similar to the number of haploidentical (Haplo) transplants, followed by unrelated donors (URD; Figure 8)

However, in adults, 46% of the transplants are from MSD, followed by 33% Haplo and 22% from URD. In children, 41% are Haplo, 35% URD and only 23% of the transplants are from MSD. There are also regional differences: in the northeast, 60% of the transplants are from MSD, while in the south, 44% are haploidentical, followed by MSD and URD in the same proportion.

Bone marrow is used in over half of the transplants in all regions, but it is 78% of the graft sources for children and 40% for the adults. Only 10 cord blood transplants (1%) were reported (Figure 9).

There is a glossary of terms available in the Patient's Portal for them to search for medical terms (Figure 10) and the graphics are very straight forward and easy to be understood (Figure 11).

Patients may look for information on survival applying filters on underlying diagnosis, age group and donor source (Figure 12).

Overall survival is shown at the Patient's Portal as a table with the percentage of patients alive at 30 days, 100 days, 6 months at one year, calculated by the Kaplan-Meier method (Figure 13). Patients are encouraged to discuss their diagnosis and expected survival with their primary physician.

In the Professional's Portal data is further detailed (Figure 14), with more filters: underlying diagnosis, age (by decade), transplant number (1-3+), donor source, gender, donor age (</> 30 years) and center (public or private) (Figure 15).

Overall survival and disease free survival are presented as Kaplan-Meier graphics with both the median follow up time and patient censoring clearly shown (Figure 16). When the number of patients in a specific dataset is less than 25, graphics are not generated and a table is shown with the results.

Causes of death are detailed in the Professional's Portal and can be filtered according to age group, type of transplant and within 100 days post-transplant or later (Figure 17).

Infections are the most important cause of death (Figure 18) and responsible for over half of the deaths within and after the 100-day time point in all donor sources.

One clear limitation of our data is the short overall follow-up time of 138 days, further detailed in each Kaplan-Meier. This data can be used to show the transplant-related mortality and survival at 30 and 100 days, but longer follow-up was needed to understand survival at 6 months and one year. Since the dataset is intended to have updates every 6-months, so we may shortly have a longer follow-up time and more reliable survival data.

Discussion

To the best of our knowledge this is the first portal were professionals, patients, public and transplant centers can look for the results of the HSCT performed in the country. It is not meant to duplicate efforts or compete with registries as the Worldwide Network for Blood and Marrow Transplantation (WBMT), CIBMTR, European Blood and Marrow Transplant (EBMT) or Brazilian Organ Transplantation Registry (Registro Brasileiro de Transplantes - RBT) of the Brazilian Organ Transplantation Association (Associação Brasileira de Transplante de Órgaos – ABTO) or Brazilian Bone Marrow Transplantation Registry (SBTMO). This website is unique and provide carefully reviewed and valuable data to primary physicians, patients, and transplant centers to understand transplant results and to plan improvements in patient care.

The Brazilian Transplantation Registry (RBT) of the Brazilian Organ Transplantation Society (ABTO) has been collecting data on transplant activity in the country since 1995, including HSCT.[5] Reporting to the ABTO has significantly increased in the past decade with the partnership with the Brazilian Bone Marrow Transplant Society (Sociedade Brasileira de Terapia Celular e Medula Óssea – SBTMO) and many centers now also include data on patient survival.[6]

Reporting consecutive patient data to the CIBMTR is compulsory in the United States to have their national Stem Cell Therapeutic Outcomes Database (SCTOD). Patients may consent for their data to be also used by the CIBMTR for research. Each HSCT centers may choose to participate reporting the minimal obligatory Transplant Essential Data (TED) only, or being a Comprehensive Report Form Center.[7] Centers sign in a contract with the CIBMTR and the forms are electronically filled in, all in the English language. There are 93 different forms as of June, 2021, that may be filled in according to the center track, underlying disease and type of transplant.[8]

Brazilian centers reporting to the CIBMTR can simply export their Data Back to Center files to our Map of BMT, avoiding any duplicate entries and assuring the integrity of their data, due to the automatic online data check available in their FormsNet3 website.

Half of the transplant centers reporting to the RBT-ABTO also report to the CIBMTR: in 2019, 1,073 transplants from 23 Brazilian centers were reported to the CIBMTR (Simione AJ, in press in this volume) and 3,805 transplants from 62 institutions were reported to the RBT.6 As of 2021, 32 transplant centers are affiliated to the CIBMTR and 74 to the RBT, so we expect to progressively increase the comprehensive report of our data.[9]

All transplant center leaders were invited to participate in our Scientific Council, that has already met couple of times do define the future directions of the portal. Since the platform launch on December 18, 2020, we will have now the first update and have data on 6-month and one year follow up.

Now, that we have the reporting system of the most complex and expensive transplants organized, we would like to scale the project up to include centers performing autologous and HSCT from related donors.

In conclusion, we strongly believe that this portal, the "Map of BMT" is a novel and important initiative that can be a model for other countries and for registries to improve transparency and access to HSCT demographics and results.

Acknowledgements

Anderson João Simioni won the IT and Informatics Best Abstracts with the paper Map of BMT in Brazil, Public Access Panel to Hematopoietic Stem Cell Transplant Data, that was an oral presentation on February 8 at the 2021 TCT Meeting of ASTCT and CIBMTR.

We would like to thank Pronon and the Ministry of Health for their support. We are would want to manifest our profound gratitude to the CIBMTR team that has helped us in every step and that received us for the in person training of our teachers, Flavia Costa, RN and Renata Loebel, RN: Dr. Mary Horowitz, Janet Brunner-Grady, the dearest Leigh Ann Laczkowski, and Dr. Marcelo Pasquini, who made us feel at home while in Milwaukee. We thank Monique Ammi who has helped all Brazilian data managers to work with the CIBMTR and has learned Portuguese to help us, far beyond her professional obligations. We are very thankful to Bruna Leticia Geraldo, who is an amazing person who travelled with us to Milwaukee and has continuously helped our team and all new data managers over the county.

We would like to acknowledge and profoundly show our appreciation for the team that worked with Ameo, training the data managers and building up the portal, for the brave data managers, most of them nurses that used their time off to learn and then had to go back to bedside at the time of the Covid pandemic, for the transplant center directors, that allowed us to develop this work and dedicate their time to the Scientific Committee, and for the transplant centers and ultimately the patients, who are the reason of our work and to whom we dedicate our lives.

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TABLE 1: Indicators selected for data collection

	Description
Patient data	Gender, Age at HSCT, Consent, Blood Type, Date Of Birth, Race/Color, educational level, Private/SUS, Date 1st Consultation, Performance Status, History of IOT, History of Fungal Infection, Cytomegalovirus Status
Disease Data	Diagnosis, Date of diagnosis, Pre-HSCT disease condition, Pre-HSCT DRM assessment, Classification of diseases
Donor Data	Gender, Age, Blood Type, Relationship (Donor/Patient), HLA Compatibility, Cytomegalovirus Status
Transplant Data	Type of transplant, Transplant Subtype, Current Transplant Number, History of Previous Transplants, HSCT Date, Conditioning Protocol, Conditioning Classification, Prophylaxis for Graft Versus Host Disease, Cell Source, Infused Cell Count
Engraftment	Neutrophil Engraftment, Platelet Engraftment, Quimerism Assessments
Graft Versus Host Disease	Acute GVHD, Chronic GVHD
Outcomes	Current Status, Date of last follow-up, Date of death, Cause of death, Relapse, Date of Relapse, Graft Loss, Date of Loss, New Neoplasm, Date of New Neoplasm, New Neoplasia Diagnosis, Veno Occlusive Disease (VOD), Performed a Second transplantation

TABLE 2: Data selected to be presented in the portal

Presentation	Description
General Data	Total transplanted patients Total number of transplants
Graphics	Transplants by Age Transplants by Gender Transplants by Educational level Transplants by Donor Type Transplants by Diagnostic Transplants by Cell Source Number of centers per region Number of Public/Private Centers by region
Results	Number of transplants per region Time between diagnosis and HSCT Time between the first consultation in the HSCT center and the transplant date Global Survival Disease-free survival Mortality

TABLE 3: Participating centers, directors and data managers

Transplant Center	City	State	Type	Director HSCT Center	Data Manager	Occupation
Associação Paulista para o Desenvolvimento da Medicina-Hospital São Paulo	São Paulo	SP	Public	Profa.Dra.Sandra de Oliveira Campos/Dr. Celso Arraes/Dr. Viniciu	Raquel P.P.Montanari Gouvea/ Isaias Olive	Administrator
Bio Sana's Serviços Médicos	São Paulo	SP	Private	Dr. Roberto Luiz da Silva/Dra. Maria Cristina M de Almeida Mace	Denise Borges R. Minari	Nurse
Casa de Saúde Santa Marcelina	São Paulo	SP	Public	Dra. Katya Parisio	Adriana Rodrigues Oliveira	Clerck
Centro de Hematologia e Hemoterapia da Universidade Estadual de Campinas (UNICAMP)	Campinas	SP	Public	Profa.Dra.Margareth Castro Ozelo/Afonso Celso Vigorito	Larissa Codogno Guzelotto	Nurse
Complexo Hospitalar de Niterói - Ímpar Servicos Hospitalares S/A	Niterói	RJ	Private	Dra. Maria Claudia Rodrigues Moreira	Andreia Ribeiro de Almeida	Nurse
Hospital Samaritano Higienópolis	São Paulo	SP	Private	Dra. Maria Fernanda Carvalho de Camargo	Paola Azenha Milani Soriano	Physician
Fundação Antonio Prudente - Hospital A.C. Camargo	São Paulo	SP	Private	Dr. Jayr Schmidt Filho	Bruna Tirapelli Gonçalves	Nurse
Fundação Doutor Amaral Carvalho	Jaú	SP	Public	Dr. Alcindo Storti	Bruna Fernanda S. Mathias	Assistant
Fundação Faculdade de Medicina de São José do Rio Preto	São José do Rio Preto	SP	Public	Dr. João Vitor Piccolo Feliciano	Laila Toniol Cardin	Biologist
Fundação Felício Rocho	Belo Horizonte	MG	Public	Dr. Guilherme Campos Muzzi	Thais Cristina da Silva	Nurse
Fundação Pio XII - Hospital de Amor	Barretos	SP	Public	Dr. George Navarro	Paula Moreira da Silva	Nurse
Grupo de Apoio ao Adolescente e à Criança com Câncer (GRAACC) - Unifesp	São Paulo	SP	Public	Dr. Victor G. Zecchin/ Dra Renata Fittipaldi	Cintia Monteiro Lustosa	Nurse
Hospital das Clínicas da Faculdade de Medicina da USP	São Paulo	SP	Public	Dr. Vanderson Geraldo Rocha/Dra. Lívia Mariano Compt	Bruna Del Guerra C. Moraes	Nutricionist
Hospital de Clínicas da Universidade Federal de Minas Gerais	Belo Horizonte	MG	Public	Dr. Gustavo Machado Teixera	Glaucia Helena Martinho	Nurse
Hospital de Clínicas de Porto Alegre	Porto Alegre	RS	Public	Dra. Liane Esteves Daudt	Raquel Schultz / Priscila de Oliveira	Student
Hospital Israelita Albert Einstein	São Paulo	SP	Private	Dr. Nelson Hamerschlak	Mariana Clapis B. Velloso	Nurse
Hospital Leforte Sociedade Assistencial Bandeirantes	São Paulo	SP	Private	Dr. Ricardo Tscuotto/Dr. Rodrigo Santucci	Lucilene Jeronima da S. Souza	Nurse
Hospital Moinhos de Vento	Porto Alegre	RS	Private	Dra. Claudia Caceres Astigarraga	Valesca Scalei Cezar	Nurse
Hospital Nossa Senhora das Graças	Curitiba	PR	Private	Dra. Elenaide C. Nunes	Cristiano de Oliveira Ribeiro	Nurse
Hospital Pequeno Príncipe-Associação Hospitalar de Proteção à Infância	Curitiba	PR	Public	Dra. Cilmara Cristina Kuwahara	Priscila Panek	Nurse
Hospital Quinta D´Or	Rio de Janeiro	RJ	Private	Dr. Renato Castro	Beatriz Carvalho Espindola	Nurse
Hospital Universitario Clementino Fraga Filho (Universidade Federal do Rio de Janeiro)	Rio de Janeiro	RJ	Public	Dr. Rony Schaffel/Dr. Marcio Nucci	Valéria Vianna Santos	Biologist
Hospital Universitário Walter Cantídeo - Universidade Federal do Ceara	Fortaleza	CE	Public	Dra. Josenília Maria Alves Gomes/Dr. Fernando Barroso Duarte	Thaisa Marjore Viana	Pharmacist
Instituto de Tratamento do Cancer Infantil (ITACI)/ ICr-HC da Faculdade de Medicina da USP	São Paulo	SP	Public	Dra. Juliana Fernandes Folloni	Gislene Santana Tusani	Nurse
Instituto Nacional do Câncer José Alencar Gomes da Silva - CEMO (INCA)	Rio de Janeiro	RJ	Public	Dr. Décio Lerner/Dr. Renato Castro	Aline Sperandio/Jéssica Di Chiara Salgado	Assistant/ Nurse
Núcleo Oncoclínicas	Belo Horizonte	MG	Private	Dr. Wellington Azevedo	Raquel Di Mambro Castro	Nurse
Real Benemérita Associação Portuguesa de Beneficência (BP-Mirante)	São Paulo	SP	Private	Dr. José Ulysses Amigo Filho	Vinícius Vitor Barbosa	Student
Real TMO Clínica Médica (Hospital Português de Beneficência- Pernambuco)	Recife	PE	Private	Dr. Rodolfo Froes Calixto	Gizeli Braga M. dos Santos	Secretary
Santa Casa de Misericórdia de Belo Horizonte	Belo Horizonte	MG	Public	Dr. Saulo Levindo Coelho/Dr. Wellington Morais de Azevedo	Danielle Resende de Pádua	Nurse
Sociedade Beneficente de Senhoras Hospital Sírio Libanês	São Paulo	SP	Private	Dra.Yana Augusta Sarkis Novis	Simone Ojima Ferreira	Nurse
Terapia Celular de Natal (Hospital Natal Center)	Natal	RN	Private	Dr. Rodolfo Daniel de A. Soares	Nayane M.F. Alves	Nurse

