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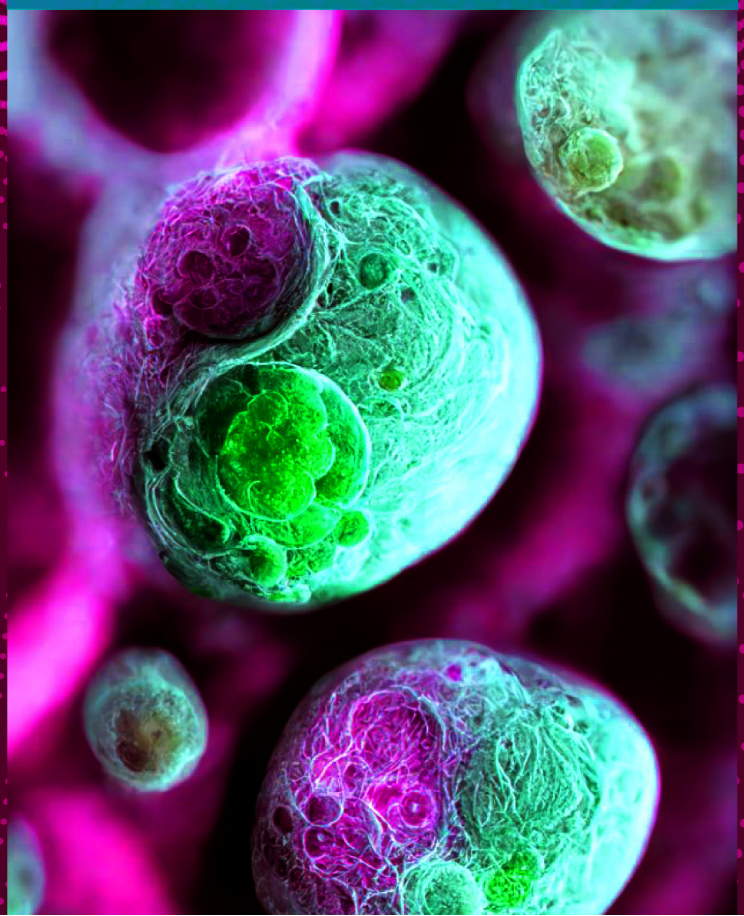

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Dear transplant colleagues

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*

Summary

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LETTER TO EDITOR

PLERIXAFOR FOR HEALTHY PERIPHERAL BLOOD HEMATOPOIETIC STEM CELL DONORS IN PEDIATRIC ALLOGENEIC HSCT

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INTRODUCTION

Achieving optimum outcomes after allogeneic hematopoietic stem cell transplant (HSCT) is dependent on the stem cell dose administered. It has been documented that for allogeneic HSCT done for malignant indications in pediatrics, a stem cell dose greater than 5 million per kg of recipients body weight was associated with better outcomes , whereas doses less than 5 million per kg could lead to failure[1]. Peripheral blood hematopoietic stem cells (PB-HSC) have become the predominant source of hematopoietic stem cells (HSC) being used worldwide for allogeneic HSCT. Optimum mobilization of these cells into the peripheral blood (PB) from the donor is imperative for a good stem cell yield on apheresis[2]. Granulocyte colony stimulating factor (G-CSF) based mobilisation of the HSC has been the predominant method of mobilizing the stem cells into the PB before apheresis. With G-CSF alone, there may be a failure to mobilize adequate number of stem cells in a significant proportion of healthy donors[3]. Mobilization of PB-HSC into the PB is facilitated with the use of plerixafor. Plerixafor reversibly inhibits the binding of SDF-1 to CXCR4, an interaction that plays an important role in the HSC retention in the bone marrow, thus increasing the number of HSC circulating in the PB. Plerixafor has been approved along with G-CSF for use for autologous HSC harvest in adults. Its use in in pediatric autologous HSCT is also expanding. However, the use of plerixafor for normal donors especially in the pediatric setting has not been studied much.

