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Dear transplant colleagues

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

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

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

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

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

Fernando Barroso Duarte *Nelson Hamerschlak*

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COMMENTARY

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PROF. DR. HANS JOCHEM-KOLB
SENIOR CONSULTANT OF LMU CONSULTANT OF TUM AND KLINIKUM MUENCHEN SPECIAL INTERESTS "ALLOGENEIC IMMUNOTHERAPY"

Dear Drs.Nelson Hamersclak and Fernando Barroso,

Congratulations for your article in the JBMCT on AI and EI! Wonderful as you relate it to Albert Einstein, Aldous Huxley, Antoine de Saint Exupery, Charlie Chaplin and Fernando Pessoa! There are two properties a good physician should have: excellent knowledge of science and great empathy for the patient. Medicine without careful science is sharlatanism, we know that many colleagues are making lots of money with some sort of sharlatanism. That does not mean we scientific doctors know everything, but we rely on reproducible studies. In some cases we extrapolate from previous science got new situations. However, extrapolations are easier with deep and extensive knowledge. The extent of knowledge is so large that we may need AI to use it. During 50 years my interest has been stem cells, physiology of persistence, recruitment and differentiation on one side and immunology on the other side. There are still secrets on their resilience against radiation and chemotherapy, their recruitment in steady state and the expansion of reproduction. We are still learning on clonal predominance and progression from CHIP two MDS and AML. In immunology we have learned that there are not only „go" signals, but also „hold" signals, and a major question is the immune memory. Regulatory T cells are extremely important as are regulatory B cells; suppressory macrophages are important in addition to stimulatory M1. We transplant hematopoietic stem cells from marrow and blood containing extensive proportions of immunocompetent cells.We know little about the immune memory of the donor, often also of the patient; HLA-compatibility and CMV serology excepted we know little about minor HAs, microbial colonization and translation of microbial peptides., latent viruses, immunizations by sexual ccntacts. Meanwhile we know that HLA-ddifferences are not equal, but peptide binding motives are more important. Immune suppression alone is not constructive, we are looking for tolerance inducing procedures. AI may help to define the roles of thousands of factors of patient and donor by evaluating gene sequencing and microbial analysis. Already AI has an enormous impact on diagnostics of the disease at an early stage. Empathy for the patient is a difficult area to teach. Kant' s philosophy may help, freely translated „treat the patient as you would like to be treated as patient". That means „tell him or her the truth, but not without giving him/her a helping hand. Accept that you can learn from your patient as he/she sees the problems. Through your knowledge you always find a way for dealing with the problems. Think of „Le petit prince" and take your responsability. There are many rules and juries that may help in your orientation, but you are the doctor of your patient hoping for the best treatment.

With best regards from a sênior,

Hans-Jochem Kolb

ORIGINAL ARTICLE

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HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR ALL: A REPORT FROM THE 2024 CONGRESS OF THE BRAZILIAN BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY SOCIETY (SBTMO)

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ABSTRACT

This article analyzes current data, and the main challenges faced in Hematopoietic cell Transplantation (HCT) in Brazil, as presented at the SBTMO 2024 meeting, with the aim of guiding future actions. Topics discussed included the waiting list for HCT transplants, access to beds for adults and pediatric patients, and the need for a more efficient distribution of resources across the country. Among the identified needs were the creation of a program to expand access to transplants through the Brazilian Unified Health System (SUS), the importance of health registries for data-driven decisions, and the development of the "Mais Saúde Amazônia" project to expand transplant centers in the Amazon region. Additionally, the provision of financial incentives for transplant centers, the implementation of mentorship programs to increase access to HCT, and the formation of a cooperative network between SBTMO (Brazilian Society of Bone Marrow Transplantation and Cellular Therapy), ABHH (Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy), ANVISA (Brazilian Health Regulatory Agency), ABRALE (Brazilian Association of Lymphoma and Leukemia), and INCA (Brazilian National Cancer Institute) to improve the integration of HCT services were discussed.

Keywords: Hematopoietic Stem Cell Transplantation. Brazil. Adult. Pediatrics.

INTRODUCTION

There are significant challenges for Hematopoietic Cell Transplantation (HCT) in Brazil[1]. Although the country has the largest public organ, tissue, and cell transplant program in the world, access to transplantation is hindered by an insufficient number of active beds for adults and even scarcer availability for pediatric patients. Despite this, there is a long waiting list that exceeds 65,000 individuals, with most of these patients waiting for solid organ transplants such as kidneys, livers, and lungs[2]. Additionally, there is a significant demand for HCT, which is a critical area requiring urgent attention. These issues were discussed with members of SBTMO, the president of ABHH, the manager of the Blood, Tissues, Cells, and Organs Management (GSTCO/2nd Directorate of ANVISA), the coordinator of REDOME (Brazilian Bone Marrow Donor Registry/INCA), and the CEO of ABRALE with the goal of improving the situation.

HCT IN BRAZIL

According to the Ministry of Health in Brazil, 88% of HCT are performed through the SUS, while 12% are carried out in private centers[1]. Brazil also has the third-largest donor registry in the world, the Brazilian Registry of Bone Marrow Donors (REDOME), which has over 5.5 million registered donors[2,3].

Currently, Brazil has 275 accredited medical transplant teams across 133 establishments: 133 for autologous transplants only, 82 for related allogeneic transplants, and 60 for unrelated allogeneic transplants. Most of these centers are concentrated in the Southeast and South regions of Brazil[4].

In 2023 and 2024, 50 new teams were authorized for autologous transplants, 33 teams for both autologous and related allogeneic transplants, and 8 teams for autologous, related allogeneic, and unrelated allogeneic transplants[4].

In 2023, according to data from the Data System of the Unified Health System (DATASUS), 2,959 bone marrow transplants were performed through the SUS. Of these, 1,851 were autologous transplants, 883 were with related donors, and 225 were with unrelated donors[4].

However, there is a significant demand for patients waiting for transplants, both autologous (for conditions such as multiple myeloma, lymphomas, and germ cell tumors) and allogeneic (particularly for acute leukemias, bone marrow failure syndromes, myelodysplastic syndromes, myeloproliferative disorders, and sickle cell anemia). Currently, there is no available data on the number of patients on the waiting list for bone marrow transplants in Brazil in the Brazilian Transplant Registry (RBT)[2]. It is important to emphasize that there no mandatory registry for HCTs performed in private hospitals, so we lack accurate data in this sector.

The waiting list for bone marrow transplants represents one of the greatest challenges. In addition to high demand, the time between diagnosis and transplant is influenced by the limited availability of specific HCT beds, as well as access to treatment, which depends on socioeconomic, ethnic, and cultural factors, the structure of public and private health systems, and the availability of a compatible donor or the appropriateness of the recipient for transplantation[5].

According to the HCT waiting list survey conducted by SBTMO on July 23, 2024, across 63 transplant centers, 1,762 patients were awaiting a HCT, with 1,164 waiting for autologous transplants and 598 for allogeneic transplants (Figure 1). Of these, 1,015 patients were on the waiting list at public centers, 556 at mixed centers, and 191 at private centers (Figure 2).

In this survey, a questionnaire was used to assess the practice of reporting transplant data. It was found that 85.7% of the centers report their data, with 68.3% reporting it to the SBTMO/CIBMTR platform, 65.1% to ABTO/RBT, and 23.8% to other platforms. The data from the 63 centers analyzed in this study represent 49.7% of the transplants performed in 2023. Among these, 67.7% were allogeneic transplants.

When analyzing the Brazilian states with the highest number of patients on the HCT waiting list, São Paulo leads with 523 patients, followed by Minas Gerais with 214, and Ceará with 184 patients (Figure 3). At the Walter Cantídio University Hospital/UFC/EBSERH in Ceará, the HCT service has been receiving patients from other regions and expects to perform over 100 transplants in its HCT service alone this year.

According to data from the CIBMTR (Center for International Blood and Marrow Transplant Research), 12,230 transplants were performed in Brazil between 2012 and 2023. Of these, 5,573 were autologous transplants and 6,657 were allogeneic, with a predominance of allogeneic transplants, as data on autologous transplants are not fully reported[5]. The primary indication for transplantation is multiple myeloma, and infection is the leading cause of death within 100 days after the procedure, highlighting the crucial importance of addressing this problem in Brazil[6].

Another unmet need in HCT in Brazil is that, despite having 165 teams authorized to perform unrelated HCT through SUS, there are insufficient available beds. Additionally, according to the REDOME, there is a shortage of collection centers to meet the demand for harvesting stem cell products for these transplants. This delay increases the risk of death for patients awaiting this potentially curative therapy.

PEDIATRIC HEMATOPOIETIC CELL TRANSPLANTATION IN BRAZIL

There is a clear need to increase the number of pediatric transplants in Brazil, especially in the North, Northeast and Central-West regions. The limited availability of pediatric transplant beds and the lack of specialized care for infants and children with rare diseases are significant constraints. According to data from the SBTMO/CIBMTR Multicentric HCT Registry, between 2012 and 2023, out of the 6,657 allogeneic transplants performed, the age group of 0 to 9 years had the highest number of procedures, with 1,195 transplants. Most of these procedures were carried out in centers in Brazil's Southeast and South regions. The primary indications for allogeneic HCT in children were non-malignant diseases, acute lymphoblastic leukemia (ALL), and aplastic anemia. Infection is also the leading cause of death within 0 to 100 days after transplantation among these patients[6].

According to the 2023 analysis of the Brazilian Transplant Registry, there is a significant disparity in the performance of pediatric transplants across different regions of Brazil, with a concentration in the South and Southeast regions, particularly in Curitiba and São Paulo. These discrepancies highlight the difficulties in accessing these procedures caused by the scarcity of specialized centers in various regions[7]. The lack of centers in different cities in the North, Northeast, and Central-West regions highlights the urgent need for a more accurate assessment of transplant demand. This evaluation will enable the mapping of available beds within SUS and promote more significant equity in access to transplants across different regions of the country[7].

BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANT AND CELLULAR THERAPY (SBTMO)

The SBTMO has experienced significant growth, with 1,537 members in 2024, reflecting a 64.7% increase from the 542 members registered in 2020. The SBTMO also has partnerships with other organizations in the field, such as EBMT, ASTCT, LABMT, and WBMT[8].

The SBTMO publishes an online journal, the Journal of Bone Marrow Transplantation and Cellular Therapy (JBMTCT), which is the first in Latin America dedicated to this topic. In its 17th edition, JBMTCT had 8,000 users in 2023 and over 35,000 page views. Between 2020 and 2024, the journal received 59 citations on Google Scholar, 24 on OpenAlex, and 19 on CrossRef, and holds a Qualis C rating and an H-index. The SBTMO consensus guidelines, including the Brazilian HCT Consensus and the Pediatric HCT Consensus, are periodically updated in JBMTCT and have played a crucial role in guiding transplant practices in Brazil and across Latin America[8,9].

Through its partnership with CIBMTR, the number of centers reporting their data to this platform has grown to over 92 centers, with 35 active HCT centers in 2023 and 1,922 new HCTs registered, coordinated by the SBTMO data managers group[6,8]. These reporting centers are certified by SNT. The CIBMTR Data Back to Center (DBtC) tool returns this information to SBTMO, contributing to the establishment of the Brazilian HCT Registry, which captures data on both HCT and CAR-T cell infusions.

The summary slides with general outcomes of HCT are published annually in JBMTCT[6]. In addition to this published information, SBTMO promotes various educational initiatives, such as regional and national meetings, interactions with FACT, and the "Young Transplant Program," which are fundamental for training residents and young professionals. The GEDECO, SBTMO's scientific working group,

has also significantly contributed by publishing numerous collaborative studies in prestigious scientific journals[8].

PROPOSALS AND PERSPECTIVES

During the meeting, several proposals were discussed, which can be summarized to guide future efforts to improve HCT in Brazil[2]:

1. **Creation of a Program to Simplify Access to Transplantation within SUS:** Develop a program to facilitate access to transplants for SUS patients across all Brazilian states, aiming to standardize and expand the available services.

2. Importance of Health Registries: Emphasize the need for detailed health registries so that managers can make informed decisions. Expand access and reduce health disparities based on recorded data.

3. Development of the "Mais Saúde Amazônia" Project: Promote the establishment of new transplant centers in the Legal Amazon region, where there is currently only one center in Belém (Pará). Encourage the growth and expansion of transplant services in the area.

4. Financial Incentives for Transplant Centers: Propose greater financial incentives for transplant centers to increase the number of transplants performed and improve their capacity to provide care.

5. Mentoring to Expand HCT Access: Implement mentoring programs to expand access to HCT in more locations, fostering the formation of new teams and the expansion of services.

6. Formation of Cooperation Networks: SBTMO and ABHH should form a network with entities such as REDOME, ABRALE, and ANVISA to improve collaboration and integration of HCT services.

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The authors thank Angelo Maiolino, President of ABHH; João Batista da Silva Junior, Manager of the Blood, Tissues, Cells, and Organs Department – GSTCO/2nd Directorate; Danielli Oliveira, Coordinator of Redome/Inca; and Catherine Moura, CEO of Abrale, for valuable discussions and insights that significantly contributed to the development of this manuscript.

FIGURE 1: Hematopoietic cell Transplantation Waiting List in Brazil by Type of Transplant

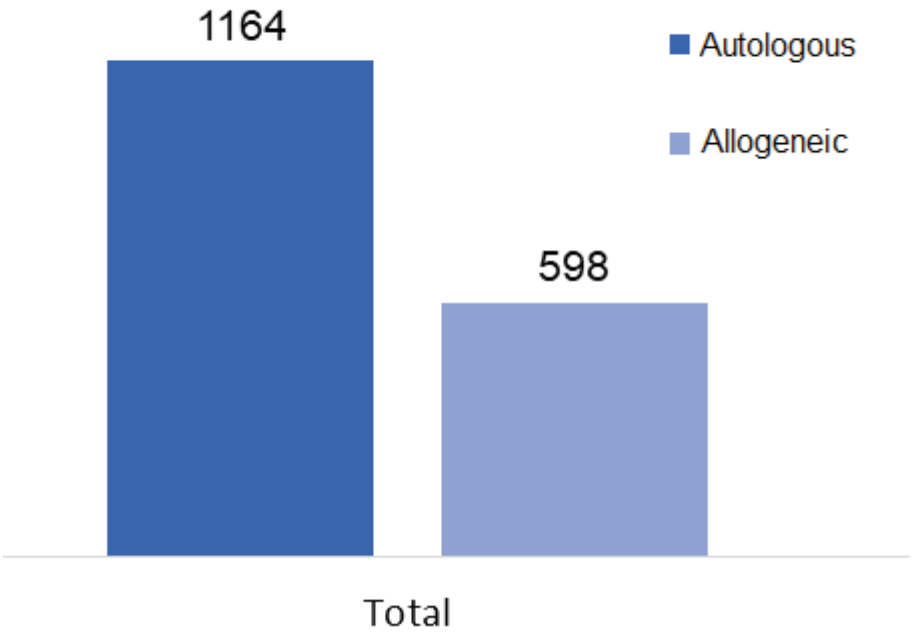


FIGURE 2: **Distribution of patients submitted to an Hematopoietic cell Transplantation by Type of Center**

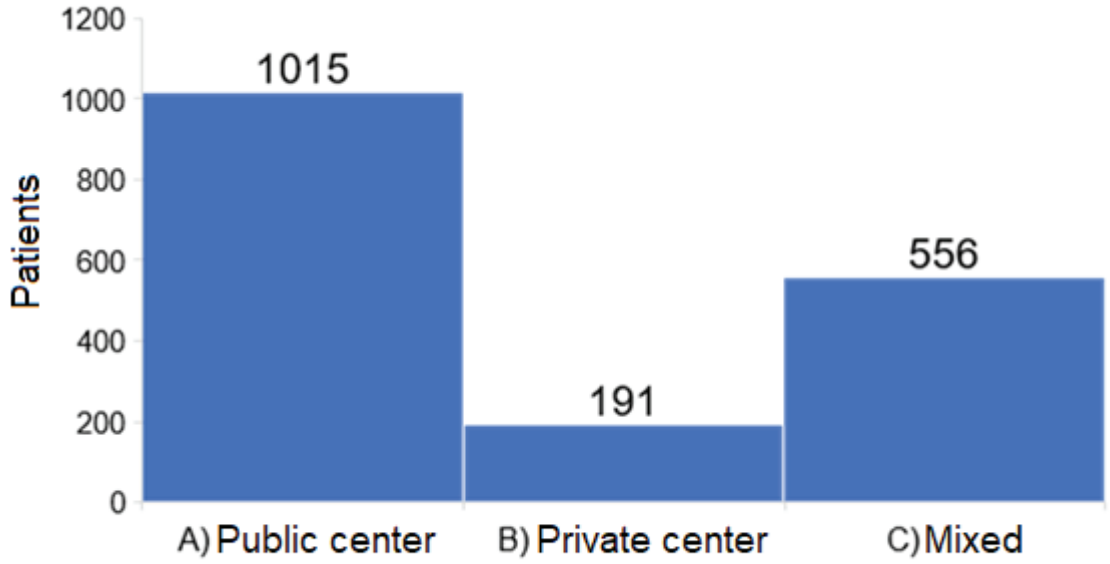
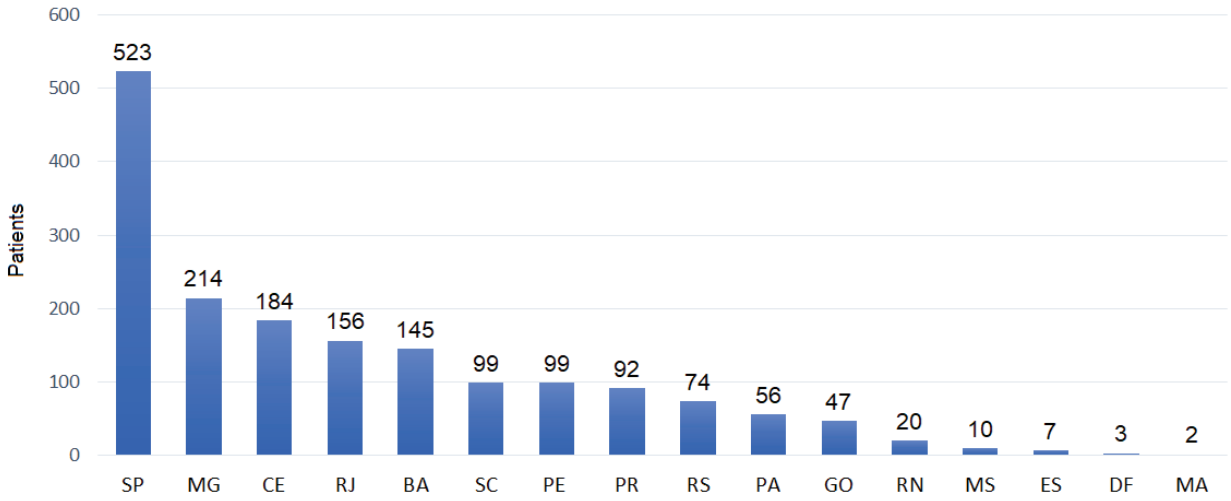


FIGURE 3: **Distribution of the waiting list by State for Hematopoietic cell Transplantation in Brazil**



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ORIGINAL ARTICLE

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EVALUATION OF ADHERENCE, SAFETY AND EFFECTIVENESS OF AN ANTIBIOTIC DE-ESCALATION STRATEGY IN PATIENTS WITH FEBRILE NEUTROPENIA DURING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Introduction: There are ongoing concerns about optimal antibiotic regimens for febrile neutropenia during autologous hematopoietic stem cell transplantation (ASCT). **Objectives:** We assessed adherence, safety, and clinical outcomes of an antibiotic de-escalation protocol at a hematopoietic stem cell transplant reference center. **Methods:** We conducted a retrospective analysis of clinical data from 100 patients who developed febrile neutropenia during autologous stem cell transplantation between January 2020 and June 2021. In addition to presenting descriptive variables, we compared clinical outcomes, including treatment duration, hospitalization length, ICU admission, and mortality, among intervention groups. **Results:** Approximately 61% of the patients underwent the antibiotic de-escalation strategy, with an adherence rate of approximately 80% and only 20 protocol deviations. Comparing intervention groups, statistically significant differences favored the de-escalation and early termination group, which had shorter hospital stays (16 vs. 18 days, p 0.01) and fewer days of antibiotic treatment (5 vs. 8 days, p 0.006). There were no differences in safety outcomes. **Conclusions:** The antibiotic de-escalation strategy demonstrated significant adherence and proved to be safe and effective, with the added benefit of shorter hospital stays and reduced antibiotic exposure.