FIGURE 1: Data processing for the Portal "Map of BMT"

FIGURE 2: The Map of Bone Marrow Transplantation Portal

FIGURE 3: Transplant data presented in the portal

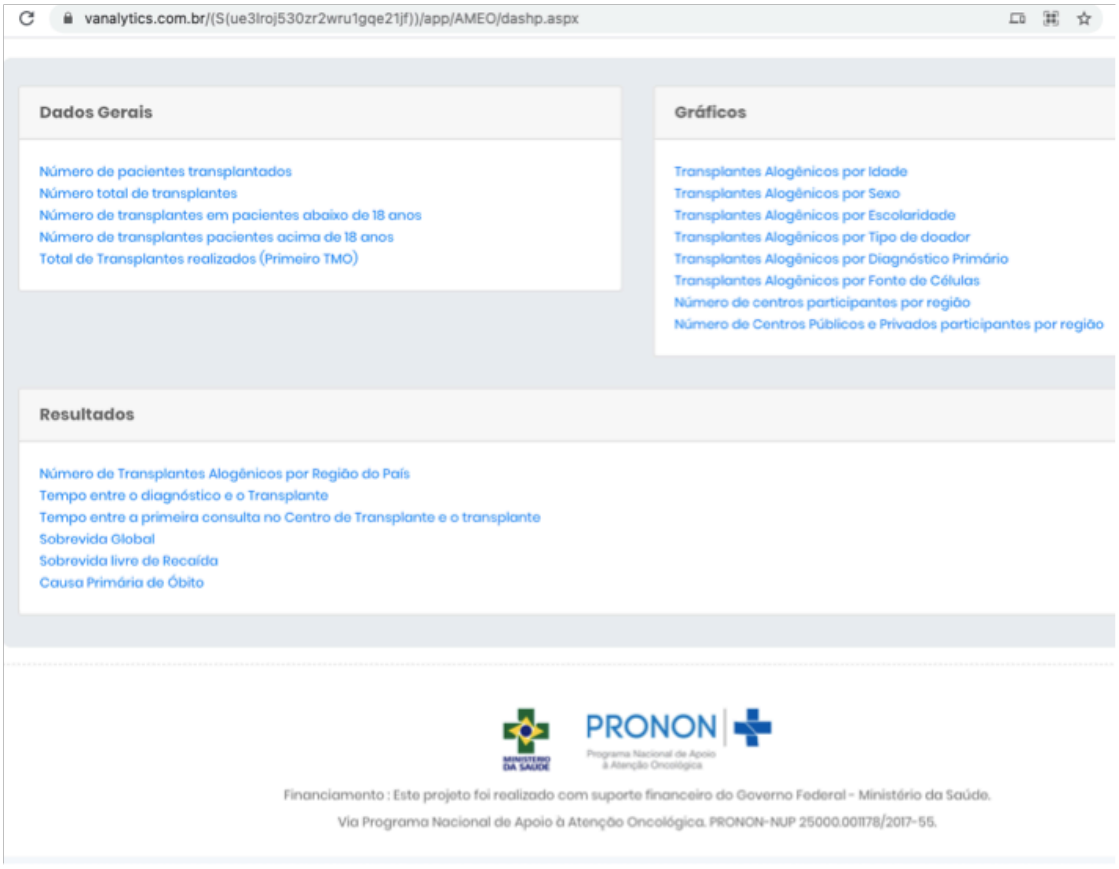


FIGURE 4: Age distribution of allogeneic transplants performed in 30 Brazilian centers between August 2019 and August 2020

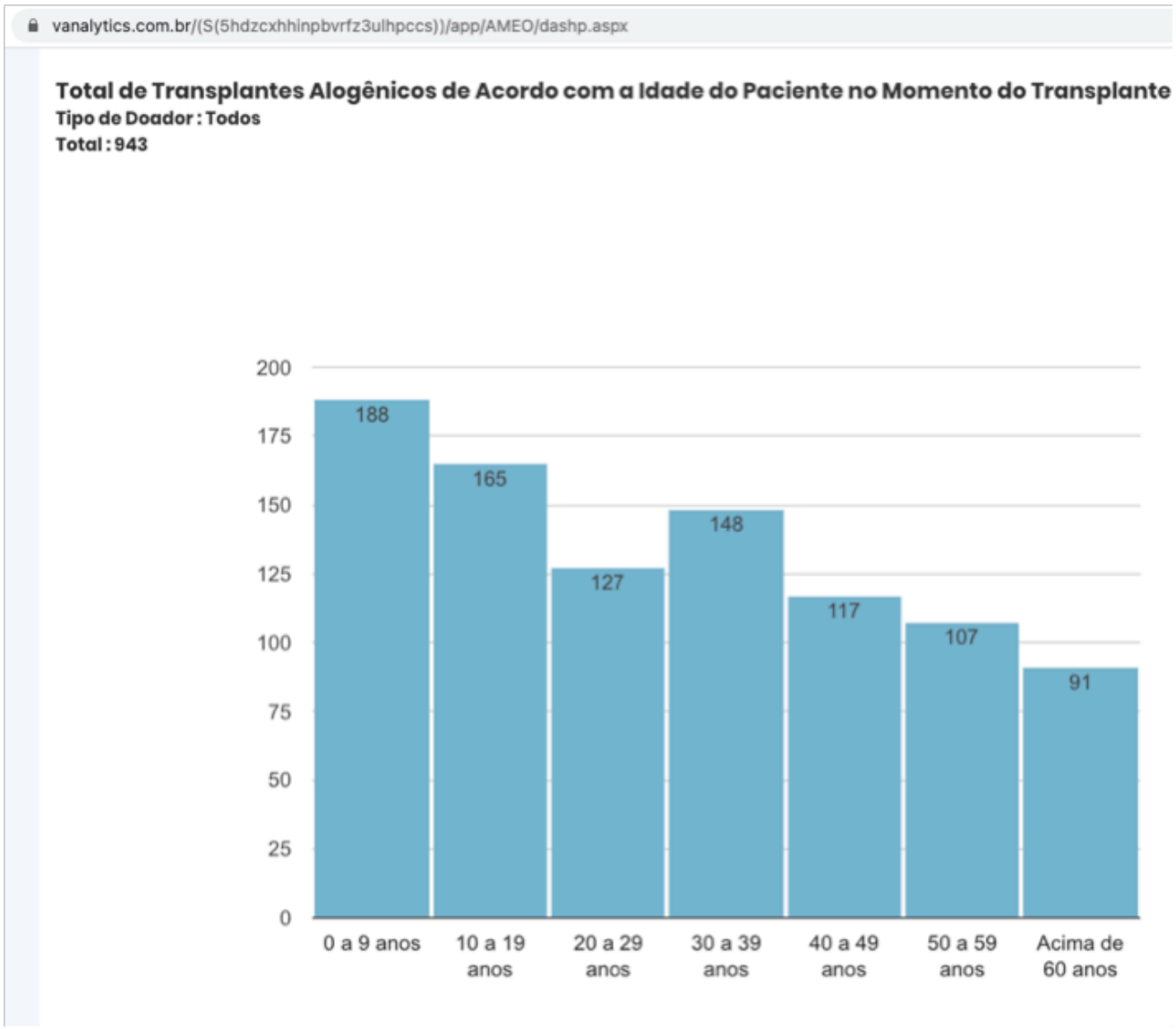


FIGURE 5: Education among 282 patients older than 18 years of age undergoing allogeneic HSCT in 30 Brazilian centers between August 2019 and August 2020

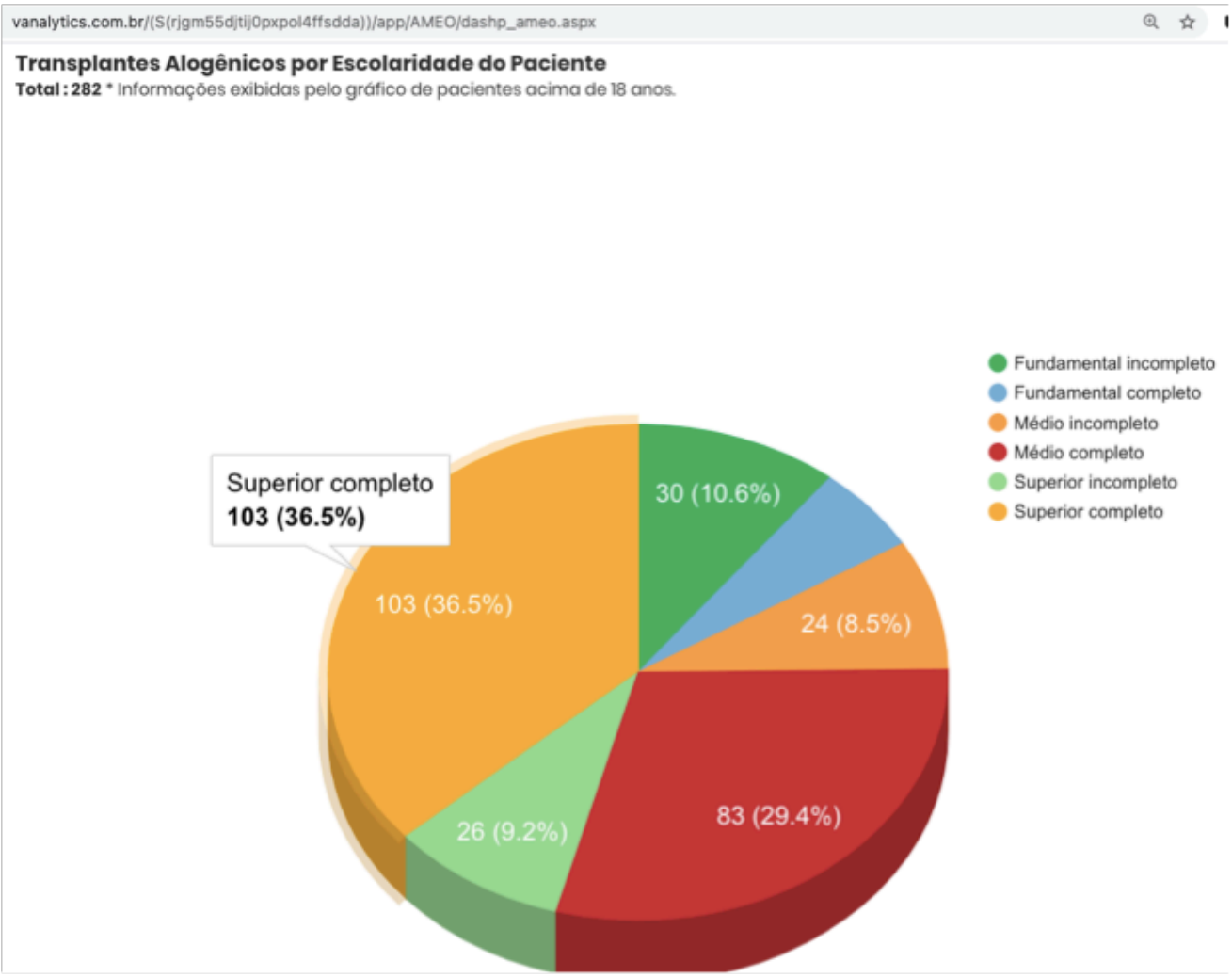


FIGURE 6: Underlying diagnoses in children undergoing allogeneic HSCT in 30 Brazilian centers between August 2019 and August 2020