We present this retrospective review of our experience with the use of plerixafor in healthy donors for our patients undergoing allogeneic HSCT.

METHODS

This study is a retrospective study conducted at a tertiary referral center in north India. Ten patients underwent matched sibling donor or haploidentical HSCT. All of the recipients were children less than 14 y old except for one who was a 20-y old male treated as a child for Philadelphia chromosome positive acute lymphoblastic leukemia and had subsequently relapsed. All donors were children except in two cases where adults were used for haploidentical HSCT. We used plerixafor along with G-CSF in 5 healthy donors for our patients undergoing allogeneic HSCT. Plerixafor was administered to the donor when it was necessary to ensure a good HSC dose e.g for haploidentical HSCT. In case the donor's weight and age were less compared to the recipient, plerixafor was used to ensure a high circulating HSC count for a successful apheresis. It was also used in situations where the amount of plasma was to be kept minimal in the harvest due to incompatibility in the blood groups of the donor and recipient.

Plerixafor was used at a dose of 0.24mg/kg, subcutaneously approximately 11 hrs prior to harvest. All donors were on G-CSF at a dose of 5 mcg/kg twice a day for 4 days before getting plerixafor. We did a CD-34 positive HSC estimation in the PB prior to administering plerixafor, but this was not used to guide the decision regarding plerixafor administration.

In 5 other donors admitted for allogeneic HSCT donation during the same time period, plerixafor was not administered and only G-CSF was used. We compared the outcomes of both the groups.

RESULTS

Ten allogeneic HSCTs were included in the analysis, 5 in which the donor received plerixafor along with G-CSF and in the other five the donor got only G-CSF. In all the HSCT, PB HSC was used. In all cases the recipients were males and the donors were females. In the group in which plerixafor was given the indication for HSCT were as follows: chronic myeloid leukemia (CML) in blast crisis=1, high risk acute lymphoblastic leukemia (ALL)=1, relapsed ALL=1, relapsed acute myeloid leukemia (AML)=1 and X-linked adrenoleukodystrophy (ALD)=1. In the group where the donor did not get plerixafor the indications were: juvenile myelomonocytic leukemia (JMML)=2, High risk ALL=1 and Relapsed AML=2. The age range was 5y-32y for the group that got pre-harvest plerixafor. (Table 1).

TABLE 1: Clinical and hematopoietic mobilization details of both groups

	Plerixafor given	**Plerixafor not given**	p-value
n	5	5	
Diagnosis	CML in blast crisis=1 High risk ALL=1 Relapsed ALL=1 Relapsed AML=1 X linked ALD=1	JMML=2 High risk ALL=1 Relapsed AML=2	
Sex	Recipient= all males Donor= all females	Recipient=all males Donor=all females	
Type of HSCT	Haploidentical=3 MSD=2	MSD=5	NS
Age of recipient (in years)	10.6+5.7	5.8+3.8	NS
Age of donor (in years)	14.8+13.1	9.4+2.9	NS
Recipient weight (in kg)	28.0+15.5	19.2+11.4	NS
Donor weight (in kg)	31.5+23.3	22.7+7.6	NS
CD 34 pre plerixafor (per cumm)	83.2+77.2	99.0+59.0	NS
CD 34 of harvest product (per cumm)	2789.2+1030.3	1319.0+647.2	0.032**
Stem cell dose (million cells/kg of recipients body weight)	9.7+2.2	7.1+4.7	NS

CML :chronic myeloid leukemia, ALL : acute lymphoblastic leukemia, AML: acute myeloid leukemia, ALD : adrenoleukodystrophy, JMML: juvenile myelomonocytic leukemia, MSD:matched sibling donor, CD: cluster differentiation .
NS: not significant , ** : independent t-test

No significant difference in terms of recipients age and weight; donors age and weight and the CD-34 count in PB pre-plerixafor were there between the two groups. However, the CD-34 HSC count in the harvested product was significantly higher in the group that received plerixafor (p=0.032). The stem cell dose transfused to the patient was also higher when the donor got plerixafor, although the difference was not significant. None of the donors suffered any side effects and underwent the subsequent apheresis uneventfully.