Keywords: Febrile neutropenia. Stem Cell Transplantation. Anti-Bacterial Agents. Drug Resistance, Microbial. Antimicrobial Stewardship.

INTRODUCTION

Autologous hematopoietic stem cell transplantation (auto-HSCT) is an accepted therapeutic option for the treatment of hematologic malignancies and some difficult-to-manage autoimmune diseases. This approach increases disease-free periods and/or improves overall survival by using high-dose chemotherapy, which leads to profound cytopenias with associated complications. Febrile neutropenia (FN) is not only very common but also remains a leading cause of early mortality associated with this treatment[1]. The accepted practice in these cases is the empirical use of broad-spectrum antibiotics until neutropenia resolves[2,3]. However, in this era of high bacterial resistance, there is significant interest in defining antibiotic use strategies that select the appropriate spectrum and duration, balancing the risk between inadequate coverage and resistance[4].

The main objective of this study is to describe the adherence, safety, clinical outcomes, and microbiological outcomes of implementing an antibiotic de-escalation protocol inspired by the guidelines of the Fourth European Conference on Infections in Leukemia (ECIL4)[5], in a group of patients undergoing auto-HSCT at a reference center in Colombia. As a secondary objective, and given that this is a study with retrospective real-life data, the different scenarios of protocol application were subcategorized and presented, and their relationship with different outcomes was analyzed to provide more resources for result analysis.

METHODS

A retrospective cohort study at Clínica Las Américas/AUNA in Medellín, Colombia, examined patients over 15 years of age, who underwent autologous transplantation between January 2020 and June 2021. The study focused on those who experienced febrile neutropenia during transplant hospitalization. Patients with incomplete data or pre-existing infections before transplant chemotherapy were excluded. The study was approved by the institutional ethics committee and endorsed by the clinical hematology program committee at the University of Antioquia. Informed consent was obtained from all patients.

Autologous transplant patients received care in isolated single rooms with contact precautions by medical and nursing staff. Vital signs and clinical evaluations occurred a minimum of 4 times daily for asymptomatic patients and more frequently when symptoms or complications were reported. Peripheral blood was the cell source, collected via a central venous catheter (subclavian or jugular) placed before conditioning. All patients received filgrastim support from the fifth day post-transplant until achieving three consecutive days with more than 500 neu/µL

Institutional protocol defined febrile neutropenia (NF) as having an absolute neutrophil count (ANC) ≤ 500 cells/µL and an isolated temperature ≥ 38.3ºC. Fever with a neutrophil count expected to reach the neutropenia threshold within 48 hours was also classified as NF (dynamic definition)[6].

Due to the high morbidity and mortality risk from extended-spectrum beta-lactamase (ESBL) germs in neutropenic patients[7-9], the protocol followed the ECIL-4 de-escalation recommendations, initiating meropenem (1 g IV every 8 hours) for NF, preceded by four blood cultures (2 aerobic, 2 anaerobic). De-escalation occurred if criteria were met within 96 hours, switching to narrower-spectrum antibiotics (Figure 1). If Gram-positive cocci were preliminarily reported in cultures, septic shock occurred, or there was a high risk of oxacillin-resistant cocci, it would lead to dual treatment with meropenem and vancomycin (or daptomycin).

"Early discontinuation" of antibiotics is defined as stoping the initial treatment within 96 hours without switching to other antibiotics. Failure to achieve defervescence within 96 hours of initiating first-line treatment is deemed as "*primary therapeutic failure*", prompting consideration for further interventions like escalating antimicrobial coverage.

"De-escalation failure" is confirmed if the fever reappears after de-escalation and the broader spectrum regimen is restarted. Methylprednisolone may be added if fever is suspected to be non-infectious[10].

FIGURE 1. De-escalation criteria and proposed de-escalation options in the institutional protocol

De-escalation criteria according to protocol:	1. Resolution of fever (defervescence) within the first 96 hours of initiating first-line treatment. 2. Absence of signs, symptoms, or paraclinical findings suggestive of sepsis or septic shock after initiation of first-line treatment. 3. Absence of signs, symptoms, or paraclinical findings suggestive of sepsis or septic shock after initiation of first-line treatment. Negative blood culture results or isolation of a germ sensitive to the antibiotic proposed for de-escalation within the first 96 hours of treatment.
First-line options	-Meropenem -Meropenem + vancomycin*
De-escalation options:	-Cefepime -Cefepime + vancomycin* -Vancomycin* as monotherapy -Discontinue all the antibiotics

*In some patients, daptomycin may be used as a replacement for vancomycin.

Treating physicians could request additional microbiological studies based on clinical context, like stool panels, urine analysis, culture, molecular tests, or imaging, to determine NF with or without an apparent focus[11].

Qualitative variables were described using absolute and relative frequencies, and comparisons were made using the $\chi 2$ test. The non-parametric Kruskal-Wallis test was used when comparing three or more groups. Quantitative variables were described with median and interquartile range values. The Mann-Whitney U test was employed after confirming non-parametric distribution through the Kolmogorov-Smirnov test. The significance level for statistical hypothesis testing was set at alpha 0.05. All analyses were performed using R software version 4.0.3 and RStudio 1.1.463

For clarity in the analysis of patients undergoing or not undergoing de-escalation, classification into intervention subgroups based on protocol adherence was proposed:

Definition of intervention groups according to protocol adherence:

Effective de-escalation (ED): Patients with febrile neutropenia who meet criteria and are successfully de-escalated by the treating physician to another antibiotic of lower spectrum.

Early suspension (ES): Patients with febrile neutropenia who meet de-escalation criteria and have antibiotics definitively discontinued within the first 96 hours of initiation as a de-escalation option.

Denial of de-escalation (DD): Patients with febrile neutropenia meeting de-escalation criteria but not de-escalated per treating physician's discretion.

De-escalation not contemplated (DNC): Patients with febrile neutropenia not meeting de-escalation criteria but de-escalated to another antibiotic against protocol.

Effective denial of de-escalation (EDD): Patients with febrile neutropenia not meeting de-escalation criteria and not de-escalated to another antibiotic effectively.

RESULTS

Participants

The institutional database included 109 adult patients who underwent autologous transplantation within the study period. Nine patients were excluded from the analysis: 2 due to insufficient data and 7 for not meeting the criteria for febrile neutropenia as an event of interest. Consequently, our analysis was based on the data of 100 patients.

Table 1 presents a comprehensive overview of patient characteristics, categorizing them based on the application of the de-escalation strategy. No statistically significant differences between the intervention subgroups were observed in clinical, sociodemographic, or primary diagnosis characteristics.

TABLE 1. Patient characteristics according to the application of the antibiotic de-escalation strategy

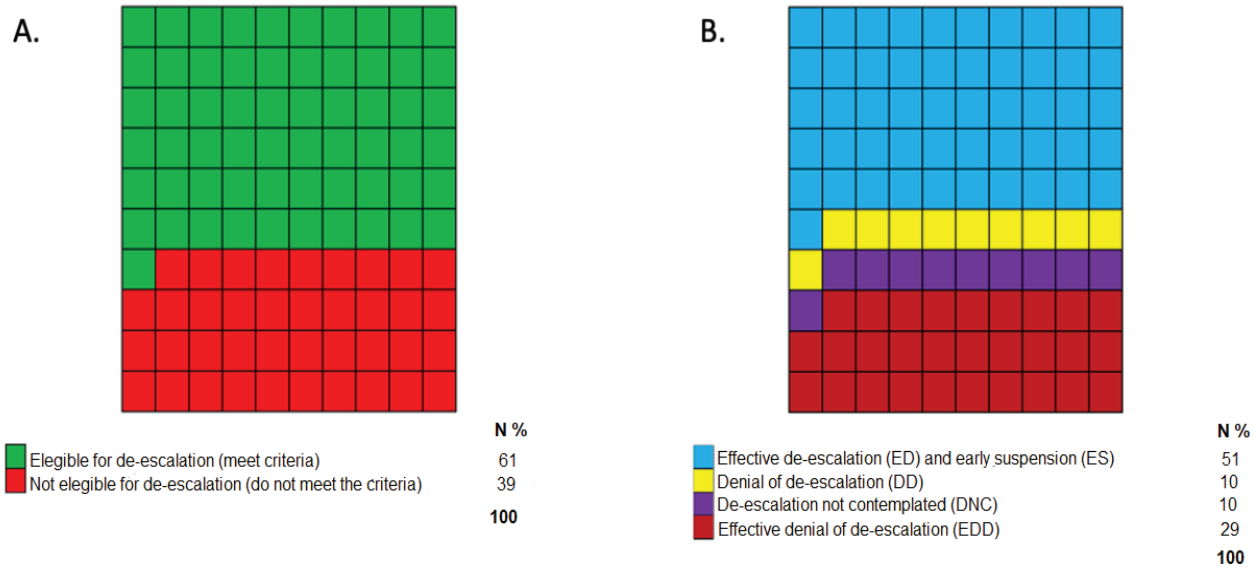
	De-escalation		
	Yes (n=61)	No (n=39)	
	n %	n %	P value
Age median (range)	56.6 (17-70)	55.9 (31-73)	0.64
Age group			
Adolescent (15-18)	1	0	0.52
Young adult (18-35)	5	2	
Middle Adult (35-65)	39	30	
Elderly (>65)	16	7	
Sex			
Female	34	25	0.53
Male	27	14	
Diagnosis			
Multiple Myeloma	40	23	0.30
Hodgkin's Lymphoma	6	2	
Non Hodgkin's Lymphomas	11	12	
Autoimmune Diseases	4	1	
Others	0	1	
ECOG			
0	1	0	0.14
1	45	26	
2	11	12	
Not defined	4	1	
DRI-TPH (SCT risk)			

Low	6	5	0.74
Intermediate	45	30	
High	1	0	
Undefined	9	4	
Disease Status			
Partial Response	31	14	0.16
Complete Response	26	24	
Non-Oncologic Disease	4	1	
Body Mass Index (BMI)			
Underweight	4	4	0.88
Normal Weight	28	16	
Overweight	20	14	
Obesity	9	5	
Antibiotic Prophylaxis			
Yes	14	9	1.0
No	47	30	

The absolute numbers are equivalent to the relative values because 100 patients were represented.

In total, 61% (61/100) of patients with NF underwent de-escalation, of which 83% (51/61) did so following the criteria established in the protocol (adherence proportion). This adherence proportion is depicted in green squares in Figure 2, which visually represents patient distribution based on eligibility criteria by protocol (A panel) and definitive intervention (B panel). The 80% (37/46) of de-escalations and 53% (8/15) of antibiotic treatment suspensions occurred before neutropenia resolution.

FIGURE 2. Distribution of patients according to de-escalation implementation. Panel A displays de-escalated patients in green and non-de-escalated patients in red. Panel B presents the specific distribution of patients according to protocol recommendations.



Clinical outcomes

Among the intervention groups based on antibiotic de-escalation, no statistically significant differences were found in the occurrence of sepsis (organ failure), admission to the intensive care unit, hospital readmission, or mortality at 30 or 100 days. However, it was found that the total days of hospital stay were shorter (16 vs. 18), and the total days of antibiotic use were reduced (5 vs. 8) among de-escalated patients compared to non-de-escalated ones, respectively.

There was 80% protocol adherence, and only 20 patients (20%) presented protocol deviations. In 10 patients, de-escalation was denied despite meeting the protocol criteria, while in the remaining cases, de-escalation occurred without indication.

Among sixty-one de-escalated patients, 20% (12/61) experienced at least one episode of fever after the antibiotic reduction. Interestingly, none of these fever recurrences happened in the patients de-escalated before neutrophil recovery. It is also important to note that 50% of these recurrences were observed in patients who underwent non-protocol de-escalation (6/10, 60%), while the remaining occurred in patients who were de-escalated as per protocol (6/51, 11%) (proportion difference p<0.0023). Only one case (1/12) of fever recurrence resulted in clinical de-escalation failure, necessitating reinstating the initial antibiotic spectrum; the rest were managed as immunologic fever (myeloid syndrome) without apparent adverse outcomes.

TABLE 2. Comparison of outcomes between intervention groups

Subgroup	General intervention groups		
	De-escalated (n=61)	Non-de-escalated (n=39)	p
Days of hospitalization	16 (12-54)	18 (13-28)	0.01
Antibiotic Duration	5 (2-11)	8 (5-14)	0.006
Documented infection	22	19	0.29
Organ failure	1	1	1
ICU/SICU	1	1	1
Hospital readmission (day of readmission)	2 (27 y 60)	3 (6, 25 y 76)	0.6
Infection with a germ resistant upon readmission	0	0	NA

Death during hospitalization	0	0	NA
30-day mortality	0	0	NA
100-day mortality	1	0	1
Composite outcomes (organ failure, readmission, and 100-day mortality)	4	4	0.774

ES ICU/SICU (Intensive Care Unit/Special Intensive Care Unit) (Intensive Care Unit)

Discussion

This study suggests that implementing an early termination and de-escalation of antibiotics protocol for auto-HSCT patients was feasible, safe, and effective in the real life seting. There were no statistically significant differences in adverse outcomes, including de-escalation failure, hospital readmission, ICU care, organ failure, recurrence of infection from resistant pathogens, or mortality during the first 100 days post-transplant between patients who underwent de-escalation and those who did not. Nevertheless, the de-escalation group did experience a shorter hospital stay and fewer days of antimicrobial exposure, which could be of significant benefit for transplantation units in terms of cost reduction and lower antibiotic exposure/resistance.

A randomized clinical trial by Aguilar-Guisado and colleagues in several Spanish transplant centers[12], including many autologous transplant patients, yielded similar results. They found that individuals who received the intervention of de-escalation or early termination of antibiotics did not experience more fever recurrences or higher mortality than controls. The experimental arm showed superiority with more antibiotic-free days (16.1 vs. 13.6 days, p 0.026) and a lower prevalence of adverse events.

The Nebraska group conducted a retrospective comparative study before and after implementing the ECIL-4 guideline recommendations[13]. While they reported no differences in mortality or hospitalization duration, there were differences in exposure to broad-spectrum antibiotics (3.09 vs. 4.69 days, p 0.069), favoring the early termination group. This group also had a lower reinfection incidence in the first 30 days post-transplant. It is important to note that this study did not clarify the distribution by transplant subtypes, and patients received prophylaxis with quinolones after the suspension of treatment, which differs from the protocol used in this study that did not involve prophylaxis after de-escalation without showing worse outcomes.

In 2019, Petteys et al. presented a retrospective study comparing early de-escalation and delayed suspension of antibiotics until neutrophil recovery[14], involving mostly autologous transplant patients. In both arms analyzed, there were no significant differences in recurrent fever (4.2% vs. 7.2%, p 0.85), bacteremia, rescaling (4.2 vs. 4.8%, p 0.64), in-hospital mortality (0 cases), or ICU admission (0 cases). However, unlike the present study, there was no reduction in treatment duration or hospitalization, possibly due to the uneven distribution of allogeneic transplant patients in the intervention arm, who typically have more extended periods of neutropenia and longer stays due to conditioning; this highlights the need to analyze transplant subtypes independently to avoid altering the results. We expect to present the results

of a parallel retrospective cohort of alo/haplotransplantation patients treated with the same febrile neutropenia protocol.

In France, Le Clech and collaborators presented the "How Long Study," which included 38 autologous transplant patients (31%)[15]. The study applied ECIL-4 recommendations in one group, requiring defervescence to suspend antibiotics. In contrast, antibiotics could be suspended five days after starting treatment in the other group, even if the patient still had a fever without a defined infectious focus. The primary composite outcome, including in-hospital mortality, ICU admission, infection with a resistant germ, or fever recurrence, did not differ between the two intervention groups (HR: 0.19-1.23, p = 0.11). In the current study, ten de-escalations were also out of protocol when the patient still had a fever, with no observed differences in adverse outcomes for this subgroup.

The adherence rate to the protocol of 80% in our study is considered satisfactory because it was not mandatory for the decision-making of the participant clinicians, and there were no on-time (or real time) feedback mechanisms during implementation. Similar studies in oncology achieved only partial adherence, ranging from 50% to 70%[16,17].

Another important aspect is that the proposed criteria for de-escalation were sensible, as patients classified as not suitable for de-escalation according to the protocol had a higher proportion of fever recurrences and microbiological isolations. This subgroup of patients represents a more uncomfortable scenario for clinicians, who usually prefer to be more prudent with antibiotic management in those cases. However, even this subgroup of patients did not present poor outcomes, raising questions about whether persistent or recurrent fever alone justifies deferring or limiting de-escalation strategies when the whole clinical condition and microbiological studies permit the contrary.

Notably, early suspension of antibiotics, considered a form of de-escalation, provided the most substantial benefits in reducing hospital stays and antibiotic use in the cohort. In this group, there were no instances of fever recurrence, even in cases where antibiotics were suspended before grafting.

The study had essential weaknesses, including being a single-center, retrospective study with a limited observation period, potentially introducing information biases and reducing external validity. The lack of microbiological analyses of colonization by resistant germs made it challenging to define the impact of interventions on patients' microbiota. Furthermore, using microbiological studies of readmissions as a proxy may underestimate this aspect. The study also faced challenges in establishing clinical and laboratory criteria for the early definition of fever origin or cause, as there are differential diagnoses for the febrile syndrome in patients undergoing auto-HSCT as myeloid reconstitution syndrome, adding complexity to the analysis. So, it is advisable to be cautious when applying these results more broadly.

In conclusion, the antibiotic protocol of early termination and de-escalation strategy in autologous transplant patients conducted at a Latin American HSCT unit demonstrated feasibility and significant adherence. This approach appeared to be safe and effective, reducing hospitalization days and exposure to broad-spectrum antibiotics. These findings align with data reported in international studies available in the literature.

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APPENDIX 1

Subgroup	Specific intervention groups					
	ES (n=15)	ED (n=36)	DD (n= 10)	DNC (n=10)	ID (29)	p
Days of hospitalization	15	16	17	18	18	0.02
Antibiotic Duration	4	6	6	9	9	0.002
Documented infection	1	15	3	6	16	0.019
Organ failure	0	0	1	1	0	0.08
ICU/SICU	0	0	1	1	0	0.08
Hospital readmission (day of readmission)	0	2	0	0	3	0.46
Death during hospitalization	0	0	0	0	0	NA
30-day mortality	0	0	0	0	0	NA
100-day mortality	0	1	0	0	0	0.77
Composite outcomes (organ failure, readmission, and 100-day mortality)	0	3	1	1	3	0.8

(Early suspension), ED (Effective de-escalation), DD (Denial of de-escalation), DNC (De-escalation not considered), ID (Ineffective de-escalation), OXA-R (Oxacillin-resistant), ESBLs (Extended-spectrum beta-lactamase), ICU/SICU (Intensive Care Unit/Special Intensive Care Unit) (Intensive Care Unit), ANC (Absolute Neutrophil Count in cells/µL), and CRP (C-Reactive Protein)

ORIGINAL ARTICLE

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10-YEAR REAL-WORLD DATA ON ACUTE MYELOID LEUKEMIA: THE PARADIGM OF A PUBLIC HEALTH CENTER IN BRAZIL

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ABSTRACT

Introduction: Despite advances in Acute Myeloid Leukemia (AML) diagnosis and treatment, the outcomes in low- and middle-income countries (LMIC) are far apart from those in high-income countries (HIC). **Objective:** To describe the clinical features and outcomes of AML patients in Brazil's public health system, we conducted a retrospective analysis of all cases of non-promyelocytic AML diagnosed within 10 years (2007- 2017) in northeastern Brazil, Bahia. **Methodology:** We analyzed the real-life outcomes of 62 patients diagnosed with non-promyelocytic AML between 2007 and 2017 at a university hospital in Northeast Brazil. We classified patients using the European LeukemiaNet 2022 guideline into favorable (n=8), intermediate (n=18), and adverse risk (n=7) groups. Twenty-nine were not otherwise classified because no cytogenetic and/or molecular tests were available at diagnosis. **Results:** Allogeneic bone marrow transplant (alloBMT) was performed in 16 patients (37%). Median overall survival (mOS) was seven months. Among patients receiving alloBMT, mOS was 49 months, while for the chemotherapy group, it was six months (P = 0.003). For 10-year real-life data, we found complete remission of 53%, 5-year OS of 27%, and a mortality rate during induction therapy of 27%, inferior to HIC. **Conclusion:** Inferior outcomes found in LMIC result from a multifactorial scenario and an unmet need in the worldwide panorama of AML.