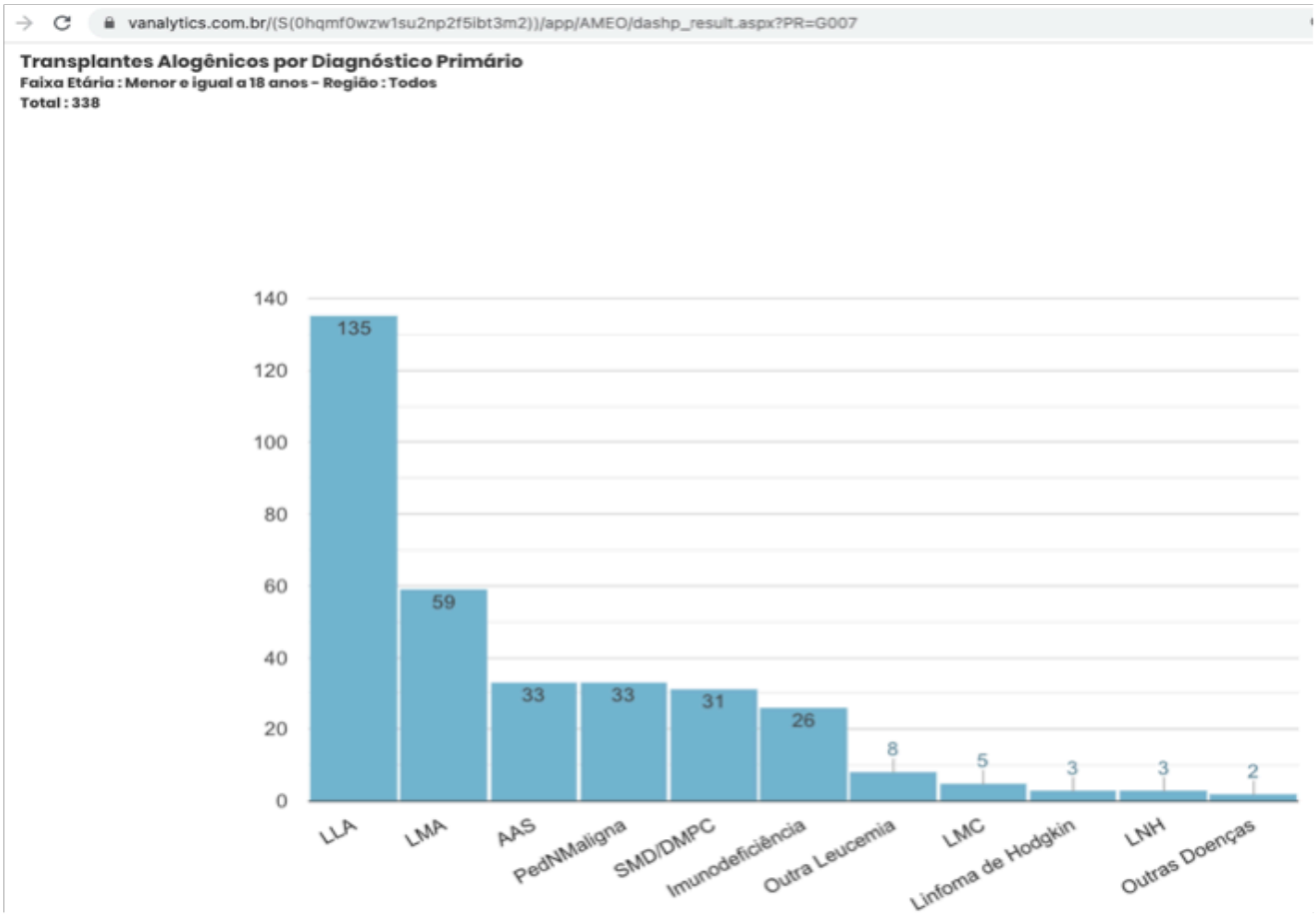


FIGURE 7: Underlying diagnoses in adults undergoing allogeneic HSCT in 30 Brazilian centers between August 2019 and August 2020

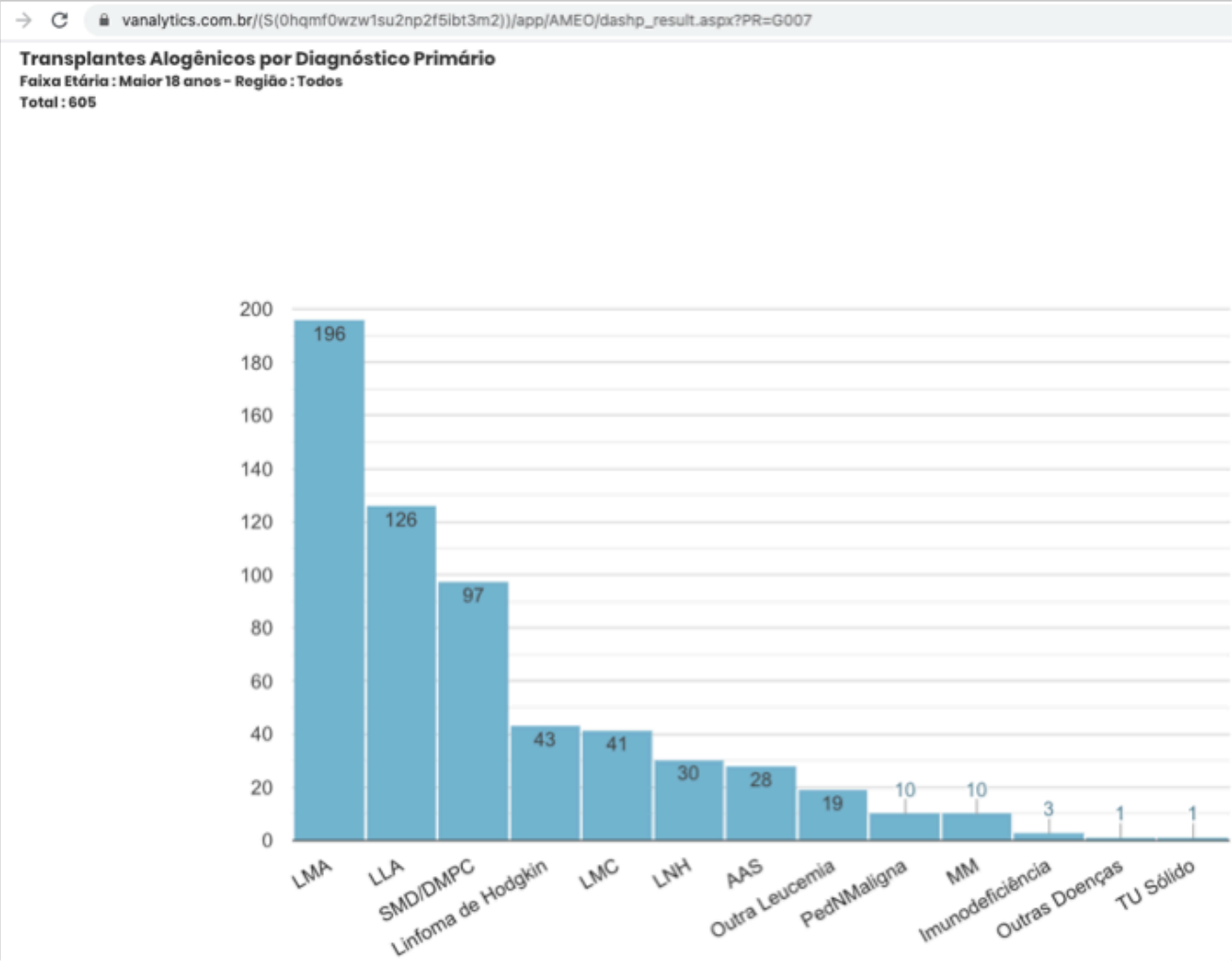


FIGURE 8: Number of transplants from HLA-identical siblings, haploidentical and unrelated donors

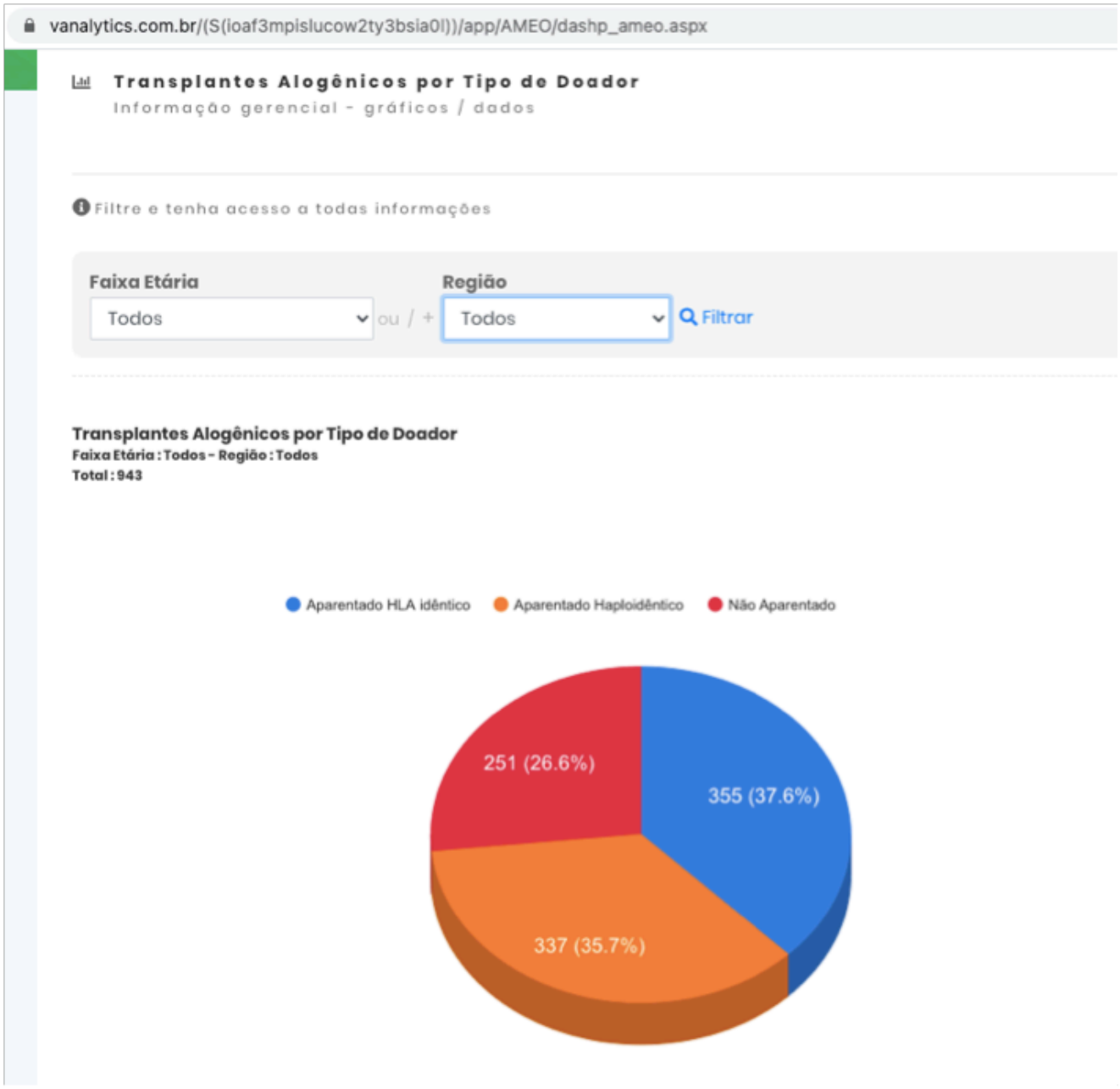


FIGURE 9: Source of stem cells for allogeneic transplants in 30 Brazilian centers between August 2019 and August 2020