DISCUSSION

In our experience ,the use of plerixafor in healthy donors , for pediatric allogeneic HSCT was safe and associated with a higher HSC count in the harvested product. The use of plerixafor is approved in adults for autologous HSC harvest in lymphomas and multiple myeloma. Recent there has been a recommendation from the EMA for plerixafor use in pediatrics for HSC collection for autologous HSCT in lymphomas and malignant solid tumors[4].

In pediatric patients undergoing allogeneic HSCT, the harvest of adequate PB HSC for a recipient with higher weigh may become difficult. Younger donors and children with smaller body weight are at risk of hemodynamic and metabolic disturbances if subjected to long apheresis procedures for HSC collection. Sevilla et al have reported that the procedure of PBSC collection in children can be associated GCSF related bone pains, thrombosis, risks of catheter insertion , low calcium and hemodynamic instability. In children <20 kg the cardiovascular problems are more frequent during PBSC collection[5]. In up to 5% of donors GCSF based regimens can result in failure of the harvest .In the event of failure of PBSC mobilization a repeat attempt at mobilization or bone marrow collection remains the only salvage option[6].

In our experience the use of plerixafor in pediatric donors (two with age 5 years and one with age of 6 years), was associated with a good rise in the peripheral blood of CD-34 counts and yielded a good HSC count in the harvested product . The two adult donors who received plerixafor also didn't experience any side effects and the drug was effective.

Plerixafor may also be used in situations where one would like to limit the amount of plasma being harvested e.g in case of ABO mismatched allogeneic HSCT . A higher peripheral blood CD-34 count allows for the required amount of stem cells to be harvested in a smaller volume and with lesser number of apheresis cycles for the donor. In case the CD 34 count pre HSCT is not optimal, the use of plerixafor can prevent a second harvest procedure.

In our experience we found that plerixafor was safe and effective in healthy pediatric and adult donors for allogeneic HSCT.

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Declaration: The research was carried out according to the guidelines of Declaration of Helsinki.

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SHORT COMMUNICATION

SECOND HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LEUKEMIAS: EVALUATING SUCCESS AND CHALLENGES

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a life-saving procedure for individuals with acute leukemias (AL). In some cases, patients may require a second bone marrow transplant due to relapse. This text explores the outcomes, success rates and challenges associated of second HSCT (sHSCT).

The defined role of the sHSCT in Acute Leukemias after relapse is to be define. Socié et al found that the success rate of second transplants for diseases like leukemia can range from 20% to 50%, with better outcomes in cases of acute leukemia compared to chronic forms. Moukalled in recent review found in patients whit acute myeloid leukemia that time between first transplantation and relapse is important prognosis factor (11% vs 34% 2-years OS in patients relapsing before and after 6 months respectively). The optimal conditioning regiment remains controversial with no statistically difference between sources types and whether the same or different donor used with reduced intensity regiment (RIC) [1,2].

MD Anderson center sHSCT 91 myeloid leukemias retrospective review between 2000 and 2019 found a median age 44 years (range, 18-73) and Overall survival (OS), disease free survival (DFS) and not relapsed mortality (NRM) rates of 36%, 27% and 18% respectively. Acute GVHD III-IV was 11% and chronic at 2 years was 18%. Most common cause of death was relapse. Presence of chronic GVHD after the first HSCT (HR 2.9 (95% CI, 1.5–5.7; p=0.001), and HCI >2(HR 2.6 (95% CI, 1.4–4.9; p=0.003)), were associated with worse outcomes. No difference to same or different donor. In last 10 years patients with >6 months remission duration after first HCT undergoing sHSCT had better outcomes (HR 2.5 CI95%1.2–5.2; p=0.02)), there was an increased use of Haploidentical (58% x 41%) and change of donors in sHSCT (67% x 39%) They noted more patients using maintenance therapy after second in the last decade (27% vs 2%, p=0.0007) [3].