Keywords: Leukemia, Myeloid, Acute. Leukemia. Developing Countries.

INTRODUCTION

Acute Myeloid Leukemia (AML) is the most frequent acute leukemia in adults, accounting for 80% of cases, and the incidence increases with age. AML originates from several genetic and epigenetic modifications in hematopoietic precursor cells, generating a clone of proliferating leukemic cells that do not differentiate in mature cells[1].

The pathogenic mechanisms associated with chromosomal and molecular modification in blast cells generated the European Leukemia Net (ELN) 2022 classification[2] based on parameters involving clinical and prognostic characteristics. According to molecular and cytogenetic profiles, AML is diagnosed into favorable, intermediate, and adverse-risk groups. Secondary AML (*s*AML), arising from a prior hematological condition or after chemotherapy for solid tumors, is a distinct subgroup involving the worst outcomes.

For many years, the treatment of Acute Myeloid Leukemia (AML) primarily relied on chemotherapy, hypomethylating agents, and bone marrow transplant (BMT), particularly allogeneic BMT (alloBMT) after relapse and based on risk stratification. Recently, however, the landscape has shifted with the advent of targeted therapies. Agents targeting FLT3, BCL2, IDH1, IDH2, and hedgehog pathways have notably improved treatment options[2]. These new therapies have shown promising results with reduced toxicity and have been explored both in initial treatment and in relapsed settings, used either as standalone treatments or in combination with other drugs.

The impact of targeted therapy on AML has been particularly transformative for specific patient groups. These include patients with adverse-risk profiles, secondary AML (sAML), and elderly patients who are often ineligible for intensive treatment due to their inability to achieve complete or long-term responses with conventional chemotherapy. With these advancements, there is a significant shift in the management and prognosis of these traditionally challenging cases of AML.

Novel exams and drugs are expensive and not readily available worldwide, especially in low and middle-income countries (LMIC) where distinct differences between private and public care are observed. Brazil is a country of continental size facing relevant socio-economic inequalities, especially in northern and northeastern regions. Three-quarters of the Brazilian population rely on the public health care system[3] and can only access novel treatments if included in clinical trials. Previous Brazilian data reported that up to half of the study subjects[1,4,5] could not be stratified using a comprehensive cytogenetic-molecular model (e.g., ELN). This scenario affects clinicians' ability to offer the best prognostic estimates to patients. In addition, decision-making involving therapeutic strategies and indication of allogeneic BMT in patients' first remission cases with missing prognostic data are equally affected.

To describe the clinical features and outcomes of AML patients in Brazil's public health system, we conducted a retrospective analysis of all cases of non-promyelocytic AML diagnosed within 10 years (2007- 2017) in northeastern Brazil, Bahia[6]. Our study is the first, to our knowledge, to look at the clinical features and outcomes of AML patients in this region.

METHODS

This retrospective single-center cohort was conducted at Professor Edgar Santos University Hospital from the Federal University of Bahia. All data collection followed the institutional ethical review committee (CAAE: 98938818.4.0000.0049).

The study population comprises patients older than 16 years diagnosed with non-promyelocytic AML in our center between January 2007 and December 2017. Each patient's data was collected from an internal database for ICD-10. A total of 62 patients were included. We used the ELN 2022 guideline for risk stratification adapted to the available data. Patients who did not perform molecular or cytogenetic tests were classified as unknown risk.

STATISTICAL ANALYSIS

Descriptive analyses were performed for patient baseline characteristics. Continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD) according to a normal distribution. We used logistic regression for univariate and multivariate data analysis, assessing death as the outcome. The variables analyzed were age, sex, hemoglobin (Hb), white blood cell (WBC), platelets, splenomegaly, hepatomegaly, adenopathy, mucocutaneous involvement,

AML origin (de novo x secondary AML), risk stratification and alloBMT. The multivariate analysis included AML origin, risk stratification, and alloBMT as predictor variables.

Survival curves were estimated using the Kaplan-Meier method, and group comparisons using a log-rank test. The impact of BMT on the overall survival of patients eligible for intensive treatment was assessed using a Cox proportional hazards model.

Overall survival (OS) was defined as the timespan from diagnosis to death from any cause; those alive or lost to follow-up were censored at the date last known as alive. Early mortality was defined as death occurring within one year of diagnosis. Relapse-free survival (RFS) was defined as the time from complete remission (CR) to the first relapse. The overall response was considered CR, CR with incomplete hematologic recovery (CRi), and partial remission (PR). CR, CRi, and PR were based on ELN 2022 guidelines.

Statistical significance was set as p-value <0.05. Statistical analysis and modeling were performed in R version 4.1.0 and SPSS version 25.

RESULTS

A total of 62 patients were included, but one patient died of intracerebral hemorrhage before receiving any treatment. The median age at diagnosis of the total cohort was 44 (ranging from 16-83 years), and 42 patients (68%) were diagnosed with *de novo* AML (Table 1). The median age for *de novo* AML was 32 years (range 16-61), and for sAML, it was 64 years (range 23-83). A total of 13 (21%) patients were ≥ 60 years old. Thirty-six patients (58%) were female. Baseline characteristics are described in Table 1.

TABLE 1. Baseline characteristics of the total cohort (n=62)

Variables	Results
Age	
Years(1)	44 (24-56)
≥ 60 years	12 (21%)
Female sex	36 (58%)
de novo AML	42 (68%)
Secondary AML	20 (32%)
Myelodysplastic syndrome (MDS)	10 (50%)
Chronic myeloproliferative disease (CMD)	8 (40%)
MDS/CMD	1 (5%)
Prior chemotherapy for solid tumor	1 (5%)
Laboratory data	
Hemoglobin (g/dl) (2)	6,8 (±1,8)
WBC (mm3) (1)	10.890 (3.357-35.777)
Platelets (mm3) (1)	30.500 (12.500 – 72.500)
Clinical data	
Splenomegaly	11 (18%)
Hepatomegaly	10 (16%)
Adenopathy	16 (26%)
Mucocutaneous involvement	8 (13%)

Median, IQR - Mean, SD

Based on the ELN 2022 guideline, eight patients (13%) were classified into a favorable risk group, 18 (29%) as intermediate, 7 (11%) as an adverse-risk group, and 29 (47%) as an unknown risk group. Only 13 patients (21%) underwent molecular mutation tests, which included FLT3, NPM1, CEBPA, and c-KIT. Thirty-seven patients (60%) were submitted to a karyotype analysis at diagnosis.

Of the 61 treated patients, 52 (85%) received intensive induction therapy, 7 (11%) non-intensive regimens, and 2 (3%) received palliative care without chemotherapy (e.g., hydroxyurea). As for patients who received intensive induction regimens, the majority (47 patients; 90%) received the 7+3 protocol. Alternative schemes (5+2, high dose cytarabine) were chosen according to clinical judgment following advanced age and morbidities. The death for intensive induction therapy was 19% (10 patients). The primary cause of death was infection (9 patients; 90%), and one patient died from disease progression. The overall induction response was 67%; 23 patients (55%) had complete remission, and 5 (12%) had partial remission. 13 (31%) were primary refractory AML, and one patient had no record of response in his chart.

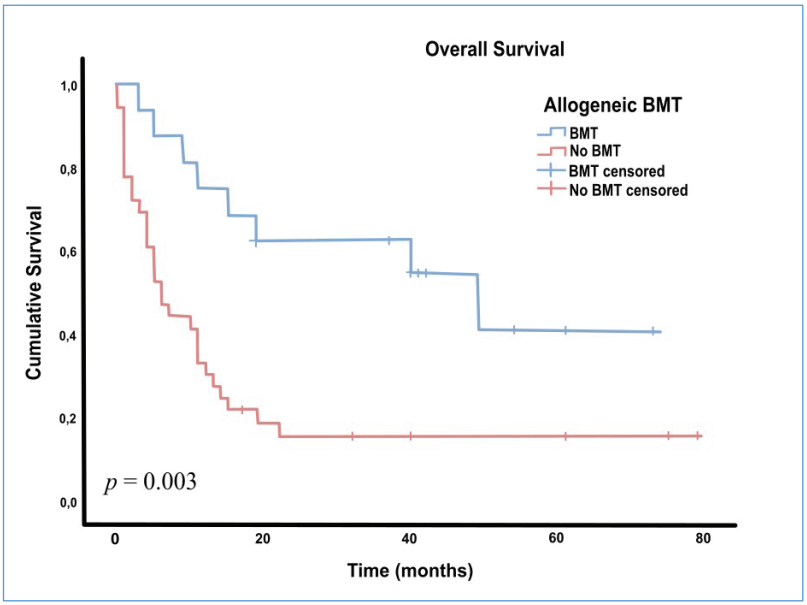
Comparing the data of *de novo* and *s*AML, *de novo* patients received intensive induction therapy, while only 10 (60%) *s*AML were eligible. The overall response rate after induction was 71% and 50%, respectively.

During the follow-up, 12 patients (29%) relapsed, and one of them twice. The median time to relapse was eight months. Analyzing patients with refractory and/or relapsed disease (n=27), 8 (30%) were classified as an unknown risk group, 6 (22%) as an adverse risk group, 9 (33%), and 4 (15%) as intermediate and low risk, respectively.

In the context of refractory or first relapsed cases, all intensive chemotherapy-eligible patients received FLAG (with or without anthracycline) as the rescue regimen (21 patients, 78%). Five cases (19%) had exclusive palliative care, and one patient used azacytidine. The mortality rate of the FLAG regimen was 24% (n=5). 11 patients (55%) achieved complete response. Four patients were submitted to a second rescue, 3 received MEC protocol, and 1 received FLAG-Mitoxantrone (15 months after the first FLAG scheme). All patients who had a third line of high-dose chemotherapy died within 60 days (N=4).

Of the 42 patients surviving induction, 16 (38%) were submitted to alloBMT. We found a survival advantage (hazard ratio, HR: 0.32, 95% CI: 0.15-0.71; p=0.005) in transplanted patients, with superior median overall survival (mOS) of 49 months compared to the chemotherapy group (6 months) (*P* = 0.003; Figure 1). Most patients (n=9, 56%) were transplanted as second-line therapy after a second remission. Autologous BMT was performed in 3 cases, and all patients died from infection, two of them in the context of graft failure.

FIGURE 1. Overall survival between BMT patients and no-BMT.



The median time from diagnosis to bone marrow transplant (BMT) was seven months. For the last date of chemotherapy, the median time was three months. Three alloBMT patients experienced a relapse after the transplant. Regarding risk stratification, one patient was classified as an adverse risk group, and the other two were unknown. The median relapse after alloBMT was eight months. All patients were submitted to a second alloBMT, but the mortality was 100%.

A total of 48 (77%) patients died during the follow-up, and most deaths (n=39, 81%) were in the first year of diagnosis (early mortality). Only 23% (n = 14) were alive during our analysis. The primary cause of death was infection (n=25, 52%), where 20% (n=5) of the cases were of fungal origin, followed by leukemia progression (n=16, 33%). Analyzing death between the intensive treatment group, 76% (n=29) died with active AML.

We performed a univariate analysis of clinical and laboratory characteristics with time of death as an outcome (Table 2) and found no association.

TABLE 2. Association between clinical and laboratory features with death

	Odds ratio (OR)	Confidence Interval (CI) 95%	P value
Age	1.0	1.0-1.1	0.06
Male sex	0.3	0.7-1.2	0.08
Hemoglobin	0.9	0.7-1.4	0.97
WBC	1.0	1.0	0.10
Platelets	1.0	1.0	0.66

Using a multivariate analysis, including AML origin, stratification risk, and alloBMT as predictor variables, we could see alloBMT's protective power (Table 3).

TABLE 3. Adjusted and unadjusted associations between alloBMT, risk stratification, and de novo AML with death as an outcome.

	Odds ratio (Confidence Interval 95%)			
	Unadjusted	p-value	Adjusted*	p-value
alloBMT	0.2 (0.05 - 0.73)	0.02	0.14 (0.03 - 0.58)	0.01
Risk stratification	1.58 (0.92 - 2.81)	0.11	1.91 (1.04 - 3.81)	0.45
De novo AML	1.6 (0.34 - 11.63)	0.59	1.18 (0.2 - 9.94)	0.86

*Each difference is adjusted to the other variables.

The mOS of the entire cohort was seven months (CI: 3.14-10.85). The mOS was shorter in patients in the unknown and adverse-risk groups (3 and 5 months, respectively) than in favorable and intermediate-risk groups (22 and 11 months, respectively, $P = 0.05$; Figure 2). The median relapse-free survival (RFS) was seven months (CI: 2.47-11.52). The patients with sAML had mOS of 3 months versus 11 months for *de novo* AML ($P = 0.024$; Figure 3).

As for patients alive during the follow-up (n=14), 8 (57%) underwent alloBMT transplant. Of the six patients who had not been submitted to transplant and survived, three were in the adverse risk group, two were in the intermediate risk group, and one was in the unknown risk group.

FIGURE 2. Overall survival according to risk classification.

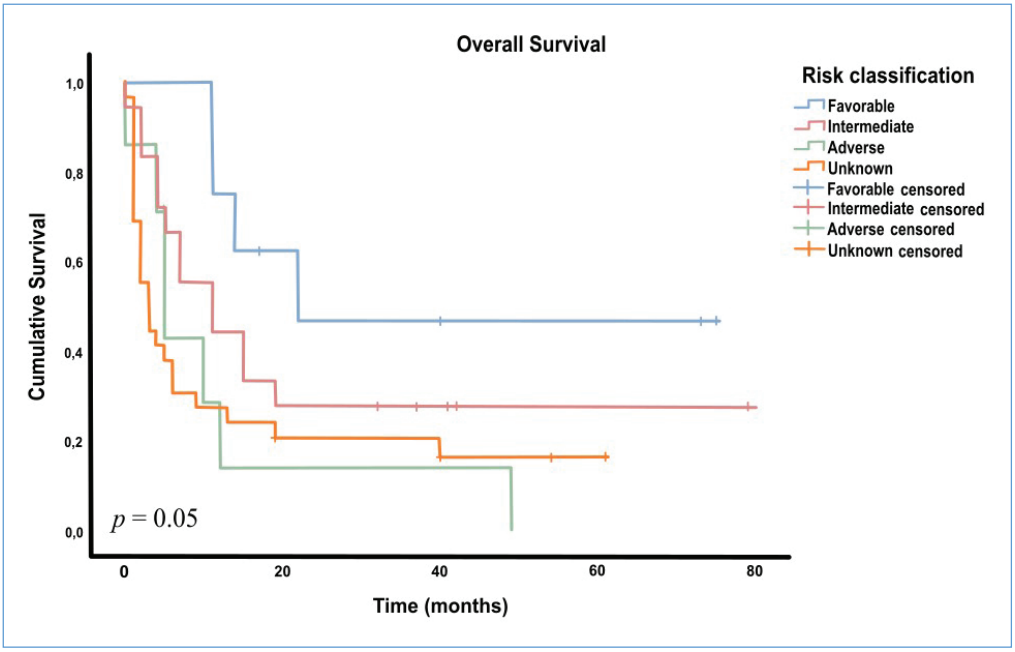
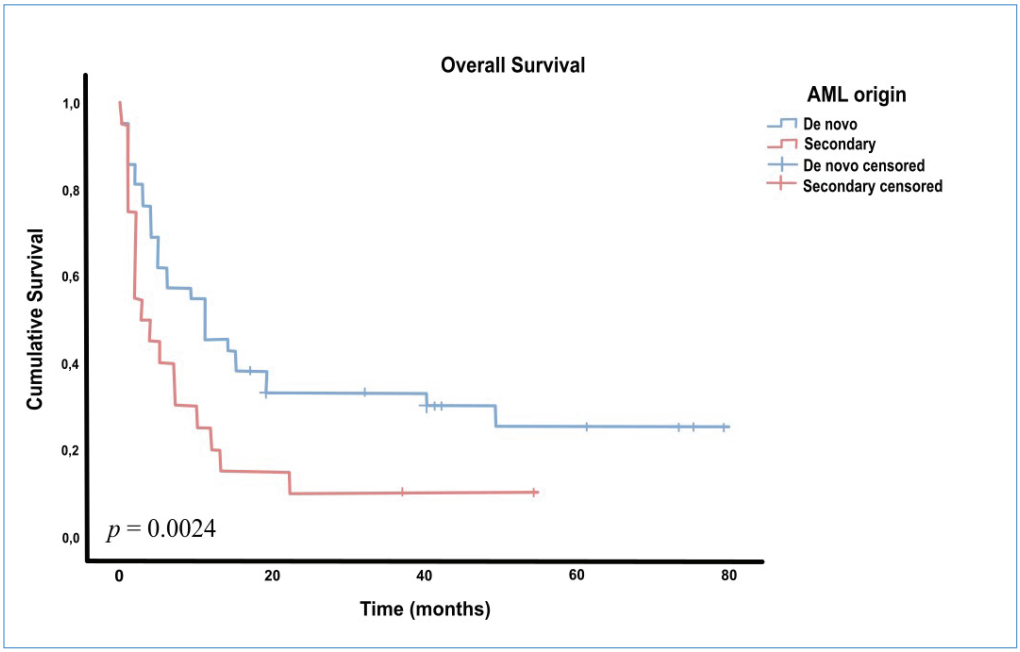


FIGURE 3. Overall survival according to AML origin.



DISCUSSION

We show real-life data for 10 years involving non-promyelocytic AML outcomes at a university hospital in Northeast Brazil, the only transplant center in the state. The results show patients' OS among AML, including favorable and intermediate-risk groups and for those receiving alloBMT. Our findings for CR (53%), 5-year OS (27%), and mortality rate during induction therapy (27%) were similar to other studies in Brazil, ranging from 48-73%, 17-25%, and 10-42% (median of 29%) respectively[4,5,7–13]. Nevertheless, our data is inferior to trials from Europe and North America[14–16], especially for *s*AML under targeted therapy, where CR rates are around 65%[17], as well as for relapsed cases.

The survival advantage among transplanted patients (mOS 49 x 11 months) was comparable to another Brazilian cohort (mOS 26.8 x 12 months) involving transplanted and non-transplanted patients, respectively[9]. The small number of patients submitted to alloBMT [17] results from inaccessibility to transplants due to the small number of available beds and the challenge of finding matched unrelated donors in a racially mixed population.

The low median age found in our cohort could reflect the problematic access to a hematologic center and a higher rate of early death of older patients before referral to a specialized hospital. Additional data is necessary to confirm this hypothesis. Although there are no randomized trials to our knowledge comparing high-income countries (HIC) with socioeconomic aspects of AML treatment, data suggest a trend of higher mortality in remission induction among patients with less favorable social conditions[11].

The higher mortality rate in our country, compared to those in higher-income countries, involves several factors: inadequate diagnostic tools, subpar hospital infrastructure characterized by a limited number of beds, overcrowded wards, and a scarcity of specialized facilities such as positive pressure beds. This scenario is prone to a higher incidence of infections and the need for effective treatments.

AML is a heterogeneous disease involving distinct molecular pathways and clinical outcomes. Several trials in HIC countries evaluate these outcomes. However, retrospective data from LMIC countries frequently describe poor outcomes. Brazil, a vast nation, experiences disparities in healthcare access across its states and between private and public sectors. Salvador, the capital of Bahia, has an estimated population of 14 million and a Human Development Index (HDI) of 0.660. This places it in the 22nd position out of the 27 states in Brazil[6].

An alarming finding here was the high number of patients not adequately stratified (39%) due to an absence of cytogenetic and molecular tests. Real-life data from university hospitals in Brazil demonstrate that 26% of patients are non-stratified[5]. Another study evaluating a few Brazilian BMT centers pointed out that 57% of the patients referred from other services did not have a karyotype test at diagnosis[4].

Recently, a Brazilian group implemented a novel scoring system that integrates clinical and laboratory characteristics (age, serum albumin, and WBC) with cytogenetic-molecular data for cases with missing information, preventing using ELN classification[2]. In the Brazilian public health system, access to real-life data and cytogenetic and molecular tests is limited, primarily due to the high costs associated with setting up a molecular biology laboratory and the challenge of having inadequately trained staff. Our study found that patients categorized as unclassifiable risk (UR) exhibited outcomes similar to those in the adverse risk groups, indicating that a significant portion might have been undertreated. The presence of a UR group is a common expectation in LMICs like Brazil. Therefore, treating these patients appropriately, considering their risk stratification, is crucial. Implementing therapeutic strategies typically reserved for non-favorable risk groups can significantly improve outcomes for UR patients. Statistically, UR group patients are more likely to belong to intermediate or adverse risk groups rather than favorable ones.