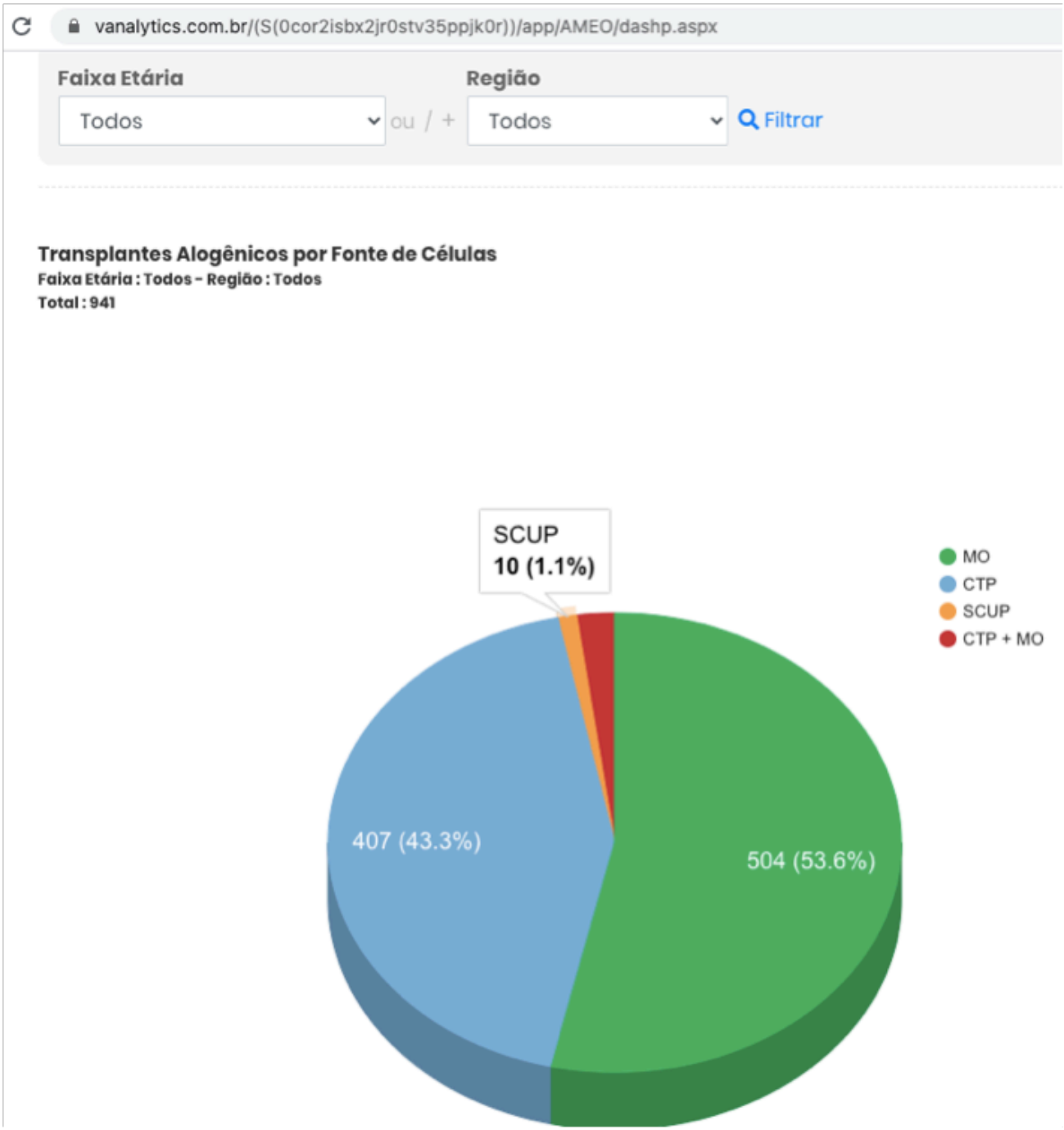


FIGURE 10: Glossary in the Patient's Portal

FIGURE 11: Graphics and Tables in the Patient's Portal

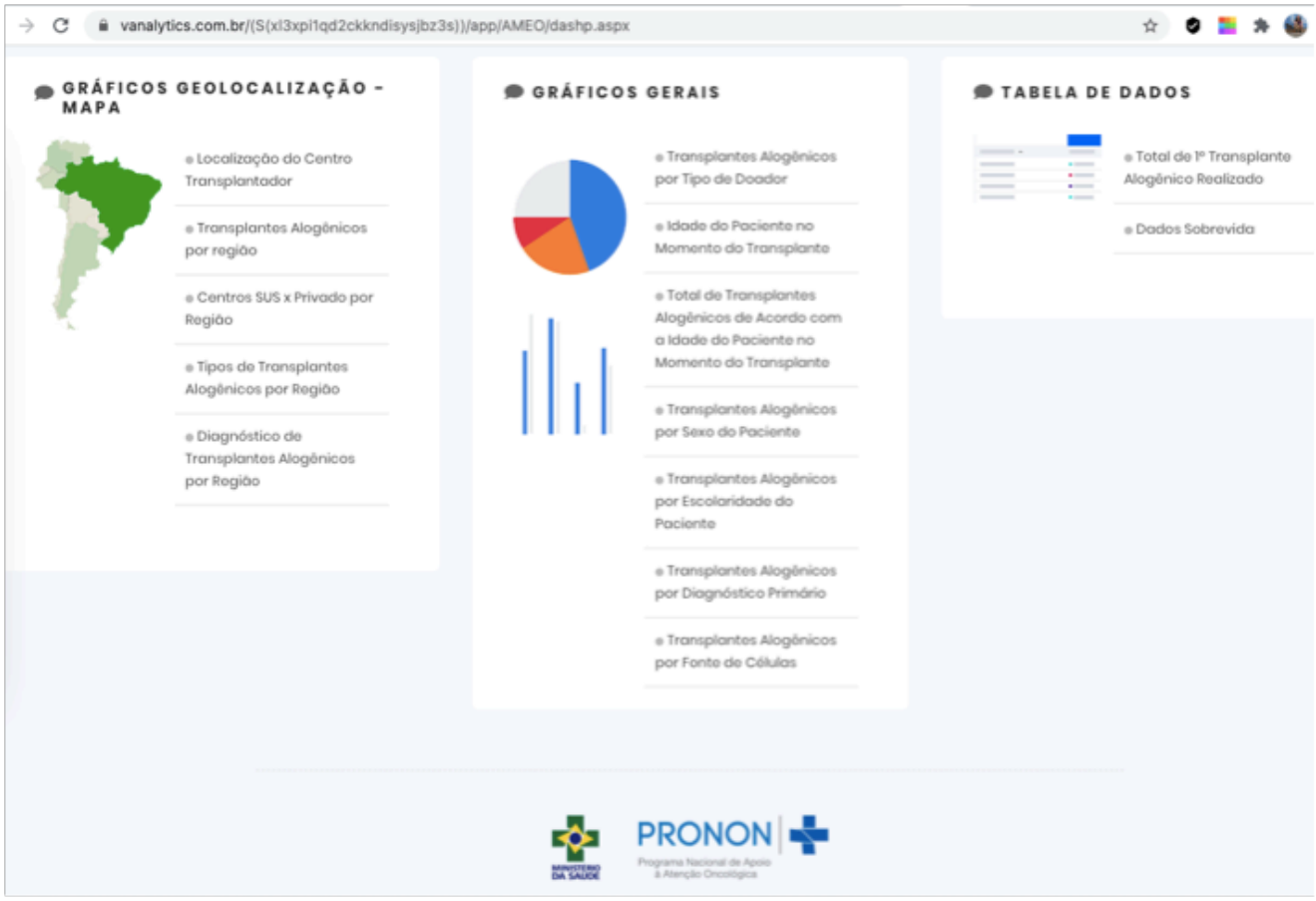


FIGURE 12: Filters that can be used by patients to build the survival table: diagnosis, age group, donor source

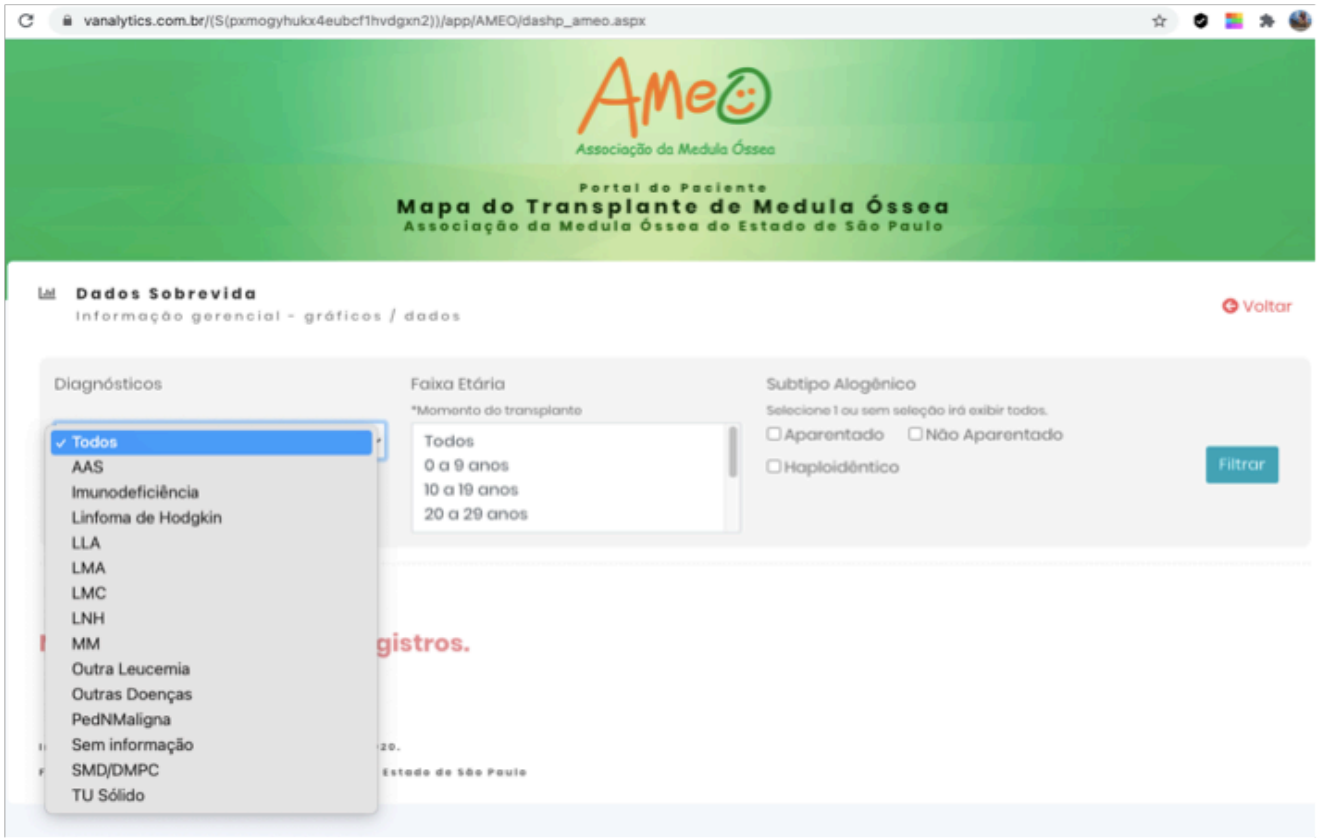


FIGURE 13: Survival of 817 patients at 30 days, 100 days, 6 months and one year after the first allogeneic transplant performed in 30 Brazilian centers between August 2019 and August 2020.