In meta-analyses from ASCT published in 2022 with 20 studies and 2770 patients the OS/DFS/NRM rates was of 34%, 30 and 51% respectively. The OS was two times higher if patient is in remission (38 x 17%) and no difference if same or different donor (HR 1.1, CI95%- 0.78-1.3) [4].

The question whether sHSTC or Donor Lymphocytes infusion (DLI), is better to myeloid disease considering the recognized benefic effect of graft versus leukemia (GVL) in this group patients, a retrospective registry study from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation(EBMT) involving 418 adults who received an allo-HCT2 (n = 137) or DLI (n = 281) for post allograft-relapsed AML showed very similar 2- years OS allo-HCT2, 26%; 5-year allo-HCT2, 19% vs 2-year OS DLI 25%; 5-year OS 15%; P = .86) and relapse before 6 months was the main prognosis factor in both groups[5].

In case of acute lymphoblastic leukemias (ALL) second transplant results are disappointing. The acute Lymphoblastic leukemia Working Party (ALWP) from EBMT studing in 245 ALL patients with median age 34(18 to 74) the 2-years OS 29,8% and DFS 19.8%. The majority procedures used unrelated donors and before car T cell availability. The EBMT registry in more recent publication in 214 ALL patients between 2004 until 2013 demonstrated 43%and 33% 2 and 5 years OS, and 34% and 31% DFS. Acute GVHD was 25% and CGVHD 22%. With no difference between same or change donor. Identified favorable prognosis factors were: more than 12 months between transplants, CGVHD after first HSTC and complete remission before de second HSTC[1];

In summary the second transplant can be a option to a select group patient and best results are in patients that relapsed 6 months after the first HSTC with complete remission, HCI <2 .Apparently wasn't difference used same donor or not and RIC regiment can be good option.

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SHORT COMMUNICATION

THE IMMUNOLOGICAL EFFECT OF HIGH-DOSE CHEMOTHERAPY IN MULTIPLE MYELOMA

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The different outcomes of autologous hematopoietic stem cell transplantation (AHSCT) may be due to engraftment with adequate numbers of hematopoietic stem cells, which is determined by bone marrow stromal cells and is significantly impaired by continuous high-dose chemotherapy. Another important factor is immunological reconstitution, which can be influenced by the bone marrow microenvironment[1].

There is a group of patients with multiple myeloma (MM) who have disease control with a long response time after AHSCT. In general, these are patients who present changes in the bone marrow microenvironment that can maintain an immunological response with antitumor action[2]. Cytoreduction is associated with changes in cytokine production and immunological activation that contribute to subsequent specific immunity with anti-tumor action. Therefore, there are several immunological changes that occur after AHSCT that suggest that long-lasting control of MM occurs for reasons other than just the cytotoxic action of melphalan chemotherapy conditioning[3].

Studies of patients with MM have demonstrated that T lymphocytes and natural killer (NK) cells become quantitatively and functionally altered in the last stage of the disease. These dysfunctions have been associated with the progression of MM and the reduced number of NK cells, pointing to a role for these cells in controlling the disease[4]. NK cell counts and function recover quickly, usually within 1 month after transplantation. Faster reconstitution of NK and T cells may contribute to improved clinical outcome[5].

Melphalan conditioning followed with hematopoietic stem cell rescue results in increased plasma levels of IL-6, IL-7, and IL-15 compared with pre-AHSCT levels in MM patients. CD3 T cells present from the autologous stem cell graft die rapidly when cultured without cytokines in vitro, and therefore addition of IL-7 or IL-15 can induce their survival and proliferation[6].

High-dose melphalan resulted in a rapid burst of inflammatory cytokines and chemokines during the cellular recovery phase after myelodepletion. After melphalan treatment, tumor cells exhibited features of immunogenic cell death, including translocation of calreticulin into the endoplasmic reticulum membrane. Furthermore, there was an increased uptake of tumor antigens by dendritic cells. Consistent with these immunomodulatory effects, melphalan treatment of tumor-bearing mice led to activation of endogenous CD8 + T cells and, more importantly, effectively drove clonal expansion and effector differentiation of tumor-specific CD4 + T cells. These findings provide insight into the immunostimulating effects of melphalan[7].