A clear-cut, real-life strategy for cases in unclassifiable risk groups is urgently needed. Therefore, every center should know its population survival curves to individualize the best treatment. We suggest that patients with inadequate risk assessment undergo consolidation therapy with alloBMT in first complete remission (CR1) as this remains the primary curative intervention and the main outcome in the real-world setting of LMIC. Although novel target drugs optimize treatment response rates, they are not universally available in public health centers.

Our study's limitations involve its retrospective nature and the small number of participants. As a suggestion, a prospective multicenter study with the collaboration of other regions of Brazil to compare outcomes and access to treatments will minimize the differences and improve the service provided by the Brazilian public healthcare system (SUS).

Finally, understanding AML pathogenesis and developing potent new treatments leads to increasingly divergent outcomes between LMICs and HICs. Consequently, the gap between diagnostic techniques and therapy remains a significant challenge in LMICs. Establishing dedicated teams and centers for acute leukemia in these regions is vital for improving patient outcomes. Such specialized centers will enhance treatment and play a crucial role in gathering valuable data for developing more effective treatment strategies for AML.

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AUTHORS CONTRIBUTION

Camilla CAPC: conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the article and revised it critically, and final approval of the version to be submitted. **Marco AS**: conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the article and revised it critically, and final approval of the version to be submitted**. Lais TS:** Drafted the article, revised it critically, and gave final approval of the version to be submitted. **Alini MOPS**: Drafted the article and revised it critically, and final approval of the version to be submitted. **Thiago F**: drafted the article, revised it critically, and gave final approval of the version to be submitted. **Felipe F**: drafted the article, revised it critically, and gave final approval of the version to be submitted.

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DISCLOSURE OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY

The data are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

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INFORMAL CAREGIVERS FOR BONE MARROW TRANSPLANTS – A QUALITATIVE STUDY ON OCCUPATIONAL LIFE: BONE MARROW TRANSPLANT CARERS – A QUALITATIVE STUDY

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ABSTRACT

OBJECTIVE: To understand the experience of informal caregivers' burden related to the task of caring for people undergoing hematopoietic stem cell transplantation. **METHOD:** Qualitative study based on interviews with six informal caregivers of onco- hematological patients who underwent hematopoietic stem cell transplantation and were admitted to the Bone Marrow Transplant Unit of a public, tertiary hospital, located in the interior of the State of São Paulo. Participants were selected through active search and recommendation from the unit's team. After ethical approval (CAAE: 64066622.9.0000.5393, on 05/29/2023), sociodemographic characterization data were collected and the interviews were audio-recorded and fully transcribed. The MAXQDA software was used for data analysis. Participant profile data were analyzed using simple descriptive statistics and qualitative data underwent thematic analysis according to Braun & Clarke. **RESULTS:** Two thematic units address the impacts of overload on the informal caregiver's occupational life and coping strategies for managing overload. **CONCLUSION:** The informal caregiver plays an important role, but this creates an overload that impacts the treatment of the sick person. Therefore, caring for caregivers and welcoming them as subjects of care can mitigate the impacts faced by caregivers during and after the transplant process.

DESCRIPTORS: Bone Marrow Transplantation. Caregiver Burden. Occupational Health.

INTRODUCTION

Caring for seriously ill people involves commitments and responsibilities inherent to the occupational role of caregiver. Occupational role is a set of activities and responsibilities associated with certain positions or functions that an individual occupiesin different contexts of their life, whether social, personal, educational or professional. This concept is crucial to understanding how people organize their lives and how they engage in their communities and environments[1].

Among the various existing occupational roles, the role of caregiver stands out, which involves a series of activities and responsibilities[2]. The act of caring for a sick person is a complex task that transcends medical issues. In addition to physical demands, it covers social relationships, work, leisure and self-care issues, the dimension of religiosity and spirituality (R/S) and may even involve financial support for the sick person. This occupation is permeated by diverse and sometimes contradictory feelings onthe part of those who may not feel prepared for it[3-7].

While formal caregivers provide professional care in the form of public or private services, informal caregivers carry out support and care tasks on a voluntary basis, to meet the specific needs of the sick person, and may be a member of the family, community or friends[8].

Hematopoietic stem cell transplantation (HSCT) is one of the most promising and potentially curative therapeutic options available for people with hematological and non-hematological neoplasms such as leukemia, myeloma, lymphoma, marrow aplasia, sickle cell anemia. However, the nature and clinical course of diseases, especially onco- hematological diseases and specifically for subjects undergoing HSCT, expose patients and their caregivers to various stressful events such as significant morbidity, symptoms, general decrease in quality of life and psychosocial and end-of-life issues[9,10].

Family caregivers suffer significant impacts throughout the care process and as the disease progresses, such as having to deal with changes in health status, impotence, frustration, depression and increased burden, due to the effects and consequences of HSCT. The way in which the family and caregiver evaluate and manage overload situations depends on multiple factors, such as the existence or absence of social supportnetworks[11-13].

Caregiver burden occurs when the demands of care exceed the personal and social resources available to the caregiver. This can compromise the various dimensionsof life and lead to a variety of negative consequences such as physical and mental exhaustion, health problems, anxiety and depression, deterioration of social relationships,disruptions in your occupational life, loss of well-being and quality of life[7].

This study sought to understand what changes can be observed in the occupational life of informal caregivers of people with hematopoietic stem cell transplants, considering their multidimensionality (physical, emotional, social, spiritual and occupational) and what coping strategies are used by informal caregivers of hematopoietic stem cell transplant recipients. bone marrow, to cope with overload and toreorganize your daily occupational life.

MATERIALS AND METHODS

This is a study with qualitative methodology, with in-depth interviews based on a script with guiding questions developed by the researchers. The selection of participantswas carried out through an active search and recommendations from professionals from the multidisciplinary team of the Bone Marrow Transplant Unit (UTMO) of a general, public, university and highly complex hospital. Six (6) caregivers of onco-hematologicalpatients who underwent allogeneic HSCT were included.

All interviews were carried out by the researcher between June 2023 and March2024, in a reserved room within the UTMO, guaranteeing the necessary privacy. They were audio recorded with the participant's consent and later transcribed in full.

Following these study inclusion criteria: being the main informal caregiver of people with onco-hematological diseases, undergoing allogeneic HSCT and who were inhospital in the post-spinal cord infusion phase, six (6) informal caregivers of patients wereinterviewed allogeneic and onco-hematological bone marrow transplants.

After clarification and signing of the Free and Informed Consent Form, data on the sociodemographic characterization of the caregivers participating in

the study and the clinical characterization of the transplanted person were collected. Next, the participantswere interviewed based on the following guiding research question: "Has playing the role of caregiver for a bone marrow transplant patient had an impact on your occupational life?"

This research followed the ethical requirements established in accordance with Resolution no. 466 of December 12, 2012[14], being approved by the Ethics Committees of the institution where the work was carried out (CAAE: 64066622.9.0000.5393) on 05/29/2023.

The information from the sociodemographic and clinical questionnaire was tabulated and analyzed in a simple descriptive way. The interviews were fully transcribed and the academic software MAXQDA - Distribution by VERBI GmbH was used to assist in data management and categorization of thematic groups. Based on the exhaustive reading of the data obtained in the interviews, following the six proposed stages of exploring the material[17] and with categorization using the MAXQDA software, two thematic units and sub-themes were established, which will be described below.

RESULTS AND DISCUSSION

The data presented in the following table demonstrate the results of the sociodemographic questionnaire according to the composition of the sample in terms of age, sex, ethnicity (color or race), marital status, religion and education of the informal caregivers who participated in the research.

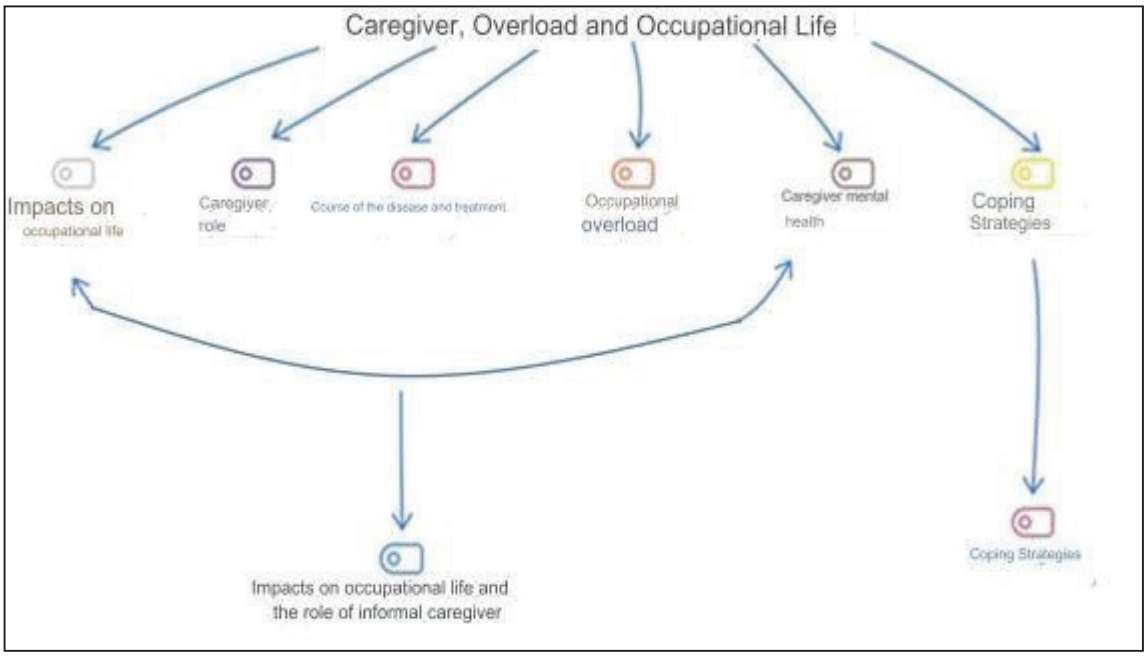
Most participants were female, married and with religious beliefs. It is noteworthy that the only man participating in the research was also the youngest person, an atheist and with completed higher education.

TABLE 1. Sociodemographic characterization of informal caregivers, 2024.

VARIABLES	DATA	FREQUENCY (N)	%
Age	20 to 30 years 31 to 41 years 42 to 52 years 53 to 63 years	1 2 2 1	16,66 33,33 33,33 16,66
Sex	Female Male	5 1	83,33 16,66
Ethnicity	White Brown	3 3	50 50
Civil state	Single Married Divorced Widower	1 3 1 1	16,66 50 16,66 16,66
Religion	Catholic Evangelical Atheist	4 1 1	66,67 16,66 16,66
Education	Incomplete elementary education Incomplete high school Complete high school Complete higher education	3 1 1 1	50 16,66 16,66 16,66

Related to the clinical characterization of the transplanted person, three subjects were diagnosed with myelodysplastic syndrome, one with T-cell lymphoma, one with myeloid leukemia and one with idiopathic myelofibrosis. Following the research inclusion criteria, all underwent allogeneic transplantation: two were haploidentical, twowere unrelated, via bone marrow bank, and two were related.

FIGURE 1. Code map – Thematic units



INTERVIEW WITH STUDY PARTICIPANTS

Based on exhaustive reading of the topics covered in the interviews and categorization using the MAXQDA software, similarities were identified in the reports based on data analysis.

In this way, two thematic units were established: Impacts on occupational life and the role of informal caregiver; Coping strategies for managing informal caregiver burdens, which will be better described below:

THEMATIC UNIT 1: IMPACTS ON OCCUPATIONAL LIFE AND THE ROLE OF INFORMAL CAREGIVER

In this category, topics related to caregivers' perception of the causes andconsequences of overload related to the exercise of the occupational role of caregiver were addressed.

SUB-THEME 1: COURSE OF THE DISEASE AND TREATMENT

The caregiver's participation is essential for carrying out HSCT, including intra- and extra-hospital care.

The exhausting journey faced by caregivers and transplant recipients throughout the illness and treatment is permeated by diagnostic challenges, difficult therapeutic decisions and the incessant search for effective and sustainable relief from pain, symptoms and suffering, emphasizing the critical need for support emotional, informational and practical for those at the center of the fight against cancer.

Even before a patient begins the procedures for a bone marrow transplant, other types of treatments occur, such as chemotherapy, radiotherapy and the use of medications, also beginning the family caregiver's care trajectory[13].

In this sense, four caregivers reported that until understanding and diagnostic investigation, the family was faced with the insecurity of not understanding what was happening to their family member's health.

> *"It was horrible. Then they returned her and it was another struggle, because she was admitted to the ICU again and there was more bleeding, because there was no treatment... We started moving to go to a teaching hospital, because I thought that was where she would have more support.Because, as I didn't know what the disease was, it probably had to be something rare, right? " (A.P., 25 years old, male, son)*

The search for effective treatment and the constant adjustment to the progression of the disease generate significant and prolonged emotional stress, which caregivers and transplant recipients must face. Authors have examined this psychological dimension, onhow caregivers process the continuous changes and challenges imposed by illness and treatment, and emphasized that uncertainty causes constant anguish[16].

At the same time that some caregivers referred to the uncertainty about undergoing HSCT, the grief of receiving an oncological diagnosis and the occupational changes brought about by the treatment within the family, they also demonstrated the expectation for marrow compatibility between donor and recipient, with the hope of healing.

In V.S.'s specific case, the transplant recipient's informal caregiver was also thedonor who was 100% compatible with her brother. for bone marrow donation, with the hope of the loved one's recovery.

> *"The day I received the news, I said: I don't believe I'm going to be able to do anything. You feel like: "I'm going to be able to do something". Because I was very excluded from the family, that was the cool part." (V.S., 54 years old, female, sister)*

Thus, in addition to physical and emotional care, HSCT involves complex aspects of socio-family relationships. Interviewee C.R. also mentioned the need for psychological support for himself and his family, reflecting the recognition of the emotional burden that cancer diagnosis and treatment bring. The need for emotional andsocio-family support was highlighted by researchers as fundamental pillars for managingcaregiver burden[4].

> *"We are worried, right, because we are afraid of bleeding, falling, hitting our head and bruising our heads, because it is a very delicate case, you know. So I was always worried... His blood pressure went up, he had a high fever, he vomited, he even ended up choking. But each case is different. But we have to be prepared for everything too."(E.O, 47 years old, female, wife)*

In the transplant process, new events require new knowledge and readaptations on the part of the informal caregiver.

SUB-THEME 2: NEW OCCUPATIONAL ROLE

The person who previously enjoyed the occupational roles of daughter, wife, sister, worker, among others, in the context of onco-hematological treatment or during hematopoietic stem cell transplantation, assumes a new occupational role of informal caregiver[13,17].

This new role is complex and multifaceted, including challenges and discoveriesthat reshape everyday life and perceptions of self and the world.

> *"At first we feel a little like that, a little lost. But now, as they say, I'm an expert. " (C.R., 39 years old, female, wife)*

> *"We go through all this, but everything has a reason in our lives... It's not easy to stay in one place... it feels like I'm in prison." (E.O, 47 years old, female, wife)*

The caregivers' statements reflect not only a journey of adaptation, but also a transformation of their capabilities and skills. The new occupational role of caregiver goes beyond daily tasks and penetrates the sphere of interpersonal relationships and identity itself.

Authors discuss how caregivers use electronic health portals to manage care, something that can empower caregivers by providing them with critical

information andcontrol over the situation. This can help mitigate some of the uncertainty and constant worry associated with your occupational role[18].

The caregiver's ability to adapt to this new role involves both resilience and grief,where successful adaptation depends on a combination of personal support, developed competence and the strategic use of available resources. There is a need for ongoing care,education and emotional support for caregivers throughout the patient's treatment process.This holistic view recognizes the burden and contribution of caregivers, suggesting the need for targeted interventions to improve their quality of life and that of the people caredfor.

Thus, support systems must provide a context for caregivers' experiences and allow for more effective management of the situation experienced by the caregiver. For some scholars, this can at least partially alleviate caregivers' fears regarding imminent risks to their health[18].

Care also encompasses the defense of patients' rights and the resolution of legal and bureaucratic issues, which is a form of care that is often invisible, but crucial. This aspect is explored by researchers, who recognized the wide range of needs of family caregivers, extending to administrative and logistical challenges[19].

The absence of an effective rotation system between different caregivers and thelack of recognition of the caregiver's work can lead to feelings of isolation and resentment,which contributes to caregiver burden. C.R. reports pressure from the family and the unwillingness of other family members to share care responsibilities[4].

> *"It's a lot of pressure from his family on me... the family thinks I'm the only one who has to stay here, no one wants to take turns with me. " (C.R., 39 years old, female, wife)*

The lack of a social support network is a significant challenge that requires attention in the development of care strategies for caregivers, ensuring that care can be shared in a more equitable and sustainable way within the family environment.

SUB-THEME 3: THE OCCUPATIONAL OVERLOAD OF THE INFORMAL CAREGIVER OF A BONE MARROW TRANSPLANT PATIENT

The interviews demonstrated that the repercussions on the participants' occupational lives are intrinsically related to the disease and the treatment of the bone marrow transplant recipient. In relation to work, for example, the caregiver faces the needto take time off work to provide support to the transplant recipient during the HSCT process, resulting in loss or reduction of income and professional challenges[11].

Caregivers like C.R. and E.S. often face the difficult decision of leaving their jobs or reducing their hours to provide the care needed by the patient. This not only compromises income and financial security, but can also lead to career challenges and a sense of loss of professional identity and purpose. E.S. suggests that this sacrifice is madein the hope of a future recovery of the loved one, demonstrating an investment in the health and well-being of the transplant recipient.

> *"I had to resign... After he got better, my boss said I should come back. But whatever we do, we can find something else. You have to have positive thinking" (E.S., 48 years old, female, mother).*

The occupational overload of informal caregivers of bone marrow transplant patients is a current reality that significantly affects their lives. The literature suggests thatburden can be alleviated by recognizing the multiple occupational roles of the caregiver and implementing support strategies that address occupational, emotional and informational needs. It is crucial that interventions are targeted to support carers in maintaining their own occupations whilst managing the care of their loved ones, to avoiddisrupting the balance in their lives and promote ongoing wellbeing[20].

Caregivers' reports about the financial impacts on the lives of the caregiver and family highlight a difficult reality, where the demands of health treatment can impose a substantial financial burden. Families are faced with the challenge of restructuring their savings to accommodate the costs associated with ongoing treatment and, often, additional expenses related to travel and accommodation.

In addition to the impacts on work and financial management, leisure and recreational activities were also highlighted by participants as occupations that were no

longer carried out regularly. Intense dedication to care often restricts the time available for leisure activities and hobbies, negatively impacting the caregiver's quality of life. Furthermore, HSCT care itself, due to neutropenia or other immunological limitations ofthe transplant recipient, makes it difficult to perform these activities[21].

> *"Saying like "ah, let's go to a barbecue" and you wouldn't go. So my life was left." (E.S., 48 years old, female, mother)*

> *"Occupational overload is the main one, especially for leisure. Because it made it impossible to see my friends and go out, as usual, to be with my mother." (A.P., 25 years old, male, son)*

Researchers recognize that caregivers tend to prioritize the health needs of the sick person over their own needs for leisure and social participation. This change in focus can have negative repercussions on the caregiver's occupational life balance, contributing to increased overload and decreased quality of life[21].

Caregiver E.S. reflected on the fact that the transplant recipient's health condition often dictates the caregiver's leisure possibilities, limiting participation in traditional social activities, such as family events. A study highlights opportunities for leisure and rest as important psychosocial needs of caregivers[19].

Furthermore, understanding the requirements of the bone marrow transplant unit regarding intense and specific care for the transplant recipient, in order to avoid and prevent opportunistic infections, informal caregivers experience social isolation together with their family member, including separation from family members and friends[22].

Caregivers E.S. and M.R. highlighted the monotony and confinement in the hospital space, which contrasts sharply with the dynamism of everyday life. AND THE. expressed a feeling of imprisonment, despite recognizing the need for isolation to care

for their family member. This feeling of seclusion is corroborated by scholars, who recognize the psychosocial difficulties faced by caregivers, including loneliness and isolation[19].

Experiments described by C.R. and E.O. highlight the difficulty of performing simple and essential tasks such as taking a shower, changing clothes and maintaining an adequate diet, due to immersion in the hospital environment and the constant demands of care. This impairment of Activities of Daily Living is recognized in the literature as an aspect of caregiver burden, where attention is so focused on the person being cared for that the caregiver's basic needs are neglected[12].