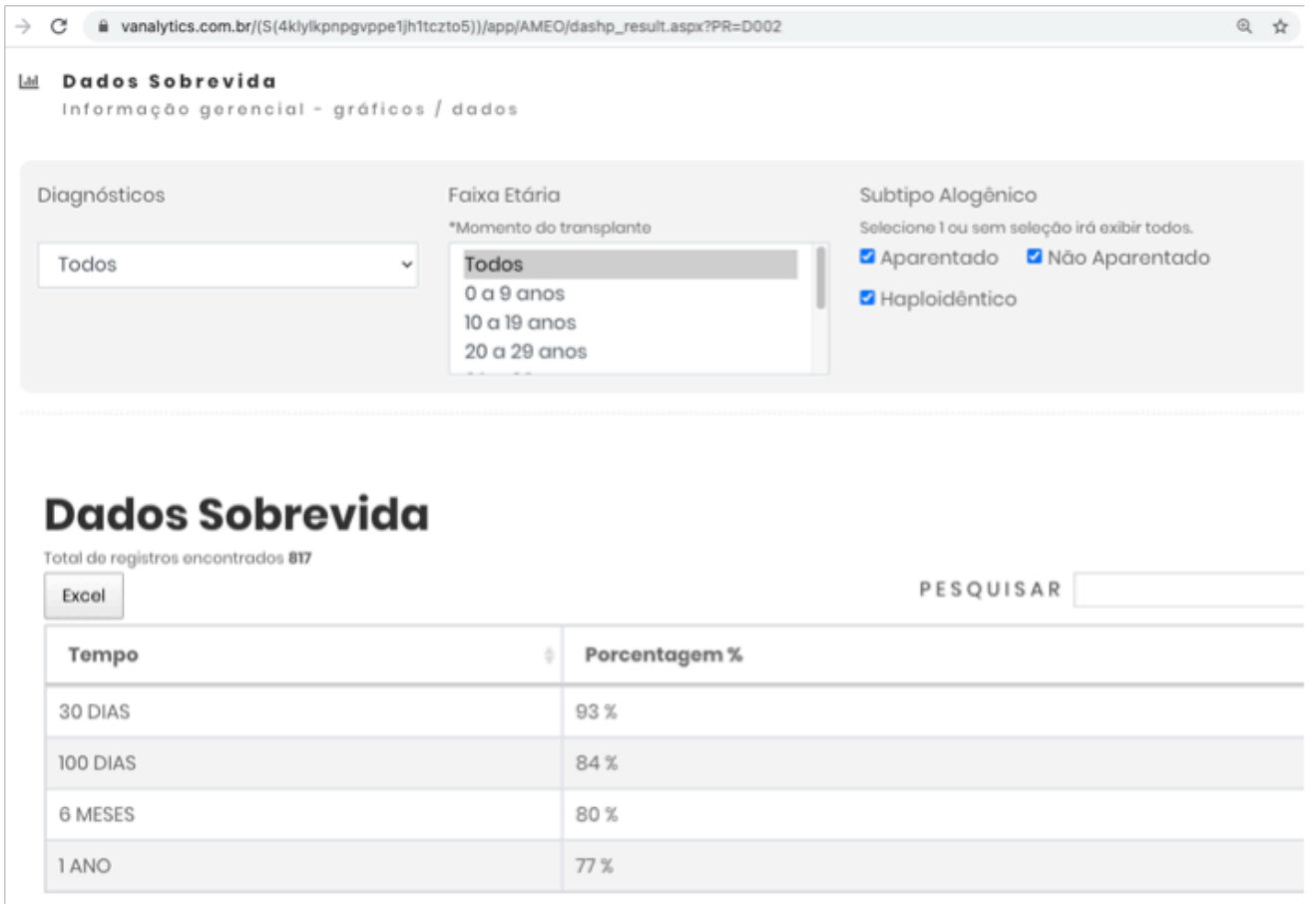


FIGURE 14: Professional's Portal

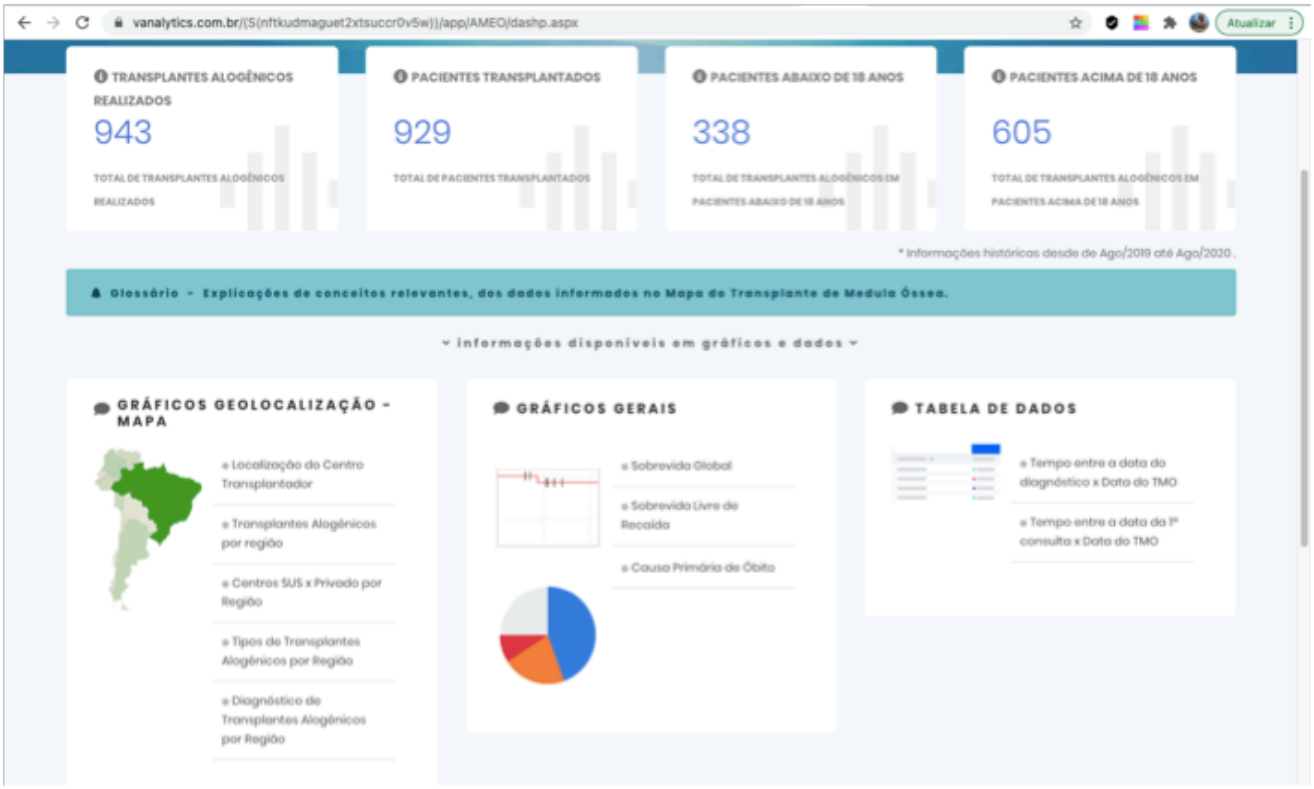


FIGURE 15: Filters that can be used in the Professional's Portal to generate Overall and Disease Free Survival Kaplan-Meier graphics

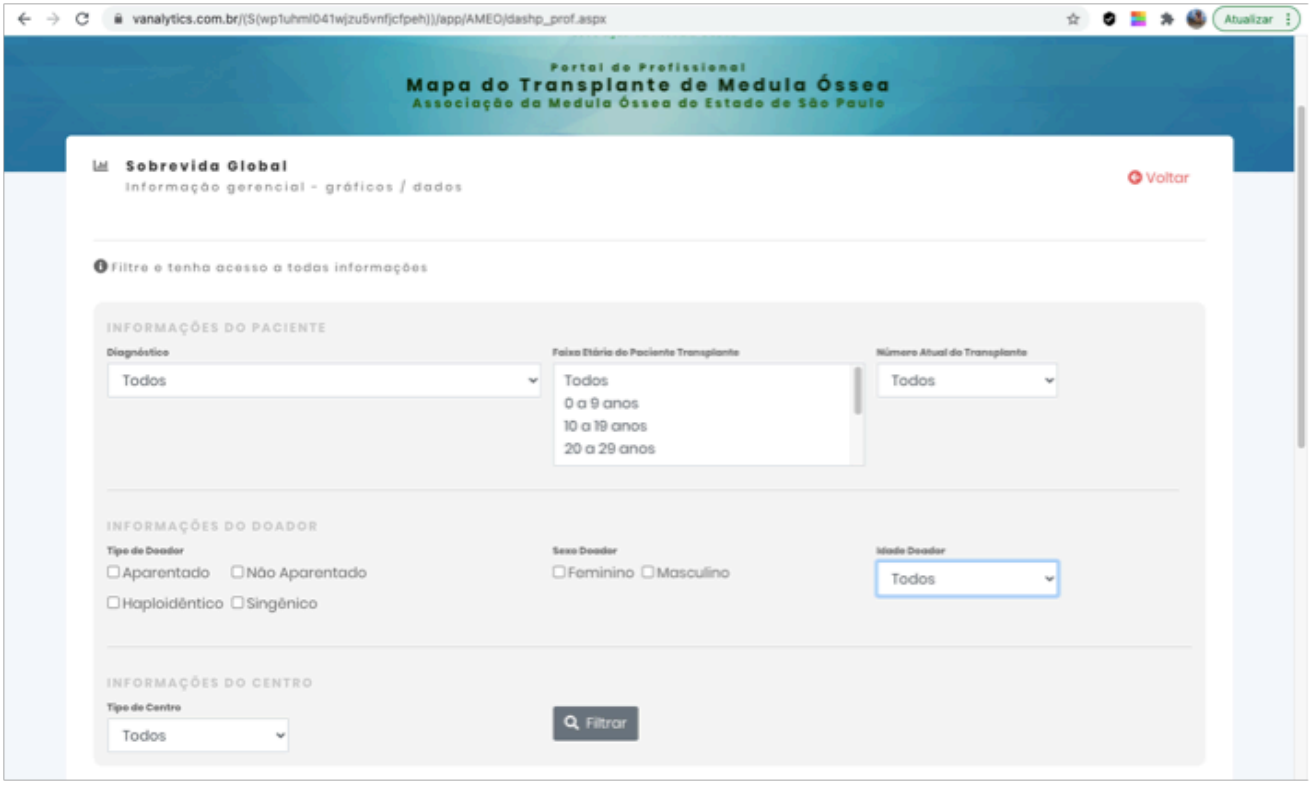


FIGURE 16: Overall survival of 789 allogeneic transplants performed in 30 Brazilian institutions between August 2019 and August 2020

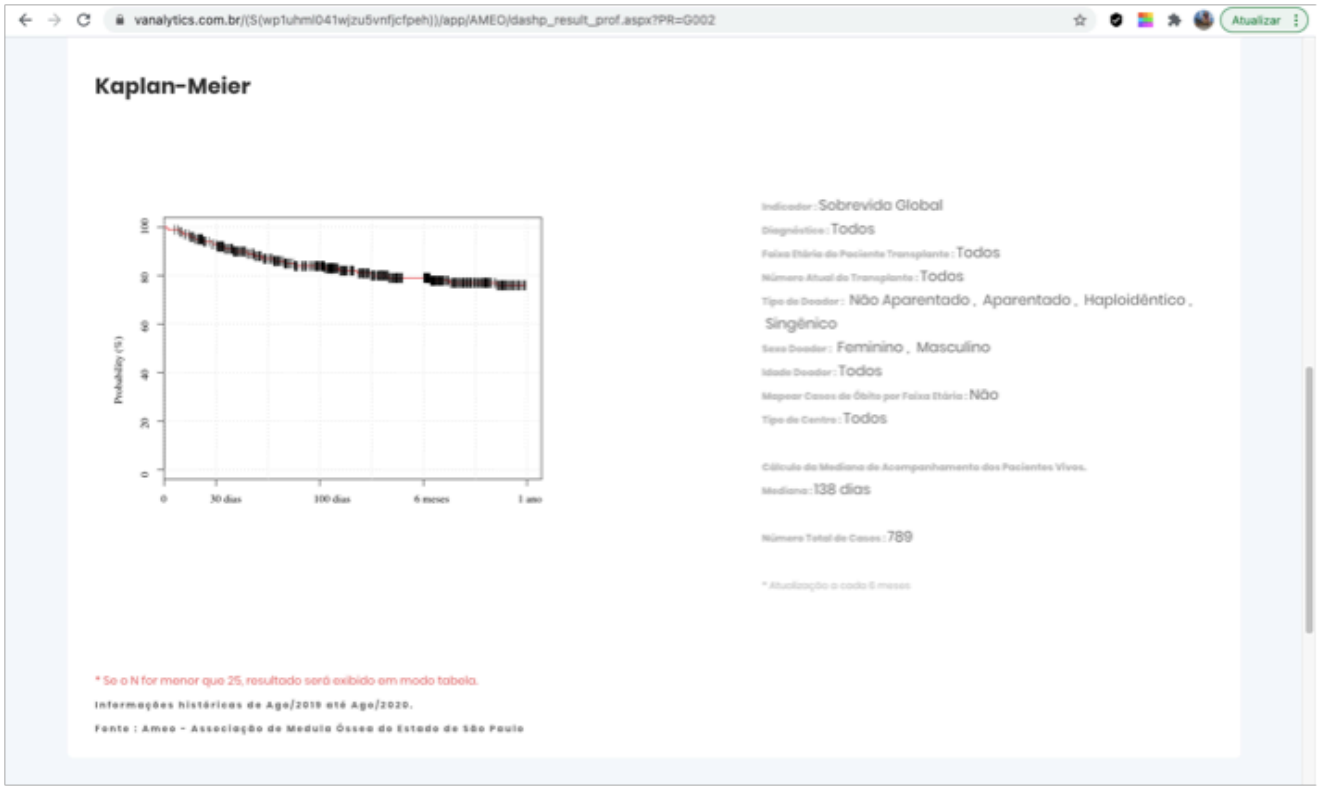


FIGURE 17: Filters that can be used to search causes of death among patients undergoing allogeneic transplants