> *"The nurse said: "you can't bring a lot of clothes, because the room is very small", do you understand? Then there are days when I wear a skirt and blouse for 2 days, then I go there and wash it. " (E.O, 47 years old, female, wife)*

E.S. expressed a common concern among caregivers: the need to maintain somelevel of self-care and normality in their lives, such as taking care of their appearance. This need for self-care is often placed on the back burner when faced with the demands of caring for a family member, but it is a critical component to maintaining the health and well-being of the caregiver.

> *"It's not because I'm a mother, that's right, I'm the one who has to take care of him. And so? Who's taking care of me? I'm getting by myself. I think I feel it. " (E.S., 48 years old, female, mother)*

E.S.'s quote, "Who is taking care of me?" highlights the need for support for caregivers. Researchers have recognized the importance of addressing caregivers' needs,

not only in terms of information and communication, but also in supporting self-care, which is fundamental to their ability to effectively care for others[22].

Informal caregivers frequently highlighted the interruptions of sleep and rest during hospitalization and the pre- and post-bone marrow infusion stages, given the need to remain awake at all times, due to the intense demands of care and also complications, such as nausea, vomiting, physical, emotional and occupational debilitation of the person being accompanied. As a result, sleep disturbances are often noticed[16].

Only two participants - the 25-year-old male caregiver, son of the transplant patient, and V.S., sister and donor of one of the patients with myelodysplastic syndrome - did not complain about interruptions in sleep, rest and eating, being able to adapt to hospital routine.

The experience of caring in an intra-hospital environment of extreme isolation, ina HSCT unit, will not be the same for all informal caregivers, and may be correlated withthe way they see the treatment, as well as what coping strategies they use.

Repercussions on caregivers' health management reported by C.R illustrate a reality where the need to care for others leads to neglect of the caregiver's own well-being.This issue is critical, especially for those already dealing with chronic pathological conditions, as evidenced by the studies cited[4, 17-18, 23-24].

> *"I had an appointment next week, but I won't be able to go to the appointment anymore, right? Because I'm going to be here." (C.R., 39 years old, female, wife)*

In addition to the changes in Activities of Daily Living, it was possible to understand the effects on the participants' Instrumental Activities of Daily Living,

increasing occupational overload, such as: caring for others, other than the sick person; financial management; community mobility and driving; religious and spiritual expression.

SUB-THEME 4: MENTAL HEALTH AND THE INFORMAL CAREGIVER OF BONE MARROW TRANSPLANT PATIENTS.

The mental health of informal caregivers of patients undergoing stem cell transplantation is severely impacted by the emotional and physical demands of the treatment process. As analyzed in a study, HSCT is not only a physical challenge for thetransplant recipient, but also an emotional ordeal for the caregiver, who must face not only the daily stress of care, but also the psychological impact of seeing a loved one in suffering[20].

Participants' accounts vividly illustrate the consequences of this ongoing stress. AND THE. describes episodes of anxiety and physical tremors as a direct response to thestress of caring for a critically ill loved one. This type of reaction is typical in situations where caregivers are in a constant state of alert, ready to respond to any new medical complication. The pressure to remain vigilant disrupts not only your sleep but also your ability to relax, contributing to a chronic state of tension and anxiety.

> *"These days I even had an anxiety attack, when he felt sick, my leg started to tremble non-stop... There's no point in getting your hair disheveled, except when he's feeling sick, and then I'm scared of something happening. thing" (E.O., 47 years old, female, wife).*

Many of the participants highlighted the impacts on their mental health throughout the treatment, brought about by feelings of anguish, unforeseen events, perspective of the present and future, uncertainties and fears. Furthermore, there was a concern about correctly carrying out care, especially in times of greater debilitation of the sick person or complications. These factors coincide with findings in the literature[16].

In addition to caring for their own mental health, there was concern on the part of informal caregivers about the mental health of the transplanted person and other family members, since the reflexes and impacts of HSCT transcend and permeate the entire family dynamic. Often, caregivers suppress their pain, fears and concerns in favor of supporting their family members, especially the transplant recipient[7, 26-27].

> *"People say: "Ah, but stay there and everything will be fine", I know, but it's difficult, because you stay in there and I can't tell him (the transplant recipient) what I'm feeling, understand? " (E.S., 48 years old, female, mother).*

> *"Because the suffering you are going through is enough, you have to take care of it and family disturbances are still on your mind" (C.R., 39 years old, female, wife).*

The possibility of planning for transplant care, depending on the diagnosis or severity of the patient's condition, was considered a negative factor, when carried out unexpectedly, and positive, when there is already knowledge, preparation and waiting for HSCT, being seen as the possibility of improvement and healing.

One of the participants described, even with all the arduous conditions of care and understanding the entire scenario experienced by her brother during the transplant, the importance of reflecting on the importance and preciousness of life:

> *"You know, it's an example I'm going to give: "guys, let's live. For the love of God, let's live." If I liked living before, now I like it even more." (V.S., 54 years old, female, sister)*

The mother of one of the transplant recipients reflected on how her son's bone marrow transplant was an important part of a process of self-construction and internal andexternal knowledge, as she previously did not understand what an onco-hematological disease was and what HSCT.

Regardless of the causes of informal caregiver burden, understanding and addressing these impacts is crucial to improving the support offered to family caregivers. Targeted interventions, such as psychosocial support programs, support groups and guidance on work-life balance strategies, are essential to mitigate the challenges faced bythese caregivers during and after the HSCT process.

By recognizing the importance of the caregiver's occupational life, it is possibleto promote a healthier and more sustainable environment for everyone involved in the care of bone marrow transplant patients.

THEMATIC UNIT 1I: COPING STRATEGIES FOR MANAGING INFORMAL CAREGIVER BURDENS.

Informal caregivers need to find ways to withstand uncertainty, fears, worries, anxiety and disruptions. Although HSCT produces negative impacts on the mental health

and occupational life of informal caregivers, coping strategies can help establish adaptive processes to new demands and impacts on occupational life[27]. However, when these strategies are not sufficient to reduce the effects of overload, a decline in the caregiver's quality of life may occur, leading to exhaustion and burnout.

There were several coping strategies mentioned by the participants in this study, to minimize the impacts and facilitate adaptation to the experience of hematopoietic stem cell transplantation. Among them, the importance of pre-HSCT guidance and knowledge stood out, either through the guidance of health professionals or through the initiative and interest of the caregivers themselves for greater discoveries and learning:

> *"I studied and researched the disease and transplantation on my own initiative. I tried not to worry my mother and father" (A.P., 25 years old, male, son).*

Another effective strategy mentioned by participants was maintaining occupational engagements, such as work and leisure, even during hospitalization, to preserve a sense of normality and continuity in their lives[28]. Remote work, for example,not only maintains financial income, but also offers a way to face the demands of the hospital environment.

Caregiver E.S. reported that she found comfort in reading, while E.O. uses brief authorized exits to breathe fresh air, emphasizing the importance of contact, even if limited, with the outside world.

A common aspect for all female participants was considering religion, faith and spirituality as important sources of security and coping, especially to deal with the most challenging moments of HSCT. The use of a spiritual approach is often seen as

comforting, given the awareness that there is no way to control all circumstances andevents[28].

> *"There was another woman who died some time ago who had a transplant and couldn't cope. So you see a lot of things, you see people "disappearing" around us, so this strength doesn't come from me. It's coming from God, isn't it?" (E.O., 47 years old, female, wife).*

> *"When I found out that I was going to be his donor, the first thing I did, after just one week, was to pray for the people who were passing by, the room we were going to stay in, all of that. It's something that I see that God had already prepared. All people. I really believe in that" (V.S., 54 years old, female, sister).*

Spirituality is a human dimension that gives meaning to life and purpose to existence. For some participants, it is a continuous and daily strategy to confront what is needed to improve the ill person's health.

Corroborating the analyzed findings, the results of this research also pointed out as coping strategies, the comparison of more critical clinical cases with family care, as away of alleviating and dealing with complications more positively and with hope[20].

> *"Everyone in the room, I don't know (other transplant recipients). So it's not just me, right, so we have to think positive. " (E.S., 48 years old, female, mother)*

Social support was mentioned as a vital component in coping strategies, as well as mutual support between caregivers and transplant recipients and between them and other family members. The ability to share responsibilities and receive encouragement from other family members and friends can significantly ease the caregiver's burden, allowing them time to rest and recover:

> *"That's how it is there (support house), we can change more often, right. Because you can't do it inside the hospital. (...) my brother will help me, he will also stay with her. " (M.R, 40 years old, female, daughter)*

> *"Because I help him (transplanted husband) and he helps me... It's like that, one helping the other." (E.O. 47 years old, female, wife)*

Establishing a routine, even within the restrictions of the hospital environment, was a coping strategy reported by E.S. to maintain some form of control over your day to day life. The participant described how creating mental visualizations of home helped her cope with uncomfortable situations and maintain emotional balance.

Regardless of the coping strategies used - maintaining religion, faith and spirituality, socio-emotional support from the caregiver-transplant dyad and other family members, friends and community, guidance and support from the multidisciplinary team or maintaining your occupational life as much as possible. possible – they can alleviate the negative situations of HSCT.

The coping strategies adopted by caregivers need to be recognized and supported by multidisciplinary health teams. Healthcare professionals must provide not only clinical guidance but also psychological, educational and spiritual support, tailoring interventions to meet the individual needs of caregivers. These collaborative efforts can increase the effectiveness of coping strategies, resulting in better outcomes for both patients and their caregivers.

Therefore, comprehensive care in the context of HSCT must encompass both physical and mental health, as well as spiritual and occupational health, considering the full extent of the treatment's impacts on the lives of those involved.

CONCLUSION

Hematopoietic stem cell transplantation (HSCT) represents a vital therapeutic approach for a wide variety of oncological and hematological diseases. Although promising in terms of treatment, the impact of this intervention is not restricted to the patient alone, extending to informal caregivers.

Informal caregivers play a crucial role in providing emotional, physical, spiritual, occupational and practical support to patients undergoing HSCT. However, they often face significant challenges that can result in substantial burden. One of the challenges lies in the intensive and prolonged nature of the care required during the transplant and post- transplant recovery process. Managing side effects, frequent visits to healthcare facilities and adapting to changes in living conditions directly impact the experience of informal caregivers.

Caregivers often face issues related to mental health, such as stress, depression and anxiety, due to the emotional burden associated with accompanying the patient on their journey. The gap in recognizing and addressing these issues can compromise not only the well-being of caregivers, but also the overall effectiveness of the transplanted person's recovery process.

The transition from the hospital environment to the home represents another critical point in this process, which worsens the burden on informal caregivers. The lack of adequate resources and detailed information about post-transplant management can contribute to caregivers' anxiety and exhaustion.

To mitigate the burden on caregivers, it is necessary to have a deep understanding of support and coping strategies that can improve the quality of life of both patients undergoing bone marrow transplantation and their informal caregivers.

Considering the growing importance of the role of informal caregivers in the context of HSCT, it is imperative to direct future research towards the development and implementation of effective interventions by the multidisciplinary health team, particularly occupational therapy, given the repercussions on life and occupationalperformance. The identification of innovative and personalized strategies, adapted to the specific needs of caregivers, can contribute to mitigating burden and strengthening the support offered during the transplant process.

Finally, it was possible to understand the effects of care on occupational life and reflect on the importance of developing more effective and caregiver-centered interventions, thus improving the overall quality of care provided to patients undergoing HSCT and to those who perform a vital role in your recovery process.

IMPLICATIONS FOR PRACTICE AND RESEARCH

The present study brings contributions to public health, as it contributes to a better understanding of the impacts of overload on the occupational life of informal caregivers of people with bone marrow transplants and to better offering services in the treatment process of transplant patients.

LIMITATIONS

Given the specific objective of this research and the exclusion criteria for data collection, non-onco-hematological patients and children were not included in the sample. Furthermore, as the Bone Marrow Transplant Unit of the Hospital where the study was carried out has only 5 beds for allogeneic transplants, with two beds intended for pediatric HSCT, the small number of beds and hospitalizations made it difficult to recruit a larger number of patients. participants.

Due to the isolation and intense care requirements of a HSCT unit, some caregivers were unable to participate on the research data collection day due to complications with patients or contact isolation due to some bacteria.

The literature review was based on an extensive bibliographic search, however, no articles by Brazilian authors and occupational therapy professionals on the topic related to the current study were found. Therefore, more studies by occupational therapists on the subject are suggested, especially of a qualitative nature and on the perception of caregivers, in order to improve strategies that alleviate the overload of the task of caring for a bone marrow transplant patient, especially in the regarding impacts on occupational life.

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

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PRE-TRANSPLANT SCREENING FOR MMP-9 IN ALLOGENEIC HSCT CANDIDATES

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ABSTRACT:

PURPOSE: InflammaDry® (Quidel Eye Health, San Diego, California), an FDA-approved point-of-care commercial test, measures matrix metalloproteinase-9 (MMP-9) levels in the tear film. MMP-9 is an inflammatory biomarker that is elevated in response to ocular surface stress, particularly observed in ocular graft-versus-host disease (oGVHD). The purpose of this study is to assess the prevalence of MMP-9 positivity and a score >4 on the OSDI-6 questionnaire in patients before allogeneic hematopoietic stem cell transplant (HSCT). **METHODS:** A prospective, observational, cross-sectional single center pilot study was conducted among 23 patients (46 eyes) undergoing planned allogenic HSCT. InflammaDry® results, OSDI-6 questionnaire results, and development of oGVHD were collected. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and chi-square test were calculated. **RESULTS:** InflammaDry® demonstrated high sensitivity (1.0) but low specificity (0.1429) for oGVHD development. The PPV was 0.25, while the NPV was 1.0. No statistical significance was found between InflammaDry® result and development of oGVHD (p-value> 0.05). **CONCLUSION:** InflammaDry® is not an effective tool for detecting the onset or predicting the risk of developing oGVHD. A significant percentage of patients exhibited ocular inflammation before allogeneic HSCT, suggesting that initiating prophylactic treatment could be valuable in reducing oGVHD development.

KEYWORDS: Matrix Metalloproteinase 9. Graft vs Host Disease. Transplantation, Homologous.

INTRODUCTION

Ocular graft versus host disease (oGVHD) is a serious complication that impacts many patients following allogeneic hematopoietic stem cell transplant (HSCT) and is associated with significant ocular morbidity and decreased quality of life. The pathophysiology of the development of oGVHD is not well-defined, but it is thought to be a complex interplay of T cell mediated damage to the lacrimal glands, eye lids, conjunctiva, and cornea.[1] Risk factors for developing oGVHD include being a male recipient of a female donor; skin, oral mucosa, liver, or GI tract involvement in acute or chronic stages of GVHD; lung involvement in chronic GVHD; history of diabetes mellitus; Epstein-Barr Virus (EBV) positive donors; and patients of Asian descent.[2] Furthermore, the prevalence of developing oGVHD is increasing as it currently affects 30-60% of patients who undergo HSCT and 60-90% of patients with systemic graft versus host disease (GVHD).[1-4]

The ocular manifestations associated with oGVHD include meibomian gland dysfunction (MGD), mechanical eyelid disorders (trichiasis, ectropion, entropion, lagophthalmos), persistent epithelial defects (PED), infectious keratitis, corneal scarring, conjunctival injection and chemosis, keratoconjunctivitis sicca, cicatricial conjunctival fibrosis, corneal perforation, and filamentary keratitis. It can also present with various ocular symptoms including redness, photophobia, excessive tearing, blurry vision, irritation, grittiness, foreign-body sensation, or burning.[1] These symptoms significantly impair vision and reduce the quality of life of these patients. A study employing the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), designed to evaluate patients' perception of their visual health status and the impact of ocular disease on their quality of life, revealed that in comparison to healthy populations without eye disease, individuals with oGVHD exhibited heightened levels of ocular pain, vision-specific role limitations, vision-specific mental health symptoms, challenges in near and distance vision, difficulties in general vision activities, increased vision-specific dependency, peripheral vision issues, and compromised general health.[5]

The diagnosis of oGVHD is based on diagnostic criteria proposed by the International Consensus Group of Ophthalmologists in 2013. The specific clinical parameters to assess oGVHD are as follows: (1) Schirmer's test without anesthesia, (2) corneal fluorescein staining, (3) conjunctival injection, and (4) ocular discomfort symptoms rated by the Ocular Surface Disease Index (OSDI). The variables are scored, and the total is used to determine disease severity (Table 1).[6]

Previously, the diagnosis of graft-versus-host disease (GVHD) was based on categorizing as acute, developing within 100 days of HSCT, or chronic, developing after 100 days following HSCT.[8] However, the NIH adjusted diagnosis guidelines to be based on the organs involved in manifesting symptoms, which then determine the difference between acute GVHD and chronic GVHD diagnosis. Specifically, symptoms involving the eye are a distinctive finding of chronic GVHD.[9]

The difficulties in the management of oGVHD are the early recognition of symptoms by the hematology/oncology providers and prompt referral to an eye care provider for evaluation. Education and training have been shown to significantly reduce the time interval between onset and symptoms to referral.[10] This is critical to identify patients in the initial stages of oGVHD and to prevent cicatricial changes to the ocular surface and vision loss. While symptom development is a key factor in recognizing the onset, studies have shown that varieties of inflammatory cytokines are present in the precorneal tear film.[11] One of the prominent cytokines is matrix metalloproteinase-9 (MMP-9).

MMP-9 is an endopeptidase that is secreted into the tears and can break tight junctions of the ocular surface epithelium, resulting in loss of ocular surface barrier function and desquamation. Multiple studies have demonstrated a significant correlation between the degree of MMP-9 elevation and clinical severity of ocular surface disease.[12-16] InflammaDry® is positive in 84.6% of patients with ocular surface disease and positive in only 6.3% of patients without ocular surface disease.[16] A recent study has shown that MMP-9 is present in over 90% of patients that have been diagnosed with oGVHD.[17] The presence of MMP-9 was shown to be present in all stages of oGVHD and persistent regardless of symptoms or therapeutic measures. An FDA approved point-of-care commercial test, InflammaDry®, a lateral flow immunoassay, was used in this study and is widely available to measure MMP-9 presence in ocular sur-

face disease patients. This test is easily administered, requires no topical anesthetic, and has minimal risk to the patient. The results can be scored as either positive or negative or can be graded on an ascending scale of 0 for a negative presence to 4, indicating a marked presence of MMP-9.[18] However, it is not known if MMP-9 is present pre-transplant in allogeneic HSCT candidates due to other chemotherapy or preconditioning procedures. If so, then testing with InflammaDry® after allogeneic HSCT would be inconclusive. Additionally, if there is MMP-9 present prior to allogeneic HSCT, pretreatment of any ocular surface inflammation could be advantageous to reduce any contributing factors in developing and exacerbating oGVHD.[19] Therefore, the purpose of this study is to determine whether MMP-9 is present prior to allogeneic HSCT using InflammaDry®.

METHODS

A prospective, observational, cross-sectional single center pilot study was conducted aimed at gathering InflammaDry® data on eligible participants undergoing planned allogeneic HSCT. This study was approved and conducted in compliance with the Medical College of Wisconsin's Institutional Review Board. The primary outcomes for this study were 1) Percent of patients who test negative on the InflammaDry® test; 2) Percent of patients who score less than 4 on the OSDI-6; 3) Percent of patients who test positive on the InflammaDry® test and 4) Percent of patients who score more than 4 on the OSDI-6. Further secondary exploratory outcomes of this study are 1) To investigate pre-transplant procedures or conditions that correlate with positive MMP-9 and 2) To establish if the presence of MMP-9 in the pre-transplant screening of allogeneic HSCT candidates would be viable screening tools in oGVHD. Prospective subjects, as defined by the inclusion/exclusion criteria, were considered for entry into the study. Determination if prospective subjects met the inclusion and exclusion criteria occurred by retrospective chart review of prospective subject's electronic medical records. Inclusion criteria required prospective subjects to be at least 18 years-old, the ability to consent, is scheduled for an allogeneic HSCT (and has not previously undergone an allogeneic HSCT) and the ability to read and speak English for completion of consent and OSDI-6 questionnaire. Exclusion criteria included prior diagnosis of ocular surface disease (keratitis sicca, meibomian gland dysfunction, infectious keratitis, exposure keratitis), prior use of topical ocular anti-inflammatories in the past 3 months, contact lens use prior to 1 month of examination, ocular surgery in past 3 months or ocular infection in past 3 months. Prospective subjects had to meet all inclusion criteria and none of the exclusion criteria in order to be considered for entry into the study. Of these prospective subjects, further retrospective chart review was completed to obtain additional background information. Information that was abstracted from the medical chart included cancer diagnosis as well as date of diagnosis; previous therapies prior to transplant [chemotherapy (including details of specific drugs), radiation (dose and location), immunotherapy, prior autologous transplants]; and ocular diagnosis (glaucoma, cataracts, ocular surface disease [dry eye, keratitis, lid malformation]).