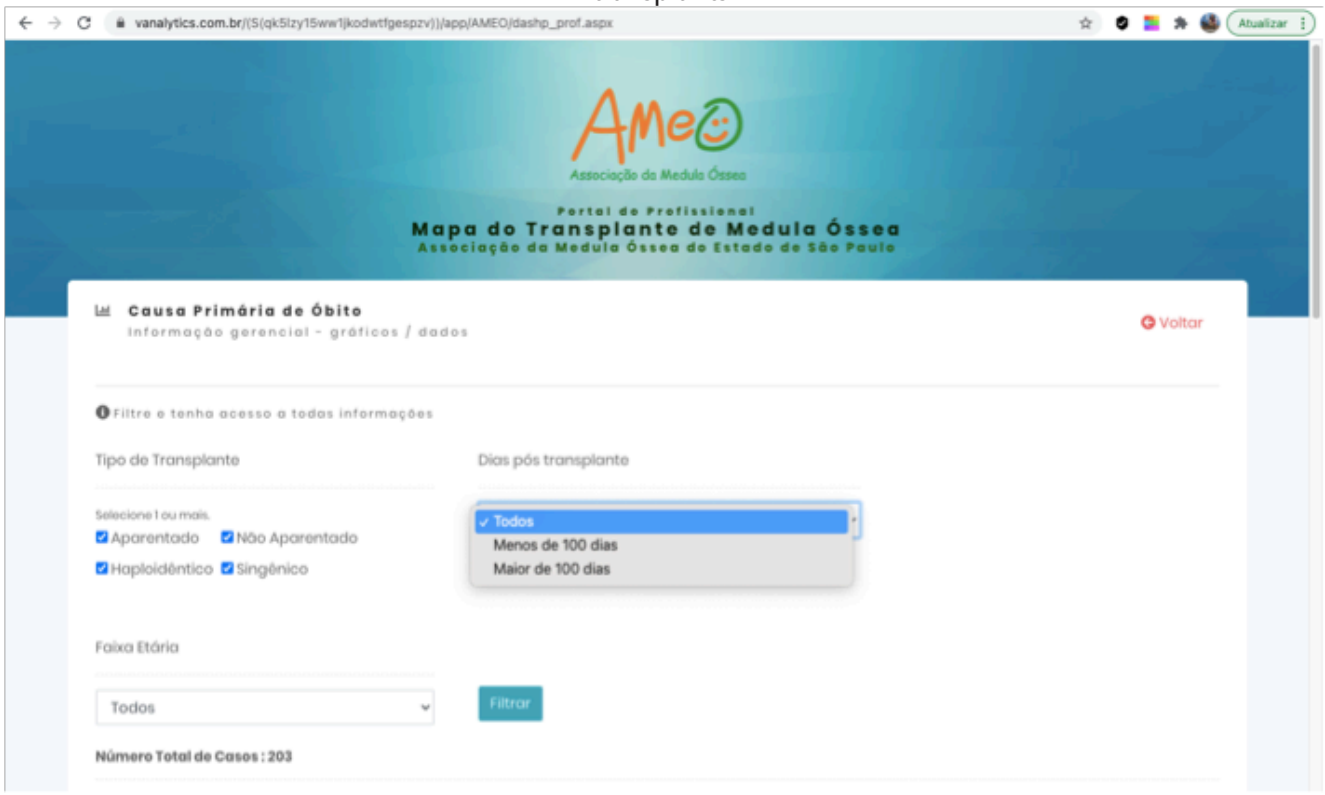
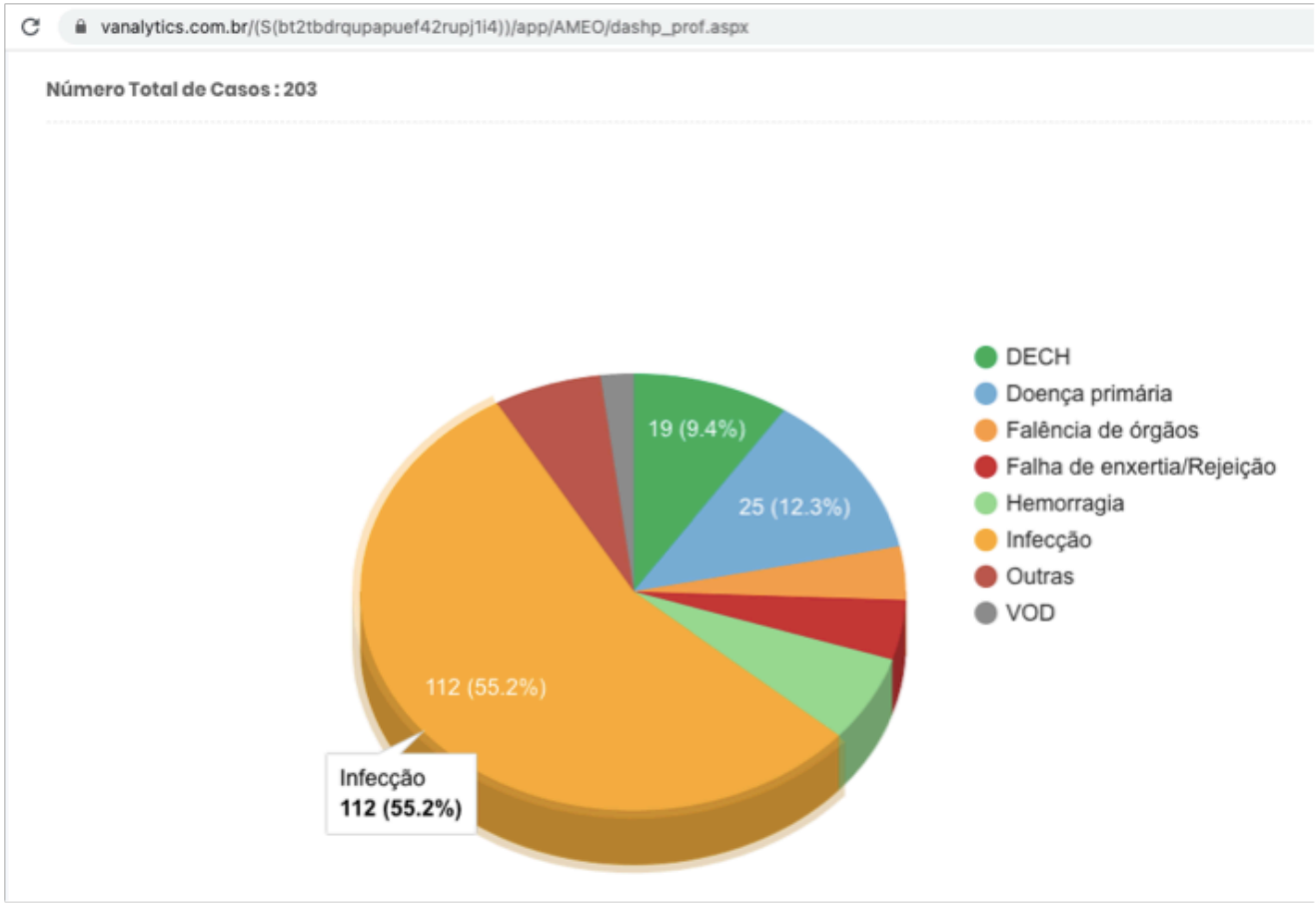


FIGURE 18: Causes of death after all allogeneic transplants



DOI: 10.46765/2675-374X.2021v2n2p102

SOME CLINICAL LESSONS FROM ONE BLOOD AND MARROW TRANSPLANTATION UNIT IN MEDELLIN, COLOMBIA

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Running title: BLOOD MARROW TRANSPLANTATION UNIT MEDELLIN

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ABSTRACT

After more than 60 years of the first successful bone marrow transplant (BMT) by D.E. Thomas for the treatment of hematological malignant diseases and more than 46 years since the first bone marrow transplant by Alberto Restrepo-Mesa in Medellin-Colombia for the treatment of a female triplet patient with paroxysmal nocturnal hemoglobinuria and aplastic anemia, in Colombia only around 750 bone marrow transplants are performed annually. With the experience accumulated during these years by each one of us, the León XIII Clinic of the Universidad de Antioquia began the hematopoietic stem cell transplantation (HSCT) program for adults in 2014. In this review, we report some clinical lessons drawn from the different phases of the HSCT in 109 adult patients with hematological malignancies. The progression-free survival (PFS) and the five-year overall survival (OS) were for autologous stem cell transplantation (ASCT) (87% and 70%), allogeneic stem cell transplantation (Allo SCT) (50% and 40%) and haploidentical stem cell transplantation (Haplo SCT) (25% and 18%) respectively.

Keywords: Bone Marrow Transplantation. Hematopoietic Stem Cell Transplantation. Hematologic Neoplasms.

INTRODUCTION

The HSCT is a treatment of some hematological malignancies with curative intention widely recognized since more of half century[1,2]. Medellin, with its School of Medicine Universidad de Antioquia, is a Colombian city pioneer in the solid organ transplantation and HSCT from the early 70´s[3].

There are available many protocols for HCST with methodological differences that well sedimented and analyzed can permit its adaptation and implementation in areas with limited technological and economical resources.

With the accumulated experience during these years, the Clínica León XIII de la Universidad de Antioquia begun in 2014 its adult HSCT program. In this report, we present some aspects such as the demographic of patients, CD34 mobilization and collection topics, preservation, time to engraftment, infectious, transfusional, hydroelectrolytical and immunological complications and their PFS and OS during six years of follow-up.

PATIENTS AND METHODS

Between May 2014 and March 2020, 109 adult patients, 66 males (61%) and 43 (39%) females, median age 43 years-old (range 15 and 74 years-old), figure 1, underwent a HSCT for treating a high-risk or relapsing hematological disease at the Clinical León XIII in Medellin, Colombia. We performed 71 (65.1%) ASCT that included 43 patients with multiple myelo-

ma (60.6%), 26 patients with lymphoma (36.6%) and two patients with amyloidosis (2.8%). Twenty patients (18.4%) received an Allo SCT: 7 patients (35%) with acute myeloid leukemia (AML) and 13 patients (65%) with acute lymphoblastic leukemia (ALL). Haplo SCT were performed in 18 patients (16.5%), including 8 AML patients (44.4%) and 10 ALL patients (55.6%). Table 1.

Conditioning regimens and prophylaxis

ASCT patients with myeloma multiple were conditioning with a single dose of melphalan (140 – 200 mg /m2). Lymphoma (HL and NHL) patients were conditioning with modified BeEAM: bendamustine 300 mg/m2, etoposide 200 mg/m2, cytarabine 200 mg/m2 and melphalan 140 mg/m2). Reduced-intensity conditioning (RIC) for Allo SCT patients with ALL was fludarabine 150 m/m2 and melphalan 200 mg/m2. RIC for AML patients was fludarabine 150 mg/m2 and Busulfan 12.8 mg/kg iv. Haplo SCT patients received the same RIC than the Allo SCT patients, adding cyclophosphamide on day +3 and +4.

Graft vs Host Disease (GvHD) prophylaxis was cyclosporine and mycophenolate. The transplantation protocols were approved by El Comité de Trasplantes de la Clínica León XIII in 2014.