Following retrospective chart review and determination of eligible prospective subjects, a subject was seen at their allogeneic HSCT consultation visit. The prospective subject was approached by a study team member who explained the study in detail, answered questions and provided a consent form to the subject. If the subject agreed to participate in the study, written informed consent followed by InflammaDry® and the OSDI-6 questionnaire were obtained. The InflammaDry® test was collected by a trained team member following manufacturer instructions (Figure 1). InflammaDry® results were recorded as either positive or negative and well as recorded on a scale of 0 to 4 (Figure 2).

InflammaDry® results were scored by two team members with the recorded result being an average of the two scores. External controls for each InflammaDry® package were performed with acceptable results for the positive and negative control.[20] The OSDI-6 questionnaire was completed by the subject and a score (0-24) was recorded. After informed consent, InflammaDry® and OSDI-6 were obtained, an additional retrospective chart review was completed for further medical history collection, including subject's age, gender, race, past medical history, and current medications. A follow-up phone call was performed by the principal investigator to determine if a subject experienced an adverse effect or had questions relating to the study or procedures performed.

Patients were followed for at least 12 months to monitor for development of oGVHD. Diagnosis of oGVHD was made using the oGVHD National Institutes of Health grading criteria.

Data analysis involved determining InflammaDry® sensitivity [number of patients who developed oGVHD with positive InflammaDry® result/ (number of patients diagnosed with oGVHD with positive InflammaDry® result plus number of patients diagnosed with oGVHD with negative InflammaDry® result)], specificity [number of patients without oGVHD diagnosis with negative InflammaDry® result/ (number of patients without oGVHD diagnosis with negative InflammaDry® result plus number of patients without oGVHD diagnosis with positive InflammaDry® result)], positive predictive value (PPV) [number of patients who developed oGVHD with positive InflammaDry® result/ number of patients with positive InflammaDry® result] and negative predictive value (NPV) [number of patients without oGVHD diagnosis with negative InflammaDry® result/ number of patients with negative InflammaDry® result]. Patients who died within analysis timeframe of 12 months were not included in calculations. Percent positivity [number of eyes with positive InflammaDry® result/ total number of eyes tested) *100] and percent negativity [number of eyes with negative InflammaDry® result/ total number of eyes tested) *100] was also calculated. A Chi-Square analysis was conducted to determine the statistical significance between InflammaDry® results and development of oGVHD. Furthermore, to evaluate InflammaDry® qualitative results, data were plotted with the x-axis as grade 0-4 and number of eyes as y-axis. Regarding evaluation of OSDI-6 questionnaire scores, all scores were used in the calculation of range, average and median along with percentage of scores ≥4 and percentage of scores <4.

RESULTS

Demographic data collected on study participants showed that the average age of subject was 61.52 years-old with an age range of 36 to 73. The races of the subjects were 91.30% White, 4.35% Black and 4.35% were of "other" race of which was not specified in the electronic medical health record. Of the sex of the subjects, 56.52% were male and 43.48% were female (Table 2).

The type of cancer each participant was diagnosed with was collected. These diagnoses included acute myeloblastic leukemia, acute lymphoblastic leukemia, prolymphocytic leukemia, aplastic anemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, myelofibrosis, angioimmunoblastic T-cell lymphoma, and chronic myelogenous leukemia. Additional information regarding bone marrow transplantation including donor demographics, source of stem cells, and condition regimens are documented. 100% of stem cells were sourced from donor peripheral blood (Table 2).

InflammaDry® results collected on 46 eyes (23 participants) showed 91.30% of eyes were positive for MMP-9 and 8.70% were negative. Of the eyes that tested positive, 32 eyes were trace positive, 7 were weak positive, 2 were positive and 1 was strongly positive (Figure 3).

A comparison of oGVHD diagnosis related to InflammaDry® results was completed (Table 3).

Each participant had either positive InflammaDry® results in both eyes or negative InflammaDry® results of both eyes, which allowed for this comparison to be possible. Of the participants who had positive InflammaDry® results, four developed oGVHD while twelve did not. Out of the four subjects who developed oGVHD, seven out of eight eyes had an InflammaDry® score of 1 (trace positive) while one eye had an InflammaDry® score 2 (weak positive). Of the participants who had negative InflammaDry® results, zero participants developed oGVHD. From these results, InflammaDry® sensitivity, specificity, PPV and NPV were calculated. InflammaDry® was found to have a sensitivity of 1, specificity of 0.1429, PPV of 0.2500 and NPV of 1. Chi-square analysis revealed a chi-square value of 0.64. With 1 degree of freedom, the p-value was >0.05, and therefore no statistical significance was found between InflammaDry® results and the development of oGVHD.

An OSDI-6 questionnaire was collected on all 23 participants. The scores ranged between 0 to 9 with an average score of 2.78 and median score of 2. The majority of participants (60.87%) had a score of less than 4 while 39.13% had a score of 4 or above (Figure 4). Of the four subjects who developed oGVHD, two had an OSDI score of 4 or greater (score of 4 and 5) while the other two subjects had an OSDI score of 1 and 0.

To further investigate potential reasons for positive InflammaDry® results, the history of ocular treatments and past medical history of the patients were evaluated (Table 4 and Table 5). Additionally, chronic GVHD characteristics and NIH score of oGVHD of participants who developed oGVHD were collected (Table 6).

DISCUSSION

While InflammaDry® was found to have a sensitivity and NPV of 1 in detecting oGVHD development, the specificity of InflammaDry® was low at 0.1429, meaning that this point-of-care test resulted in many false positives. Additionally, the PPV of InflammaDry® was low at 0.2500, meaning that while the majority of participants had a positive InflammaDry® result, few participants developed oGVHD. No significant difference was found between patients who developed oGVHD versus patients who did not develop oGVHD and their InflammaDry® result (p-value> 0.05). Overall, these results conclude that InflammaDry® has limited application in determining which patients are at risk of developing oGVHD. Furthermore, InflammaDry® was positive in 91.30% of eyes that were tested, meaning that most participants were experiencing ocular inflammation, whether symptomatic or asymptomatic. Literature has shown that prophylactic treatment may be helpful in reducing development of oGVHD; however, no participants in this study chose to initiate treatment. Given that the vast majority of eyes tested positive and that it can be assumed InflammaDry® would continue to test positive following completion of HSCT, InflammaDry® would not be a helpful tool for providers to use to help determine if a patient is developing oGVHD.

Each participant completed an OSDI-6 form with score result possibilities of 0 to 24. The higher the score indicates more severe ocular surface disease symptoms; however, even a score of 4 or more suggests that the participant has ocular surface disease.[21] OSDI-6 results show that most participants (60.87%) were experiencing little to no ocular surface disease symptoms and did not have ocular surface disease (Figure 4). In fact, the average OSDI-6 score was 2.78 and median score of 2. However, 91.30% of participants had a positive InflammaDry® test (Figure 3). This indicates ocular inflammation is present but participants are asymptomatic. This ocular inflammation may be secondary to multiple causes including history of chemotherapy, systemic diseases, history of ocular disease and ocular treatments. Four participants developed oGVHD, all of which had positive InflammaDry® tests of both eyes. Two of these participants had systemic autoimmune diseases; rheumatoid arthritis and rosacea, both of which have been shown to cause ocular inflammation.[22,23] The participant diagnosed with rheumatoid arthritis also had Type II DM, which is a known risk factor for the development of oGVHD.[3] The inflammation detected by InflammaDry® may also be due to history of ocular disease and treatments (Table 4).

Three subjects, each of which had positive InflammaDry® testing and one of which developed oGVHD, had previously undergone cataract surgery, which is highly associated with ocular surface disease and therefore may have caused ocular inflammation in these participants.[19] In contrast, one patient was receiving intravitreal bevacizumab for exudative macular degeneration. Subconjunctival bevacizumab has been shown to be effective in ocular surface disease treatment and can therefore decrease ocular inflammation.[24] However, this patient, who was not receiving other ocular treatments and did not have additional ocular diseases, had positive InflammaDry® results in both eyes, suggesting that another cause for ocular inflammation may be secondary to other medications this patient was receiving such as chemotherapy.

A limitation of this study is the small sample size. At the start of the study, it was expected that 35-40 subjects would be recruited over three months. However, over nine months 124 subjects were screened for eligibility. Of these subjects, 75 were eligible for participation following the inclusion and exclusion criteria. However, only 23 subjects were enrolled in the study. Reasons for non-enrolment were for the following reasons: subject not wishing to participate in study or team member was unable to meet with subject during their allogeneic bone marrow transplant consultation visit. To combat the low recruitment rates, an information pamphlet about the study was made and included in the information packet each patient received at their allogeneic HSCT consultation visit. The addition of the pamphlet was implemented two months after the study was initiated. However, given the continued difficulty of recruit-

ing patients after extension of study period, it was decided to conclude the study with only 23 participants. The small sample size may be a limitation of this study. However, despite the smaller than expected participant recruitment, the data shows strong evidence that InflammaDry® should not be used as a screening tool to detect the onset of oGVHD given that there was no significant difference in the development of oGVHD based on InflammaDry® results (p-value > 0.05).

Another limitation of this study is the generalizability. While the study recruited nearly a 50:50 ratio of genders (56.52% male and 43.48% female), this study lacked variability in the race of participants. The majority of participants (91.30%) were White. This lack of variety may have been secondary to the population that was being screened given that Whites have a higher rate of developing leukemia of all types as compared to Black and Asian-Pacific Islanders.[25]

Lastly, another limitation of this study is the amount of data that was able to be collected. Past medical history, treatment history and follow-up history were limited by the fact that only information gathered within our hospital system's electronic health record (EHR) was able to be collected. Any data (diagnoses, surgical history, past medical history, etc.) not documented in our system could not be collected or included in our data analysis. Additionally, there is the possibility of non-documentation of oGVHD development within the EHR, which could have further impacted our data collection.

CONCLUSION

Of the eligible participants undergoing planned allogeneic HSCT, 91.30% tested positive for InflammaDry®, suggesting participants were already experiencing ocular inflammation secondary to multiple factors including chemotherapy, systemic disease, or previous ocular therapies. However, only 39.13% of participants were noted to be experiencing ocular surface disease symptoms related to this detected ocular inflammation. Despite the evidence that these participants have MMP-9 present in their tear film, on patient follow-up after completion of allogeneic HSCT, InflammaDry® was found to have a low specificity of 0.1429 and low PPV of 0.25. No statistical significance was found between InflammaDry® result and development of oGVHD (p-value > 0.05). These data suggests that InflammaDry® would not be a useful tool to detect the onset of oGVHD nor would InflammaDry® be helpful to predict which patients are at risk of developing oGVHD. While InflammaDry® may not be the tool for earlier detection of oGVHD, this study clearly showed that a high percentage of patients have ocular inflammation prior to undergoing allogeneic HSCT. Therefore, initiation of prophylactic treatment may be the best option for decreasing risk of development of oGVHD. Given that oGVHD continues to be a cause of high morbidity and reduced quality of life of patients, further research should be completed to determine a test for earlier detection of the disease along with determining prophylactic treatment regimen.

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TABLE 1: Ocular Surface Disease Index (OSDI-6) developed by Dr. Heiko Pult and Dr. James Wolffsohn to efficiently detect ocular surface disease based on patient symptoms. Adapted from Pult, 2019.[7]

Ocular Surface Disease Index 6 (OSDI-6)					
	Constantly	**Mostly**	**Often**	**Sometimes**	**Never**
Light sensitivity	4	3	2	1	0
Blurred vision	4	3	2	1	0
Difficulty driving at night	4	3	2	1	0
Difficulty watching TV (or similar)	4	3	2	1	0
Ocular discomfort during windy conditions	4	3	2	1	0
Ocular discomfort in places or areas with low humidity	4	3	2	1	0

The scores for each symptom are summed to obtain a total score. If the subtotal score is greater than 4, ocular surface disease is likely present

TABLE 2. Demographic information of subjects; N=23. Demographic data collected includes age, race, gender, and diagnosis of participants; donor age and gender; and conditioning regimen and course of stem cells used for bone marrow transplant.

Demographics		
Age	Range (years)	Median (years)
	36-73	63
Race	Number of Participants	Percentage of Participants (%)
White	21	91.30
Black	1	4.35
Other	1	4.35
Gender	Number of Participants	Percentage of Participants (%)
Male	13	56.52
Female	10	43.48
Donor Age	Range (years)	Median (years)
	19-62	27
Donor/Patient Gender	Number of Participants	Percentage of Participants (%)
Female/female	8	34.78
Male/male	8	34.78
Female/male OR Male/female	7	30.43
Diagnosis at Transplant	Number of Participants	Percentage of Participants (%)
Myelodysplastic Syndrome (MDS)	7	30.43
Acute Myeloblastic Leukemia	4	17.39

Myelofibrosis	3	13.04
Acute Lymphoblastic Leukemia (ALL)	2	8.70
Chronic Myelomonocytic Leukemia	1	4.35
MDS/Myeloproliferative Neoplasm	1	4.35
Angioimmunoblastic T-cell Lymphoma	1	4.35
Chronic Myeloid Leukemia/ALL	1	4.35
T-cell Prolymphocytic Leukemia	1	4.35
Acute Undifferentiated Leukemia	1	4.35
Aplastic Anemia	1	4.35
Conditioning Regimen	Number of Participants	Percentage of Participants (%)
Reduced Intensity	20	86.96
Non-myeloablative	3	13.04
Source of Stem Cells	Number of Participants	Percentage of Patients (%)
Peripheral Blood	23	100

TABLE 3. Comparison of InflammaDry® test results to subjects diagnosed with oGVHD and subjects who have not been diagnosed with oGVHD. N=18 participants.

	Subjects Diagnosed with oGVHD	Subjects without Diagnosis of oGVHD	Total
Positive InflammaDry® Test	4	12	16
Negative InflammaDry® Test	0	2	2
Total	4	14	18

TABLE 4. History of ocular treatments in participants. Treatments of participants who tested positive for InflammaDry® are compared to treatments of participants who tested negative for InflammaDry®. N=23 participants.

Ocular Treatments in InflammaDry® Positive Participants	Number of Participants
Radial keratotomy	1
Bimatoprost	1
Cataract surgery	3
Fluoroquinolone topical antibiotic	2
Prednisolone acetate	1
Polyethylene glycol	1
Intraocular Avastin	1
Polyvinyl alcohol	2
No treatment	14
Ocular Treatments in InflammaDry® Negative Participants	
No treatment	2

TABLE 5. Past medical history (PMH) of participants. PMH of participants who tested positive for InflammaDry® are compared to PMH of participants who tested negative for InflammaDry®. N=23 participants.

Past Medical History in InflammaDry® Positive Participants	Number of Participants
Asthma	1
Hyperlipidemia	1
Rosacea	1
Spinal stenosis	1
Rheumatoid arthritis	1
Type II Diabetes Mellitus	1
Past Medical History in InflammaDry® Negative Participants	Number of Participants
Polycystic kidney disease	1
Hypertension	6
Hyperlipidemia	6
Migraine	2
Transverse myelitis	1
Coronary artery disease	2
Stroke	1
Thrombus (deep vein thrombosis, pulmonary embolism)	3
Type II Diabetes Mellitus	1
Calcium pyrophosphate deposition disease	1
Inflammatory arthritis	1
Asthma	1

TABLE 6. Characteristics of chronic GVHD of participants who developed ocular GVHD. N=4 participants.

Participant	Number of Sites Involved	Location of Sites Involved	NIH Score of oGVHD
1	3	Gastrointestinal, Skin, Eyes	3
2	3	Gastrointestinal, Skin, Eyes	2
3	2	Skin, Eyes	2
4	3	Gastrointestinal, Skin, Eyes	1

FIGURES

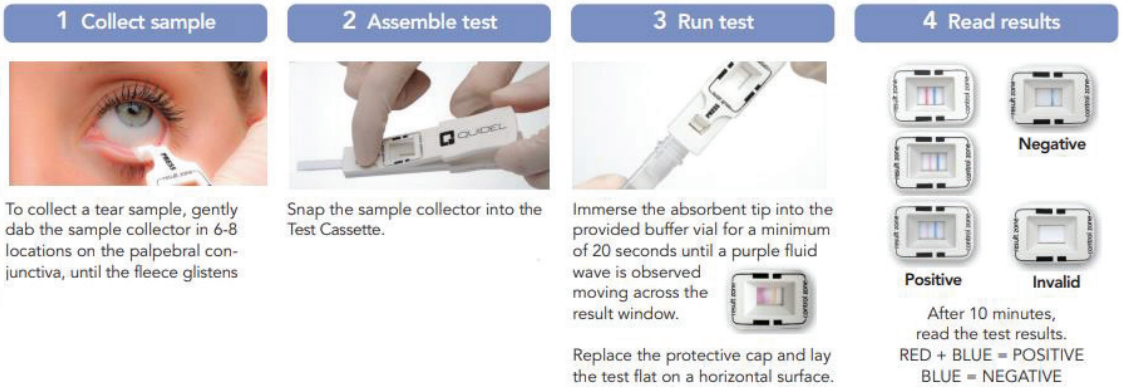


FIGURE 1. Four step process on correct usage of InflammaDry®, adapted from InflammaDry®, 2021.20 InflammaDry® Result

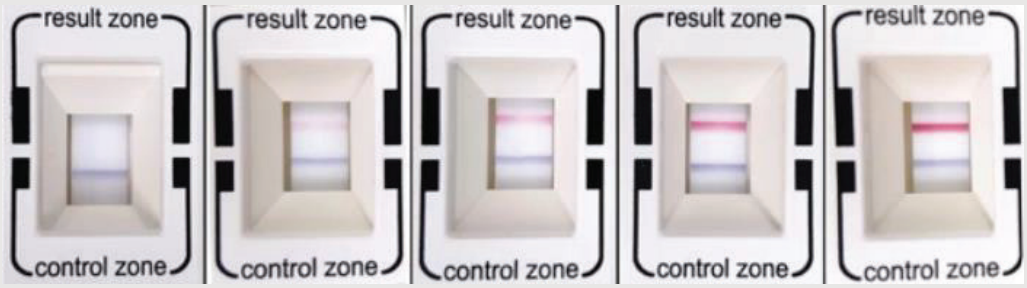
InflammaDry® Result					
	result zone / control zone	result zone / control zone	result zone / control zone	result zone / control zone	result zone / control zone
Interpretation	Negative	Trace	Weak Positive	Positive	Strong Positive
Grade	0	1	2	3	4

FIGURE 2. **InflammaDry® grading assessment, adapted from Kim, 2021.18**

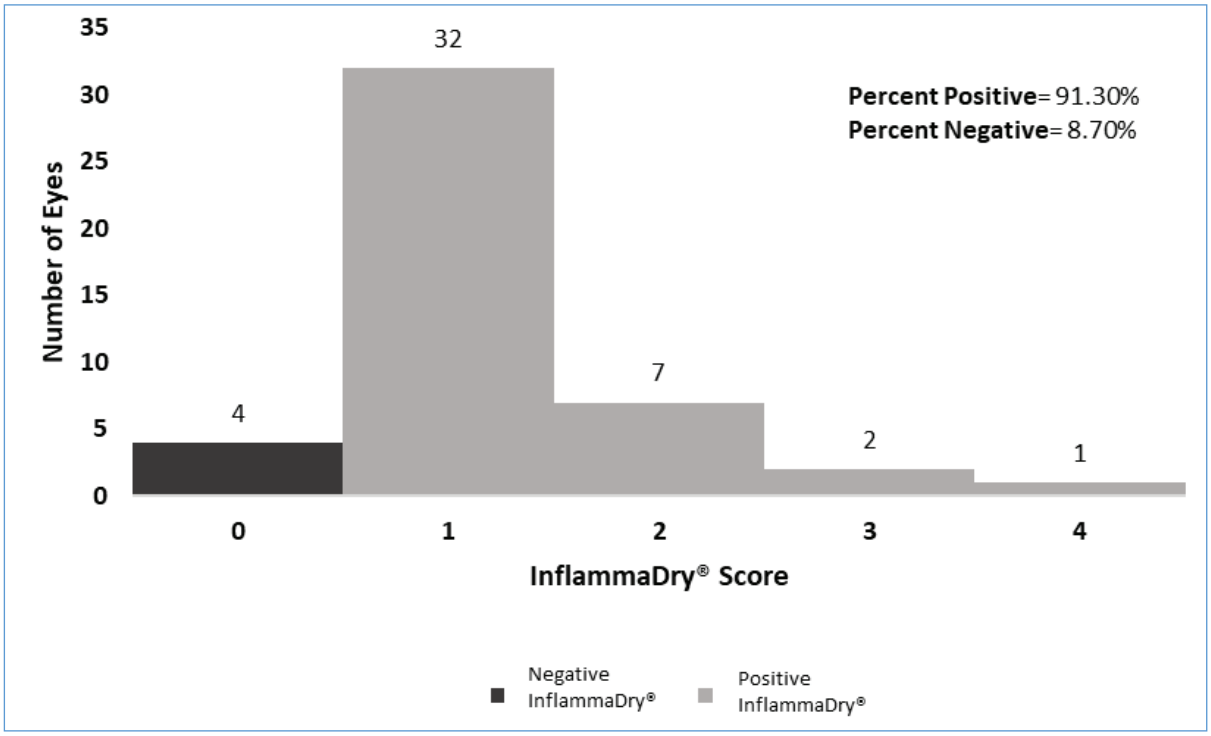
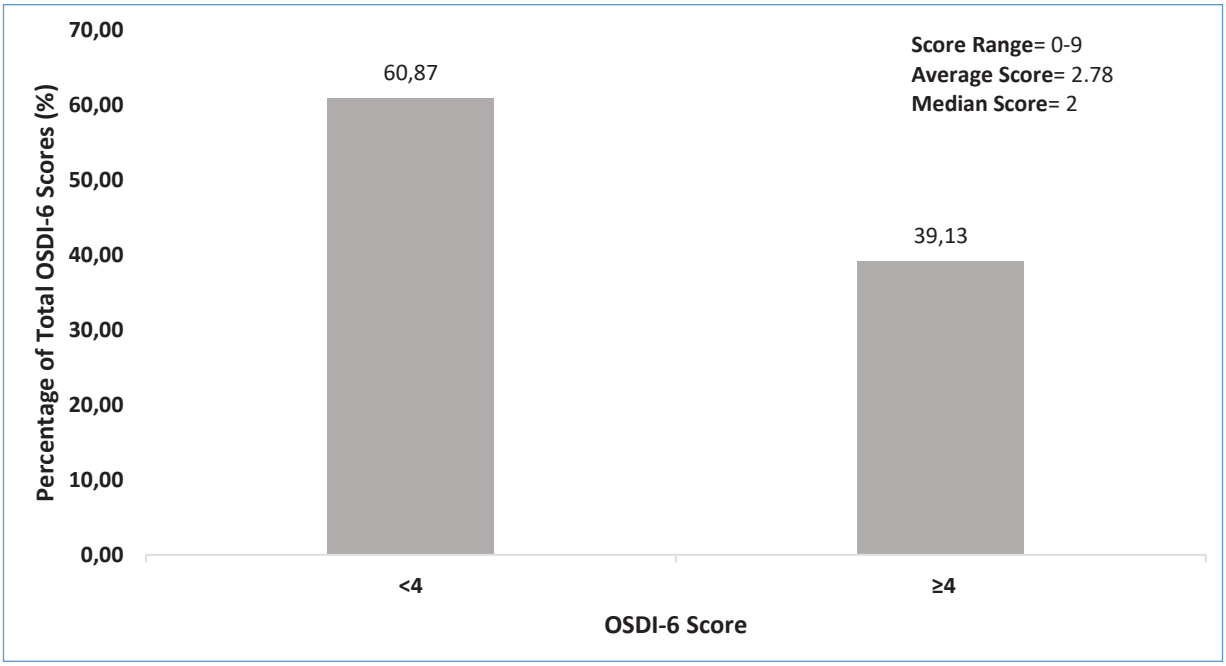


FIGURE 3. **Analysis of InflammaDry® test results. Positive InflammaDry® tests were scored on a scale of 1 (trace) to 4 (strong positive). Negative InflammaDry® tests were given a score of 0. N=46 eyes (23 participants). Of the 46 eyes tested with InflammaDry®, 91.30% resulted positive and 8.70% resulted negative.**



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ORIGINAL ARTICLE

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PATIENT BLOOD MANAGEMENT (PBM) STRATEGIES IN BONE MARROW TRANSPLANTATION UNIT - IMPACT ON PRIMARY OUTCOMES: PBM IN BONE MARROW TRANSPLANTATION

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ABSTRACT

Objective: Hematopoietic Stem Cell Transplant (HCT) recipients are among the largest consumers of allogeneic red blood cells and platelets. The impact of Patient Blood Management (PBM) strategies on these recipients is poorly understood. Therefore, we evaluated the PBM strategies and their impact on patients undergoing autologous and allogeneic HCT. **Methodology**: We conducted a retrospective analysis of 333 patients who underwent HCT at the Bone Marrow Transplant Center of the Walter Cantídio University Hospital (HUWC) from 2018 to 2022. Clinical data were collected from medical records. Statistical analysis was performed using Jamovi software version 2.03, with a statistical significance level of p = 0.05. **Results:** The mean age of the patients was 45 years, with 50.5% being male. Of the transplants performed, 62.8% were autologous. The most common diagnosis was plasma cell neoplasia 36.3%. Restrictive strategies were adopted, and the transfusion parameters during HSCT hospitalization were as follows: Hemoglobin <7g/dL, platelets <50,000/µL in case of bleeding or lumbar puncture, <20,000/µL in the presence of fever or central venous access puncture, and

<10,000/µL prophylactically. The transfusion requests consisted of 1 unit of red blood cells and 1 unit of platelet "buffy coat" per administration. During hospitalization, 94.3% of the patients received platelet transfusions, and 50.1% received red blood cells. Patients undergoing allogeneic HCT required more transfusions, experienced more transfusion reactions, and had a higher number of deaths during hospitalization compared to those undergoing autologous HCT ($p<0.0001$). The most frequent transfusion reactions were febrile non-hemolytic (15%). The number of red blood cell and platelet transfusions showed a strong ($p<0.5$) and significant ($p<0.01$) correlation with the collected volume and engraftment time. There was no correlation between the number of transfusions and age or patient survival after hospital discharge. The number of transfusions during this period did not have a significant impact on survival. However, higher mortality was observed among patients who received more transfusions and those who underwent allogeneic HCT. **Conclusion:** The implementation of PBM for HCT recipients was associated with a significant reduction in allogeneic red blood cell and platelet transfusions and a reduction in transfusion-related costs, without any negative impact on clinical outcomes.

Keywords: Blood Transfusion. Erythrocytes. Blood Platelets.

INTRODUCTION

The transfusion of blood components is a widely used therapeutic strategy, often aiming to alleviate symptoms and improve patients' quality of life. However, studies have shown that the adoption of restrictive transfusions is non-inferior and may even improve outcomes in some cases[1].

In Brazil, over 2.95 million transfusions were performed in 2019[2], which has led to increased concern regarding transfusion risks and the promotion of initiatives to rationalize the use of blood components. In this context, in 2021, the World Health Organization issued an alert about the need to adopt Patient Blood Management (PBM) worldwide[2].

This method is patient-centered, preemptive, preventive, and multidisciplinary[3], based on three principles: reducing blood loss, correcting anemia, and treating coagulopathies[2]. PBM is more easily utilized in elective surgical and clinical procedures, where it is possible to diagnose and intervene preemptively in patients with anemia and coagulopathy[4,5]. However, it is a challenging strategy limited to some centers due to lack of knowledge and resources[4].

Implementing PBM is even more challenging in patients with onco-hematological diseases[6] since cytopenias occur routinely, both as a consequence of the underlying disease and chemotherapy treatment[7,8]. Thus, red blood cells and platelets are the main blood components transfused peri-transplant and are fundamental therapies for these patients[4,7]. This study aimed to evaluate restrictive transfusion strategies and their impacts on patients undergoing bone marrow transplantation (BMT)

MATERIALS AND METHODS

This descriptive and retrospective observational study was conducted at the Bone Marrow Transplant Center of Walter Cantídio University Hospital (HUWC-UFC), with the support of the Ceará Blood Center (HEMOCE). The study period covered from January 1, 2018, to December 31, 2022.

Data collection was performed by reviewing medical records and the Blood Bank System (SBS) of HEMOCE. The collected data included clinical, laboratory, and treatment information for patients treated at the transplant center during the study period.

The data were presented as mean and standard deviation for continuous variables, as well as median and interquartile range when not normally distributed. For categorical variables, percentages were used. The variables of interest, including survival, age, and the volume of collected tests, were transformed into tertiles to facilitate analysis.

Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Correlation was assessed using Spearman's rank correlation coefficient. Differences between groups were evaluated using the Kruskal-Wallis test for continuous variables. The association between categorical variables using the Chi-square test, followed by Kendall's Tau-B for ordinal data, or the odds ratio when in 2x2 tables. All statistical tests were performed using Jamovi software version 2.03, with a two-sided approach, and the level of statistical significance was set at $\alpha = 0.05$.

RESULTS

The sample consisted of 333 patients with a mean age of 45 years, of whom 168 (50.5%) were male and 165 (49.5%) were female. Sixty percent of the total patients had some comorbidity, with arterial hypertension being the most frequent (21%). Regarding the type of transplant, 62.8% were autologous and 37.2% were allogeneic. The main diagnoses of patients undergoing BMT were plasma cell neoplasia (36.3%) (Table 1).

Restrictive strategies are adopted in the studied center, and transfusion triggers during BMT hospitalization were: Hemoglobin (Hb) < 7g/dL, platelets <50,000 µL if bleeding or lumbar puncture, <20,000 µL in the presence of fever or central venous access puncture, and <10,000µL prophylactically. The reviewed transfusion requests consisted of 1 unit of red blood cells (RBCs) and 1 unit of platelet "buffy coat" per administration.

Analysis of the transfusion profile during hospitalization for transplantation showed that 167 patients (50.1%) received red blood cell transfusions and 314 (94.3%) received platelet transfusions(Table 1). Allogeneic transplant patients received more transfusions (26.4) and had significantly more transfusion reactions (23.7%) and more deaths during hospitalization when compared to autologous patients (p<.0001) (Table 2). Among the patients who developed transfusion reactions, 15% experienced febrile non-hemolytic reactions, followed by allergic reactions in 8.7% of cases (Table 3). In 3 patients (1%), more than one transfusion reaction was observed.

Analyzing the total population, red blood cell transfusions had a median of 1 unit (0-35 units), while platelet transfusions had a median of 3 units (0-48 doses). The median pre-transfusion hemoglobin (Hb) and platelet count were 6.5g/dL and 9832 µL, respectively. The lost volume in laboratory test collection throughout hospitalization was also analyzed to assess one of the pillars of PBM, which aims to avoid blood loss. In this analysis, the median volume collected was 241.6 ml (Table 3).

In this study, we compared the PBM results of the present study at HUWC with data from Canadian centers.we observed a lower average pre-transfusion hemoglobin level (6.23 g/dL vs. 7.09 g/dL), but with a similar median regarding the number of red blood cell and platelet transfusions. However, in allogeneic transplantation, we observed superior results in the present study regarding red blood cell transfusions and platelet transfusions compared to the Canadian study[11] (Table 4).

In the Spearman correlation matrix, the number of red blood cell and platelet transfusions had a strong (>0.5) and significant (p <0.01) correlation with the collected volume, as well as the engraftment time, meaning that patients who lost more volume in tests or had a longer aplasia time also received more transfusions. There was no evidence of correlation between the number of transfusions, pre-transfusion hemoglobin, and platelet count with age or patient survival after hospital discharge, demonstrating that elderly patients did not require more transfusions and adapted well to the restrictive strategy adopted.

The number of transfusions during this period did not impact survival, which was expected because post-hospital discharge survival is influenced by many other factors. In the analysis of in-hospital mortality, there was higher mortality in patients who received more transfusions and in those undergoing allogeneic transplantation. However, this is a study

bias because some patients, especially those undergoing allogeneic BMT, tend to undergo more tests and transfusions due to their severity, and causality cannot be attributed.

DISCUSSION

A review study comparing restrictive transfusion strategies with liberal ones also did not show an impact on mortality up to 30 days after transplantation and reduced by 43% the risk of a patient receiving a transfusion[9], without affecting the quality of life of these patients[10].

A Canadian study published in 2023 was the first randomized study addressing restrictive strategy in BMT, comparing restrictive transfusion (Hb <7g/dL) with liberal (Hb <9g/dL). The analysis showed that restrictive transfusion was non-inferior to liberal and there was a reduction in transfusion reactions[11], consistent with the present study.

When comparing the restrictive strategy used in this randomized study with that of HUWC, it was identified that HUWC had a lower mean pre-transfusion hemoglobin but a similar median regarding the number of red blood cell and platelet transfusions, except when comparing platelet transfusions only in allogeneic transplant, in which case, HUWC had a higher mean of transfusions[11].

This study suggests that restrictive strategies are effective in reducing blood component transfusions in BMT, as well as reducing patients' exposure to transfusion risks, and reducing costs, without harming patients. Thus, education regarding transfusion medicine is essential so that patients are not exposed to a higher risk of alloimmunization, transfusion graft disease, among others, as there is no evidence that a liberal transfusion strategy improves the quality of life and outcome of these patients[12].

CONCLUSION

Therefore, the existence of clear transfusion triggers associated with a patient-centered approach allows for the rationalization of blood component use efficiently and without harm. Hence, it is necessary to conduct more studies that can confirm these findings so that PBM can be effectively implemented in bone marrow transplantation.

TABLE 1: Patient and transplant characteristics of the study population (N = 333)

Characteristics	
Age at diagnosis, median years (range)	45 (30 - 60)
Patient sex, n (%)	
Male	168 (50.5)
Female	165 (49.5)
Transplant type, n (%)	
Autologous	209 (62.8)
Allogeneic	124 (37.2)
Underlying disease	
Myeloma/ plasmacytic disorder	121 (36.3)
Hodgkin's lymphoma	46 (13.8)
Non-Hodgkin's lymphoma	36 (10.8)
Acute Lymphoblastic Leukemia/lymphoblastic lymphoma	35(10.5)
Acute myeloid leukemia" (AML)	30 (9)
Aplasia	18(5.4)
Myelodysplastic syndrome	12 (3.6)
Chronic Myeloid Leukemia	12 (3.6)
Others*	23 (6.9)
Comorbiditiesn (%)	
hypertension	70 (21)
Smoking	37 (11)
Elitism	16 (5)
Chronic Kidney Disease	14 (4)
lung disease	5 (2)
Congestive Heart Failure	5 (2)
Others	54 (55)
Red blood cell transfusion	167 (50.1)
Platelet transfusion	314 (94.3)

*Others diseases include Chronic Lymphocytic Leukemia (CLL), Chronic Myelomonocytic Leukemia (CMML), Mantle Cell Lymphoma, Follicular Lymphoma, and Marginal Zone Lymphoma.

TABLE 2: Association between type of transplant and transfusions (N = 333).

	Red blood cell transfusion			
Type of Transplant	Yes	No	Total	p value
Autologous	80	129	209	<0.0001
Allogeneic	88	36	124	
	Platelet transfusion			
Type of Transplant	Yes	No	Total	
Autologous	197	12	209	0.970
Allogeneic	117	7	124	
	Transfusion reaction			
Type of Transplant	Yes	No	Total	
Autologous	32	177	209	<0.0001
Allogeneic	49	75	124	
	Death during hospitalization			
Type of Transplant	Yes	No	Total	
Autologous	4	205	209	0.0001
Allogeneic	16	108	124	

Note: P<0,05;

TABLE 3: Analysis of Transfusion Data

Variable	n (%)	Median (IQR)	Mean (SD)
Red blood cell transfusion.	167 (50.1)		
Pre-transfusion HB	155	6.50 (0.60)	6.23 (0.807)
Nº of red blood cell transfusions.	333	1 (3)	2.43 (4.594)
Time to red blood cell independence.	145	9 (5)	12.07 (7.714)
Platelet transfusion	314 (94.3)	-	-
Pre-transfusion platelets.	83	9832.00 (7222.5)	13127.81 (9979.079)
Nº of platelet transfusions.	83	3 (3)	5.29 (7.387)
Pre-transfusion platelets.	333	9 (3)	11.05 (8.552)
Time to platelet independence.	293		
Transfusion reaction occurrence	79(23.7)	-	-
Types of reaction			
Allergic reaction	29(8.7)	-	-
Febrile non-hemolytic reaction	50(15)	-	-
(TACO)	3(1)	-	-
Death during hospitalization	20(6)	-	-
Graft engraftment time	309	11 (5)	12.48 (4.083)
Collected volume	331	241.60 (141.95)	285.10 (190.279)

Note: Hemoglobin (Hb), Interquartile Range (IQR), Standard deviation (SD), Transfusion-Associated Circulatory Overload (TACO).

TABLE 4: Comparative analysis of restrictive transfusion strategy outcomes in autologous and allogeneic hematopoietic stem cell transplantation patients.

Total transplants	HUWC		Canadian center	
Variable	Mean	Median	Mean	Median
Pre-transfusion Hb	6.23	6.5	7.09	6.9
Number of red blood cell transfusions	2.43	1	2.73	2
Number of platelet transfusions	5.29	3	5.97	2
Autologous				
Pre-transfusion Hb	6.5	6.6	7.1	6.9
Number of red blood cell transfusions	0.8	0	1.32	0
Number of platelet transfusions	2.9	2	2.23	2
Allogeneic				
Pre-transfusion Hb	5.9	6.25	7.07	6.9
Number of red blood cell transfusions	5.11	3	4.12	2
Number of platelet transfusions	9.2	6	5.97	2

Note: HUWC=Walter Cantideo University Hospital; HB=hemoglobin

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ORIGINAL ARTICLE

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EMERGING ACTIVITY OF CELLULAR IMMUNOTHERAPY FOR TREATMENT OF CANCER IN BRAZIL: REPORT FROM THE BRAZILIAN REGISTRY

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ABSTRACT

Chimeric antigen receptor T-cells (CAR T cells) are genetically modified cellular immunotherapies approved for standard of care treatment of patients with lymphoma and leukemia worldwide. Here we report the initial activity in Brazilian centers through the collaboration between the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) and Center for International Blood and Marrow Transplant Research (CIBMTR). A total of 38 patients who received CAR T cells between 2020 and 2023. The median age was 47 years (range 4-77). Indications include Non-Hodgkin Lymphoma (NHL; 26 cases; 68%), Acute Lymphoblastic Leukemia (ALL; 9 cases; 24%), and Multiple Myeloma (MM; 3 cases; 8%). 84% (75% - 24 NHL cases and 25% - 8 ALL cases) were commercial. This report demonstrates the initial implementation of CAR T cells in Brazil among centers that report to the SBTMO/CIBMTR. This infrastructure will assist in further capturing the activity, assessing the outcomes, and complying with regulatory requirements.

Keywords: CAR-T cells; cancer immunotherapy; chimeric antigen receptor (CAR); Data Management, CIBMTR, SBTMO, Brazilian Summary Slides.

INTRODUCTION

Chimeric antigen receptor T-cells (CAR T cells) are genetically modified cellular immunotherapies directed against different antigens expressed in tumors cells. The initial utilization of CAR T cell was established for treatment acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) with excellent results among patients with advanced phases of these diseases. CAR T cells were initially approved for commercialization by the FDA in the US in 2017 and since then several CAR T cell products were approved for standard of care treatment of relapse and refractory ALL, NHL and multiple myeloma. Since 2020, Brazilian Health Regulatory Agency (Anvisa) has registered four CAR-T gene therapy products for leukemia, lymphoma, and myeloma treatment: Kymriah® (tisagenlecleucel), approval date: February 23, 2022; Carvykti® (ciltacabtagene autoleucel), approval date: April 1, 2022; Yescarta® (axicabtagene ciloleucel), approval date: October 26, 2022, and Tecartus® (brexucabtageno autoleucel), approval date: January 30, 2024.

The treatment using genetically modified cells have potential risks for late effects for recipients manufacturing process may lead to the development of subsequent malignancies, including insertional mutagenesis or through the presence of replication competent retrovirus or lentivirus[1]. Brazil's National Health Surveillance Agency (Anvisa) has adopted the requirement from other national regulatory health authorities in requiring that recipients of these therapies to be followed for 15 years for assessment of safety outcomes, including the development of subsequent neoplasms.