CD34+ mobilization

Autologous and allogeneic stem cells were mobilized in an outpatient basis with single dose of pegfilgrastim 6 mg SQ five days before of first of the two 13.000 ml leukapheresis scheduled. Half dose of Plerixafor, 10 mg SQ the night before to each apheresis section, was used to improve the yield of CD34+ in patients with myeloma or lymphoma at high risk of poor mobilization, especially those with history of several prior lines of therapy and low cellularity bone marrow biopsy. None ASCT patient received chemotherapy for mobilization.

CD34+ were determined in the apheresis product by flow cytometry. Autologous and allogeneic cells in bags were stored at 4°C up to six days, allowing, in the meantime, to give the conditioning regimen[4]. The reinfusion of the refrigerated stem cells (0 day) was carry out up to six days later and at least 24 hours after last dose of melphalan or VP16.

Prophylaxis

After last peripheral blood stem cells harvest, patients were hyper hydrated with fluids and received diuretics to maintain a stable hydric-electrolyte balance over the administration of appropriate conditioning regimen. Patients were isolated in rooms with HEPA filters. Antivirals and antifungal therapies were administered post-SCT infusion and continued until immune recovery. Weekly monitoring CMV load and aspergillar antigenemia permited us modify prophylaxis. No routine prophylactic antibiotics were administeed. If fever developed, blood cultures were done and empiric antibiotics were started according to clinical and local microbiological guides. All patients received a single 6 mg dose pegfilgrastim on day +5. Dates of neutrophils and platelet sustained engraftment were recorded. Nutritional support was introduced when patients had grade III-IV mucositis and until its resolution. Blood products transfused were filtered and never irradiated. (GvHD) prophylaxis and treatment in allogeneic and haploidentical patients included one or several combinations of immunosupressors agents.

Statistics

The main endpoint of the study was PFS from time of HSCT to last follow-up, relapse or death unless otherwise specified. Clinical and biological characteristics of ASCT, Allo SCT and Haplo SCT patients were compared by the Chi square test. Survival analysis was performed by the Kaplan–Meier method. The adjusted associations between baseline characteristics and treatment modality and OS was estimated by Cox regression. Statistical significance was defined as p value < 0.05. The analysis was performed with SPSS v.22.0. (SPSS lic, Chicago, IL, USA).

RESULTS

Stem Cell Mobilization

Autologous or allogeneic stem cell infusion will rescue patients who have received any conditioning regimen above indicated. Performing this procedure without stem cells can result in prolonged pancytopenia and the most adults would not survive to the prolonged neutropenia period. In our unit, stem cells were always extracted by two apheresis from peripheral blood mobilized with single dose pegfilgrastim in an outpatient's basis in ASCT patients or in allogeneic donors. Plerixafor, 10 mg SC before each apheresis section was given to 25 ASCT patients (35%) with myeloma or lymphoma and high risk of poor mobilization due to history of several lines of therapy and with low cellularity bone marrow biopsy[5]. As shown in figure 1, the allogeneic stem cell donors yielded a median of 7.8 x 10^6 95% IC (7.1 – 9.6) CD34+ / kg after the scheduled leukapheresis; enough to rescue patients with allogeneic transplantation.

In autologous transplant group mobilized with pegfilgrastim only, it was yielded a median of 4.1 x 10^6 95% CI (3.75 – 5.03) CD34+ / kg. In plerixafor + pegfilgrastim group it was 5.1 x 10^6 95 IC (4.3 – 7.3) CD34 +/ kg (p=0.44). Figure 2.

In both transplantation settings, the CD34+ levels achieved were good enough to obtain a long-term robust engraftment.

Engraftment

Myeloid engraftment was successful in autologous and allogeneic transplants on median day + 12.45, and day + 13.5, 95% CI (-0.37 – 3.25) (p=0.015) respectively. Platelet transfusion independency was reached on day + 16.65 and + 21.34, 95% CI (-3.94 – 146.36) respectively (p= 0.004) being earlier in autologous transplantation as expected. No graft failure complicated this period. Table 2.

Infections during neutropenia before engraftment

Fever was presented in about 95% of autologous patients and in almost all allogeneic patients and usually on the first week when nadir of the neutropenia reached. In addition to clinical continuous monitoring of patients, daily C-reactive protein (CRP) changes were recorded and served as an early warning of infection.

It is appropriate to point out that CPR did not informed about a specific microbiological isolation type (p=ns), but it was a tendency to be higher in gram-negative sepsis and frequently associated to abdominal pain (mucositis), rigors and cardiovascular instability[6]. Blood cultures were positive in 27% of fever episodes. Piperacillin sodium / tazobactam sodium, cefepime hydrochloride and meropenem were the antibiotics most common used at begin in accord with clinical status of each patient. If oro-esophageal mucositis appeared vancomycin was added to the regimen. De-escalation of antibiotics was done according to sensibility. Invasive fungal infections (IFI) were detected in 2 (10.5%) allogeneic and 4 (22.2%) haploidentical patients suspected with thorax CT and galactomannan and always treated with voriconazole.

Transfusions

As we noted above, both RBC and platelet bags were not irradiated but filtered using BioR 01 Plus BS PF filter and BioP Plus BBSS PF respectively and allowing < 2 x 10(5) WBC / bag. We did not detect any case of graft failure neither transfusional acute GvHD neither febrile reactions or bacteremia.

RBC transfusions were on average 7.7 units / patient in haploidentical transplants, 1.9 units / patient in allogeneic transplants and 1.8 units / patient in autologous transplants. In other hand, platelet by apheresis transfusional support were on average 22.1 units / patient in haploidentical patients, 12 units / patient in allogeneic transplants and 4.1 units / patient in autologous patients. So, this is confirming the grade of hematological toxicity of each one type of transplant.

Mortality at 30 and 100 days

Mortality in the first 30 days was 5.8% and as shown in table 4, 32 (29.4%) patients died from transplanted related toxicity on the first 100 days. From these, 12 (71%) were Haplo SCT patients, 11 (61%) Allo SCT patients and 9 (13%) ASCT patients. Acute and chronic GvHD (8.1%) and relapse disease (28.1%) were the complications most frequently related with mortality. In each case there was a mixture with infectious, hemorrhagic and hydro electrolyte complications.

Survival after relapse

For all types de HSCT, without discrimination, median PFS and OS rates were 70% and 50% at 60 months respectively. Discriminating the median PFS and OS rate at 60 months according to the type HSCT, for ASCT were 90% and 70%, for Allo SCT was 50% and 40% and Haplo SCT 25% and 18% respectively. Figures 3, 4.

Survival after relapse

Twenty-four (22%) patients of all categories relapsed. Eighteen (75%) of them died at median of 12 months. Only six (25%) relapsed ASCT patients are alive at 6 years.

DISCUSSION

HSCT is a treatment for some hematological malignancies with curative intention, widely recognized since more of half century[1,2]. Medellin, with its School of Medicine of La Universidad de Antioquia, is a Colombian city pioneer in the solid organ transplantation and HSCT from the early 70´s[3].

In this retrospective review we presented the clinical lessons learned from day-to-day at our Hematopoietic Transplants Unit. It shows the practical results of our protocols in order to facilitate and stimulate other colleagues working in countries with restricted health budget for developing hematopoietic transplantation units without deteriorating the quality of the hematological service provided.

The mobilization of autologous peripheral stem cells with pegfilgrastim (PEGylated GSCF) +/- plerixafor in an outpatient basis without chemotherapy was equally successful and more cost-effective for CD34 cells mobilization as it had been reported with other options widely used in this setting[7,8]. The collection time of apheresis began on the fifth day when the highest number of leukocytes was observed. These results confirm the importance of studying the bone marrow biopsies of some hyper treated patients before their autologous transplant in order to asses the minimal residual disease in myeloma patients and hematopoietic cellularity for planning plerixafor in low doses in advance and saving time and costs in the procedures[9-12]. Pegfilgrastim-induced mobilization was used too permitting the collecting of an optimal number of CD34 cells in allogeneic healthy donors[10,11]. There were not related complications but clinical data on HSCT will need to be studied and verified.

One or two apheresis bags harvested as described above were refrigerated at 4°C, up one week permitting conditioning regimen administration for autologous transplantation [(4)]. This practice is a standard in the Unit since 1992 as published. Now other HSCT Units in Latin-American report the same results. In this way, potential savings in complex facilities of cryopreservation could permit to many other Centers in the geographical area offer this treatment for benign and malignant hematological diseases[12-15].

As proof of quality of the mobilization, harvesting and refrigeration, the CD34 counts were enough to engraftment quickly and restoring normal hematopoiesis as has been reported with others methods in the world[16].

During the first month post transplantation or the neutropenic phase, the support was with antimicrobials, antifungals and antivirals as were needed and as it makes everywhere. The medullary failure post conditioning with high doses chemotherapy was supported with no irradiated blood products but both red blood and platelet but filtered using BioR 01 Plus BS PF filter and BioP Plus BBSS PF respectively and allowing < 2 x 10(5) WBC / bag. In any case we do not detected graft failure neither hyper acute GvHD neither febrile reactions or bacteremia as published by others[17-19]. Our experience leads us to believe that with modern leukoreduction techniques in use now, the irradiation of blood products may not be as necessary as it was once. To confirm this hypothesis, further studies are needed[20,21]. Mortality in this period of time was acceptably low, 5.8%.

TRM at 100 days was very similar to reported by others, 13% for ASCT, 61% in Allo SCT and 71% in Haplo SCT. Toxicity was in direct relation with HLA disparity as expected. At 5 years, OS and PFS was in autologous 87% and 70%, allogeneic 50% and 39%, haploidentical 25% and 18% respectively. Final data show acceptable numbers of PFS and OS and are very similar to reported by others anywhere and it expects for adding new era drugs as antivirals, immunosuppressors combinations and biologicals for enhancing results[22-26].

In summary, this simple but systematic and comprehensive approach can permit to many hematologic services in under developed areas for offering more quantity and quality of live to patients suffering hematological malignancies.

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TABLE 1 - Demographic data of 109 patients

	ASCT	Allo SCT	Haplo SCT	Total
GENDER				
Male	42 (65%)	13 (20%)	10 (15%)	65 (100%)
Female	28 (64%)	7 (16%)	9 (20%)	44 (100%)
Total	70 (64%)	19 (18%)	19 (18%)	109 (100%)
AGE (median 48.5 yo)				
15-29	6 (27%)	4 (18%)	12 (55%)	22 (100%)
30-49	25 (57%)	13 (29%)	6 (14%)	44 (100%)
50-69	35 (90%)	3 (8%)	1 (2%)	39 (100%)
>70	4 (100%)	0 (0%)	0 (0%)	4 (100%)
Total	70 (64%)	20 (18%)	19 (18%)	109 (100%)
DIAGNOSIS				
Myeloma	43 (100%)	0 (0%)	0 (0%)	43 (100%)
Lymphoma	26 (100%)	0 (0%)	0 (0%)	26 (100%)
ALL	0 (0%)	13 (57%)	10 (43%)	23 (100%)
AML	0 (0%)	7 (47%)	8 (53%)	15 (100%)
Others	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Total	71 (65%)	20 (18%)	18 (17%)	109 (100%)

The group was an adult population, with a ratio M/F of 1.47 and an median age 48.5 years. Multiple myeloma and lymphomas were the most common diseases in auto HSCT and Acute leukemias in allo and haplo H,

FIGURE 1 - Mobilization of CD34 with pegfilgrastim in allo SCT (n=38)

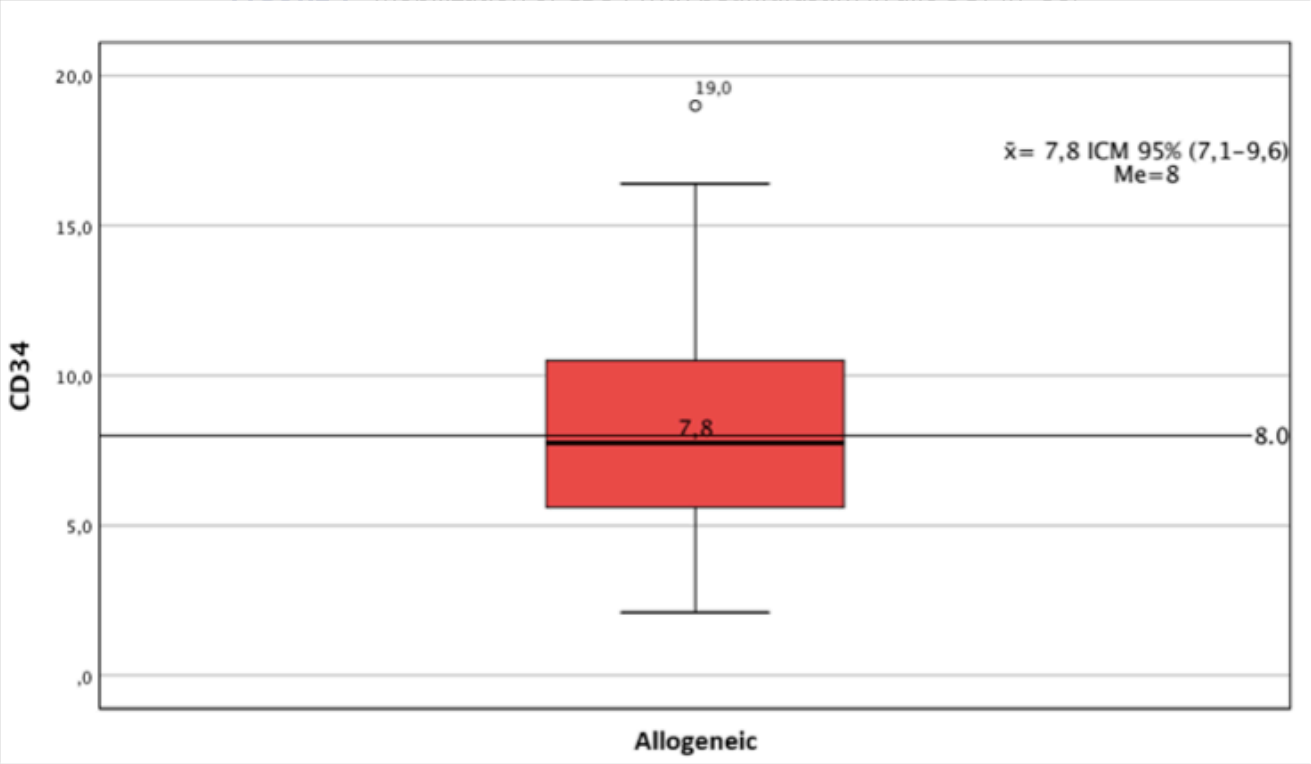
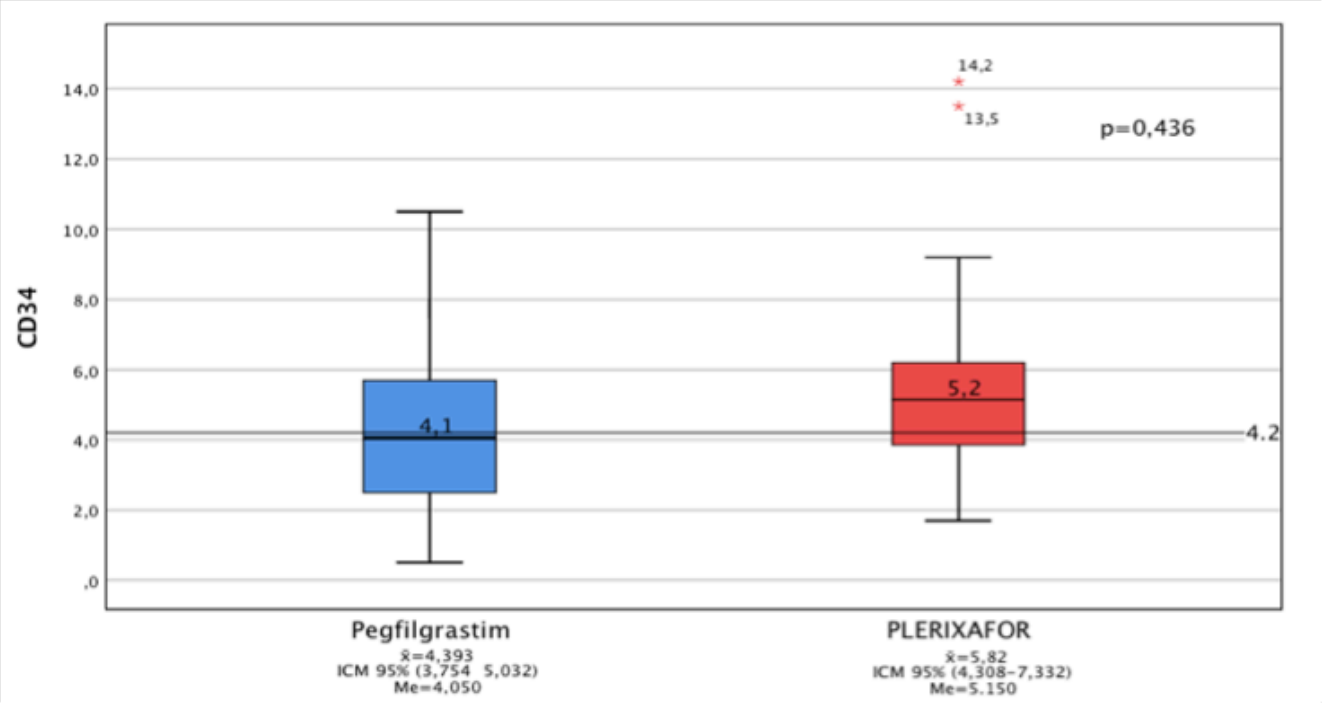


FIGURE 2 - Mobilization of CD34 in ASCT (n=71)



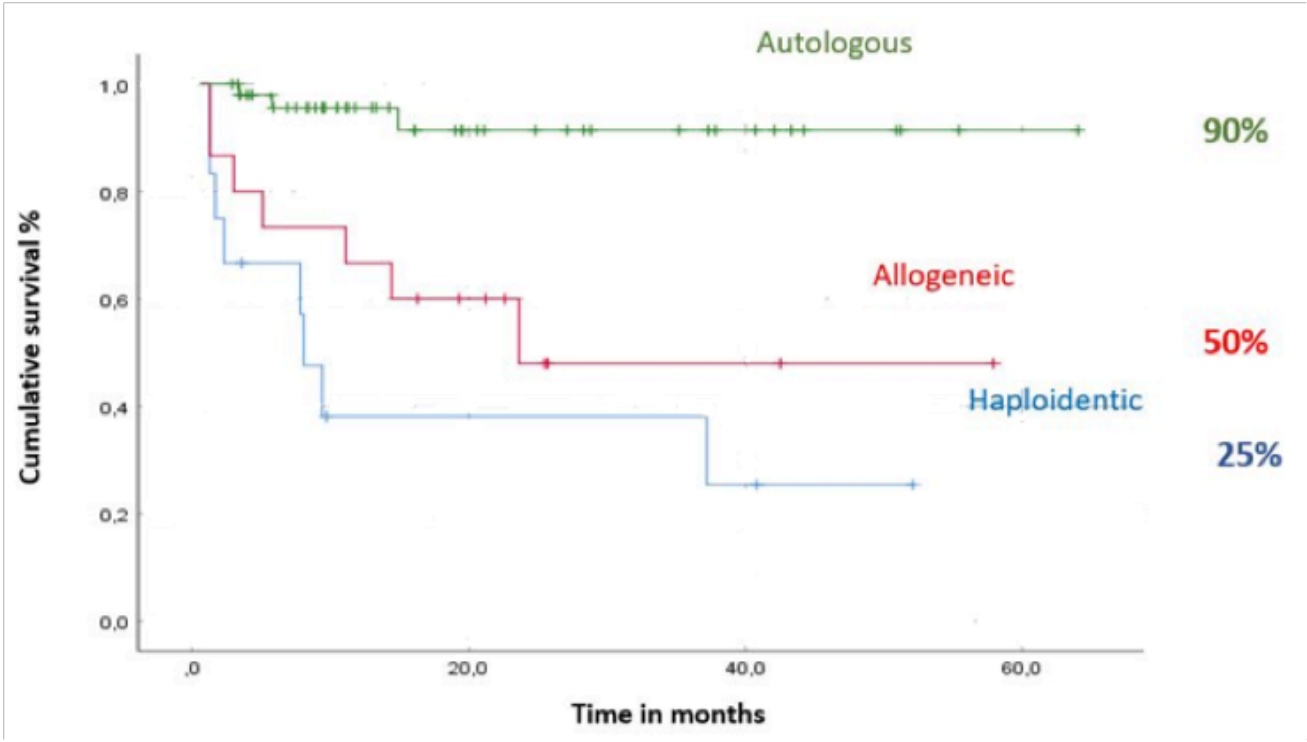
In autologous transplant group mobilized with pegfilgrastim only, it was yielded a median of 4.1 x 10^6 95% CI (3.75 – 5.03) CD34+ / kg. In plerixafor + pegfilgrastim group it was 5.1 x 10^6 95 IC (4.3 – 7.3) CD34 +/ kg (p=0.44).

TABLE 2 - Engraftment day

	n	$\bar{x}$ day	p
Myeloid			
Allogeneic	36	13,5	
			0,015 ICM 95% (-3,94 a 146,36)
Autologous	69	12,45	
Total	105		
Platelet			
Allogeneic	34	21,34	
			0,004 95% (-0,37 A 3,25)
Autologous	67	16,65	
Total	101		

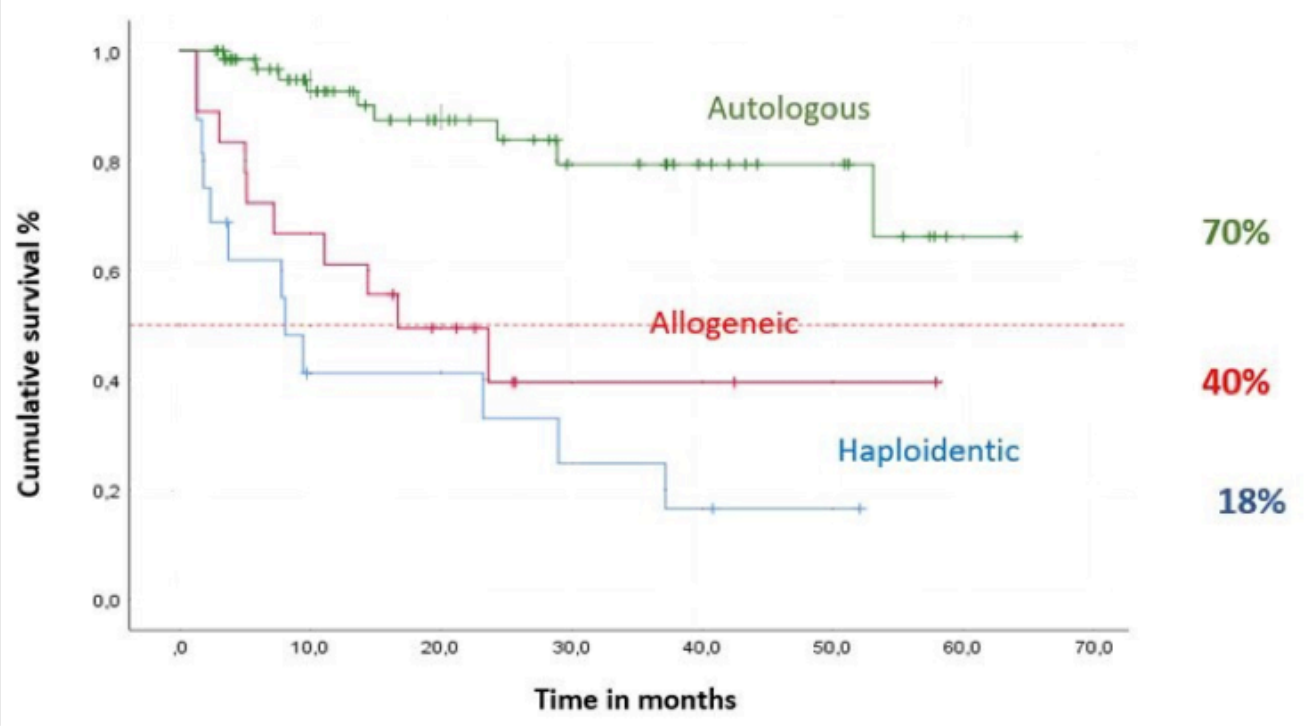
Myeloid and platelet engraftment was successful in autologous and allogeneic transplants. No engraftment failure was recorded.

FIGURE 3 - PFS (n=78/102)



For all types de HSCT, PFS rates was 70% for ASCT, 50% for Allo SCT and 25% for Haplo SCTat 60 months respectively.

FIGURE 4 – OS in HSCT transplants 2014 2020



Discriminating the median OS rate at 60 months according to the type HSCT, for ASCT was 70%, for Allo SCT was 40% and for Haplo 18% respectively