The manufacturing process for CAR T cell follows a multi-step process, starting with the leukapheresis, manufacturing, lymphodepleting chemotherapy and infusion. In 2019, the Centro de Terapia Celular do Hemocentro de Ribeirão Preto (CTC-USP) used the experimental CAR-T cell therapy on blood cancers patients, specifically lymphoma and leukemia, who had exhausted all other treatment options. Many of these patients achieved remission[2,3].

Through the experience and results obtained by Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) in managing hematopoietic cell transplant (HCT) Brazilian cases via partnership with Center for International Blood and Marrow Transplant Research (CIBMTR), using the North American center infrastructure.

The first CAR-T cell therapy procedure registered at the CIBMTR occurred in 2020. Over the years, the number of Brazilian centers reporting to the CIBMTR has increased, facilitating the establishment of a comprehensive database for evaluating CAR-T cell therapies within the country. This growth has also contributed to the development of the Hematopoietic Stem Cell Transplantation Brazilian Registry (HSCTBR). Data reported by Brazilian centers to the CIBMTR is aggregated and shared with the SBTMO. The CAR-T cell therapy activities at Brazilian centers will be published annually on the SBTMO website, providing a valuable resource for

the community of advanced cell therapy centers in Brazil. This initiative enhances collaboration, data sharing, and the cellular therapies progress in Brazil.

OBJECTIVE

Our objective is to report the initial CAR-T cell activities in Brazilian transplant centers in the past four years.

METHODS

Data Sources

Brazilian advanced cell therapy centers report their data to the CIBMTR, using the electronic FormsNet3 platform. That process is protected by double authentication entry requirements for all system users. The compiled, standardized, and codified data returns to SBTMO through the Data Back to Centers (DBtC) tool, enabling the analysis of CAR-T cell outcomes throughout the country.

The spreadsheet was imported into Power BI Desktop (PBI). Functions were created to count the number of CAR-T cell performed and the number of participating centers, to translate columns into Portuguese, to categorize and classify diseases, and to group variables.

Selection

Patients who received CAR T cell products at Brazilian centers between 2020 and 2023 and were reported to the CIBMTR and shared with SBTMO.

Data from 38 CAR-T cells infused between 2020 and 2023 were extracted from the CIBMTR portal using the DBtC, gathering information from 8 Brazilian centers. There was complete information about the type of CAR-T cell and diagnoses.

Definitions and Outcomes

Patients were classified as pediatric (0-17 years of age) or adults (≥18 years of age).

The CAR-T cells were classified as non-commercial and commercial.

A bar graph was used to evaluate the age distribution and infusions per year.

A pie chart was used to evaluate indications for the CAR-T cell therapy and the percentage of commercial and academic CAR-T cells.

Statistical analysis

Descriptive statistics was used for categorical data, with the number of cases and percentage. Graphics were generated by PBI and exported to Microsoft PowerPoint for publication. Overall survival was estimated by the Kaplan Meier method, survival analyses were per-

Ethical considerations

Ethics approval for utilization of the CIBMTR platform for the Brazilian Registry for research was obtained from the national Institutional Review Board (IRB) in 2019 (Conep CAAE: 65575317.5.1001.0071, principal investigator Dr. Nelson Hamerschlak).

All procedures of the present study followed the ethical standards of the responsible committees of the institution and national guidelines and adhered to the revised version of the Helsinki Declaration of 1975 and the Resolution No. 466/2012, of the National Council of Health.

RESULTS

From 2020 to 2023, a total of 38 autologous CAR-T cell infusions were reported from 8 Brazilian centers (Table 1), of which 47% (18) had undergone a previous HCT. The number of CAR-Ts registered with the CIBMTR over the years has been: one patient registered in 2020, one in 2021, four in 2022 and 32 in the year of 2023 (Figure 1), 75% (6) performed in the state of São Paulo and 25% (2) in the state of Paraná. Adults were 82% (31) of the cases, with overall median age of 47 years (range 4-77). The median age for NHL, MM ALL were 58 years (range 23-77), 67 (range 49-74) and 9 (range 4-26), respectively (Figure 2).

The main global indications for CAR-T cell therapy in Brazil between 2020 and 2023 were NHL (26 cases; 68%), ALL (9 cases; 24%), and MM (3 cases; 8%) (Figure 3).

Among the 38 reported infusions, 84% were commercial (24 NHL and 8 ALL), and 16% were non-commercial (3 MM, 2 NHL and 1 ALL) (Figure 4). Of the total recorded cases, 89% of patients with ALL underwent a prior transplant, followed by 67% of patients with MM, and 31% of patients with NHL (Figure 5).

Of the 32 commercial products registered with the CIBMTR, 97% (n=31) were Kymriah® (23 cases, NHL and 8 cases, ALL) and 3% (n=1) Yescarta® to NHL.

The median follow-up of all alive patients was 136 days (range 87-736). Of the 25 cases with NHL follow-up, overall survival at 150 days was 73% (95% CI: 57%-95%) (Figure 6) and 60% (95% CI: 33%-100%) for ALL, N=8 (Figure 7).

DISCUSSION

With the publication of the first specific health regulations for Advanced Therapy Products (ATPs), Brazil has joined a small group of countries with regulatory frameworks for the development and use of these innovative products.[4] There are nine Brazilian academic CAR-T cells initiatives (table 2).

According to Anvisa, it is required to conduct a 15-year post-CAR-T cell therapy follow-up. However, some industries have different protocols and registries for following up after Car-T cell, which makes it challenging to know the long-term outcomes of this new therapy.

This report outlines the initiate experience of CAR T cells in Brazil thought the reporting to the CIBMTR/ Brazilian Registry of Cellular therapies. The activity is increasing as new products are available, starting with one case per year in 2020 and reaching 38 cases by December 2023.

During this period (2020 to 2023), eight treatment centers contributed with the initial summary of CAR-T cell therapies, indicating increased involvement and collaboration among the Brazilian institutions in this innovative treatment approach. The starting with one case in 2020 and reaching 32 cases by December 2023. The predominant indication for adults is NHL (26) and MM (3). For pediatric patients, the only indication is ALL (7).

When comparing the main indications for CAR-T therapy between Brazil, USA, Canada, and Israel, a similar profile is observed, with a prevalence of DLBCL, followed by ALL. Most CAR-T cells infusions reported to the CIBMTR are commercial, with only 6% reporting non-commercial CAR-T cells.[5]

Despite the short follow-up time, it was possible to analyze the OS of NHL and ALL, with a median of 150 days, with the respective results: 73% (95% CI: 57%-95%) and 60% (95% CI: 33%-100%).

The Brazilian Summary Slides are published yearly and fully available to active centers in the HSCTBR through the SBTMO data request flow (Figure 8).

CONCLUSION

The partnership between SBTMO and CIBMTR led to the creation of the Brazilian registry of HCT and cell therapy. Analyses of Brazilian CAR-T cell data have resulted in the development of the Brazilian Summary Slides, contributing to a deeper understanding of national CAR-T cell outcomes, and providing centers with a national and international reference.

Enhancing the commitment of CAR-T cell centers to report the data is paramount to optimize the transplant registry, ensure the availability of a standardized structure to be used to collected and monitor long-term outcomes after these therapies. The regulatory requirement from ANVISA for long term follow up for CAR T cell recipients, the current infrastructure can be leverage to fulfill this requirement. The challenge now is to the utilization of this resources by all Brazilian treatment centers to have a better assessment of this activity and outcomes of these novel therapies.

ACKNOWLEDGEMENTS

- Dr. Nelson Hamerschlak, Dr. Vergilio Antonio Rensi Colturato and Dr. Fernando Barroso Duarte have been influential advocates for the progress of HCT and CAR-T cell in Brazil, having catalyzed significant advances in the field since 2016.

- Dr. Marcelo Pasquini facilitates direct collaboration with the CIBMTR, ensuring that the latest research updates and best practices are disseminated within the community.

- Monique Ammi has played an active role facilitating the affiliation of Brazilian centers and has been pivotal in educating and supporting data managers involved in HCT and CAR-T cell initiatives.

- The multidisciplinary CAR-T cell teams across the country, through their dedicated efforts, directly contribute to the ongoing development and success of this specialized field of medicine.

- Finally, the invaluable contribution of patients who have undergone CAR-T cell cannot be overstated, as their willingness to share data and participate in scientific research is critical to advancing knowledge and improving outcomes in this important area of healthcare.

TABLE 1. CAR-T cell centers]

A.C. Camargo Cancer Center
Albert Einstein Hospital
CTMO-HCFMUSP
Hospital Nossa Senhora das Graças - IP
Hospital Pequeno Príncipe
Hospital Samaritano
Hospital Sírio Libanês
Real e Benemérita Sociedade de Beneficiência Portuguesa de São Paulo

TABLE 2. Brazilian academic CAR-T cells initiatives

	STUDY	CENTER	STATUS
1	A Phase I Clinical Trial Using Genetically Engineered Autologous T Cells to Express Chimeric Antigen Receptor (CAR) for Treatment of Patients with Refractory or Relapsed CD19-positive B Lymphoid Malignancies (CARTHIAE-1) NCT05705570 https://classic.clinicaltrials.gov/ct2/show/NCT05705570	Hospital Israelita Albert Einstein	Recruiting First academic CAR-T initiative approved by Anvisa in Brazil 2023
2	CD19-directed CAR-T Cell Therapy for R/R Acute Leukemia and Lymphoma (CARTHEDRALL) HEMO-02-CART NCT06101381 https://classic.clinicaltrials.gov/ct2/show/NCT06101381	Group leader: Ribeirão Preto Medical School, University of São Paulo (USP)	Recruiting for the trial after being the first academic compassionate CD19 use in the country for ALL and B-DLGL Multicentric Clinical Trial approved by Anvisa in 2024
	RBR-7cr9yvf Development of CAR-T cells to treat malignant B neoplasms UTN code: U1111-1250-6114 CAAE: 30173220.5.0000.0071 https://ensaiosclinicos.gov.br/rg/RBR-7cr9yvf	Hospital Israelita Albert Einstein	Phase I not yet recruiting. Lymphoma, B-ALL, B-Lymphoblastic Lymphoma, Adult T cell Leukemia and Lymphoma
3	Platform for B cell CD 19 diseases	São Paulo Medical School, University of São Paulo (USP)	Under development
4	anti CD19 CAR-T cells via Transposon Sleeping Beauty	National Cancer Institute - INCA	Under development
5	CD19 Lymphoma Prodigy Platform with Barcelona vector	Federal University of Ceará/HEMOCE and Barcelona	Under development
6	Caring Cross: Triple CAR-T (CD19, CD 20 and CD22) for B Cell malignancies Schneider D, et al. Trispecific CD19-CD20-CD22-targeting duoCAR-T cells eliminate antigen-heterogeneous B cell tumors in preclinical models. Sci Transl Med. 2021 Mar 24;13(586): eabc6401 https://portal.fiocruz.br/en/news/2024/03/fiocruz-and-caring-cross-announce-agreement-car-t-therapy-brazil-and-latin-america	Oswaldo Cruz Foundation (Fiocruz) National Cancer Institute - INCA Hospital Israelita Albert Einstein USP São Paulo	Under development

7	BCMA vector development	Hospital Israelita Albert Einstein	Finished study on laboratory bench and preparing study in animal mode
8	BCMA multicentric academic study+ Barcelona	Barcelona Federal University of Ceará / HEMOCE 3. São Paulo Medical School, University of São Paulo (USP) 4.Hospital Israelita Albert Einstein	Protocol preparation
9	HUBs for cell therapy	1. Instituto Butantan (SP, Brazil) 2. Ribeirão Preto Medical School, University of São Paulo	Producing products in Ribeirão Preto

Source: Information kindly provided by Dr. Nelson Hamerschlak.

FIGURE 1. Number of CAR-T cell infusions per year

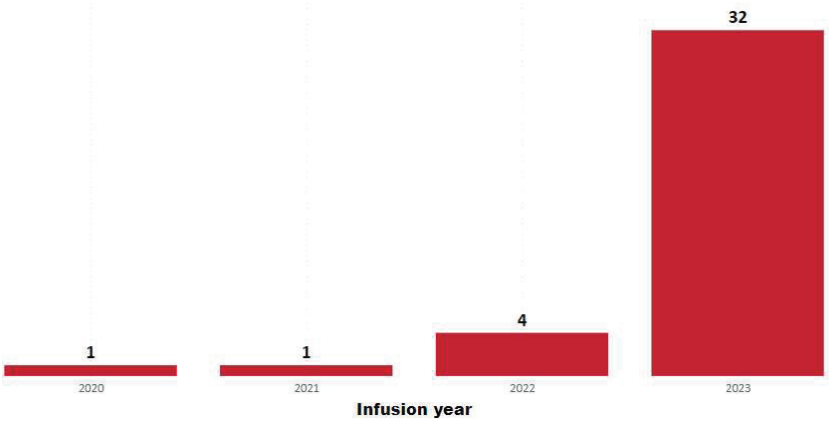


FIGURE 2. Distribution of CAR-T cell recipients by age

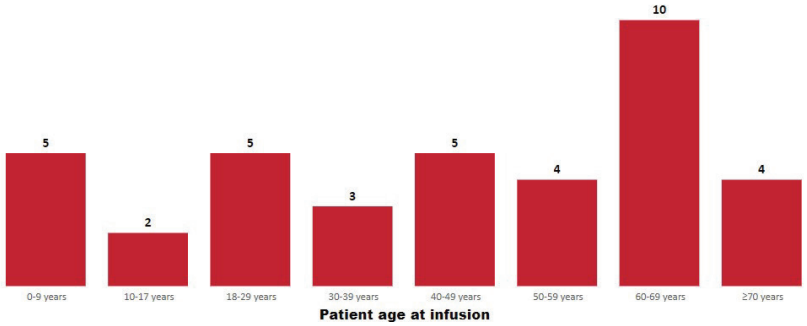


FIGURE 3. CAR-T cell indications

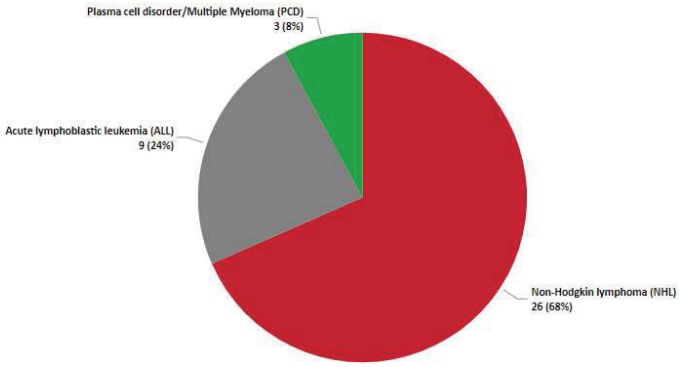


FIGURE 4. CAR-T cell indications by commercial and non-commercial product

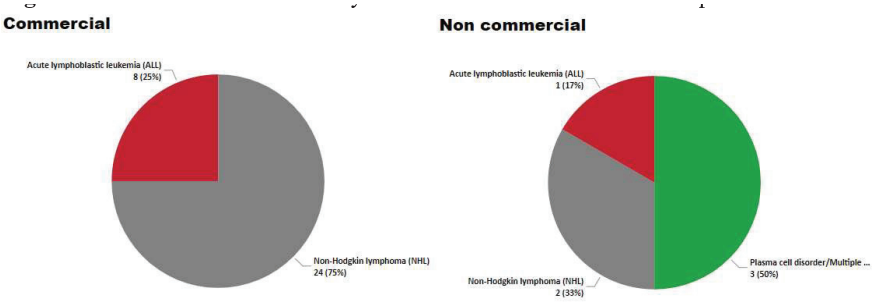


FIGURE 5. **Use of Car T infusions with prior HCT for diseases**

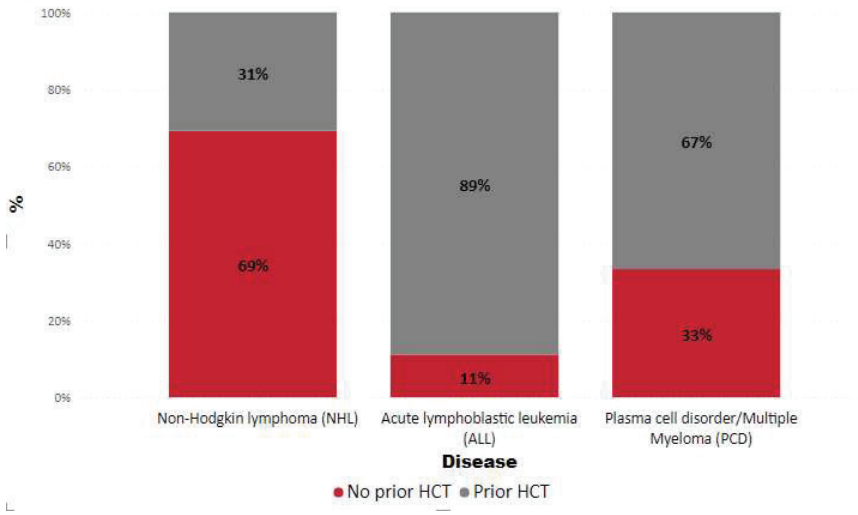


FIGURE 6. **Overal Survival Non-Hodgkin lymphoma. The survival estimates at 150 days were 73% (95% CI, 57-95).**

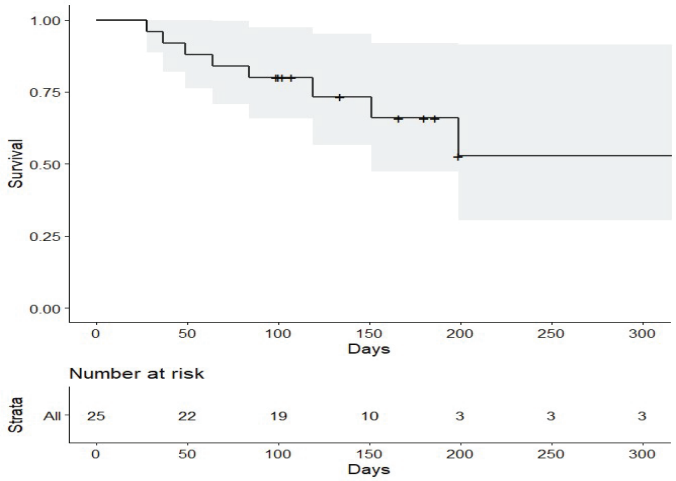


FIGURE 7. Overal Survival Acute leukemia. The survival estimates at 150 days were 60% (95% CI, 33-100).

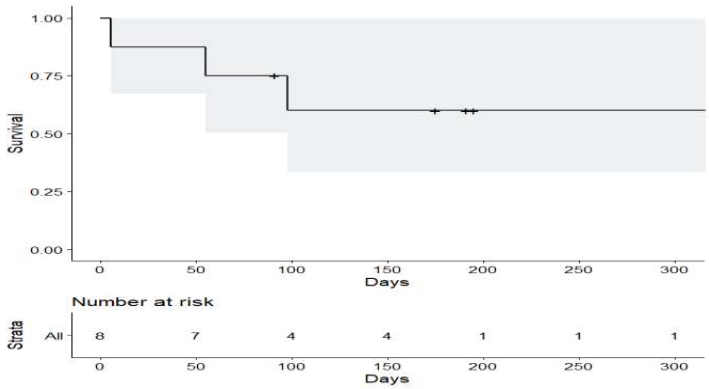
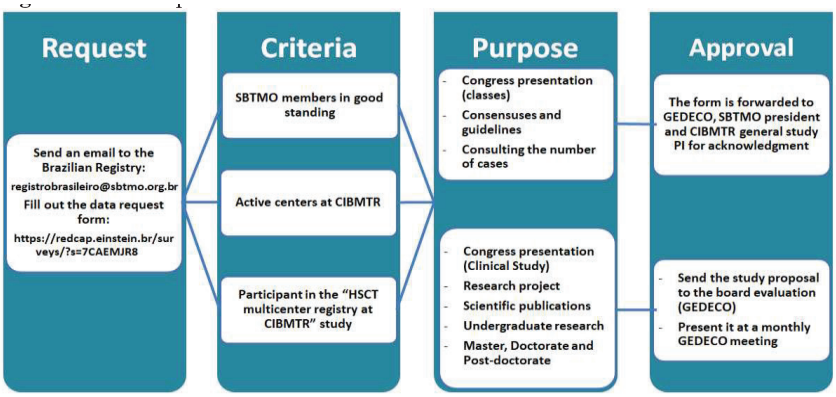


FIGURE 8. Data request flow



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