More studies in this area are needed to better understand why there are different responses and survival rates in myeloma patients who undergoing to AHSCT and thus enable a better response to this therapy. In the future, it could help in the development of cellular therapies similar to those carried out in patients with acute myeloid leukemia[8].

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RECOMMENDATIONS FOR COVID-19 PREVENTION AND TESTING FOR HEMATOPOIETIC CELL TRANSPLANT CENTERS IN BRAZIL - SEPTEMBER 2023

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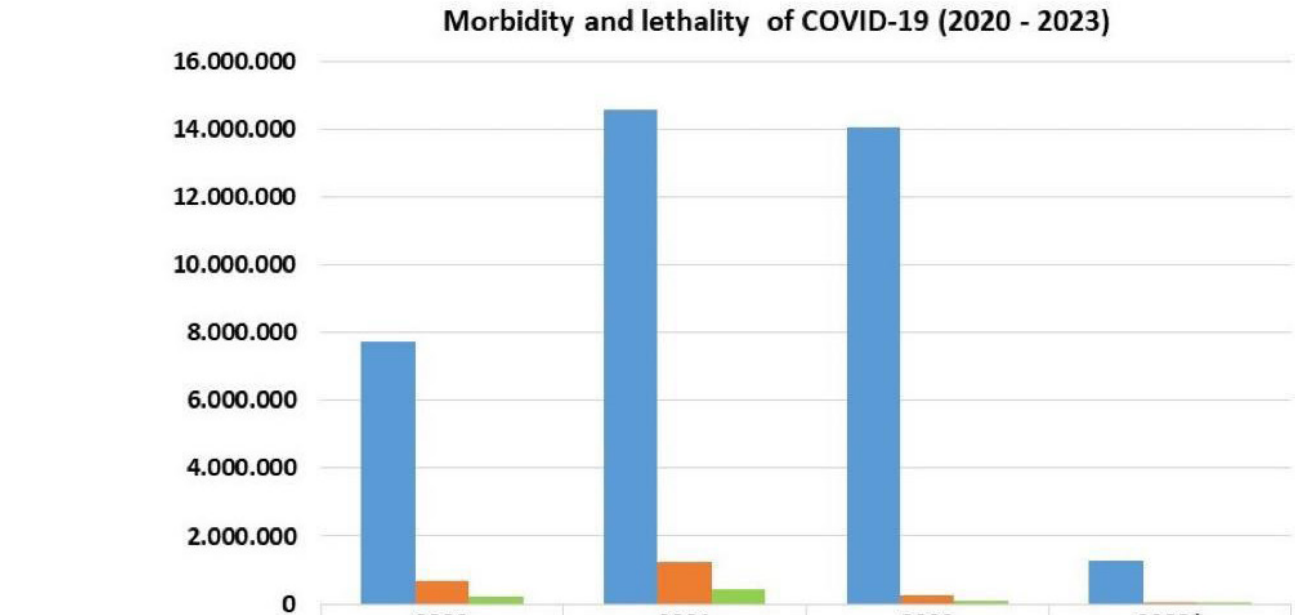
CURRENT SITUATION OF COVID-19

From February 2020 to May 2023, 37,625,916 cases of COVID-19 were recorded in Brazil, which led to 2,173,359 hospitalizations due to severe acute respiratory syndrome (SARS) with 703,291 deaths due to COVID-191. More than 14 million cases were registered in 2021 and 2022. However, there was a significant drop in the number of hospitalizations for SARS and the COVID-19 fatality rate in 2022, which certainly reflects the impact of mass vaccination in the country, started in February 2021 (figure 1).

FIGURE 1. Number of COVID-19 cases, SARS hospitalizations and COVID-19 deaths (2020-2023).

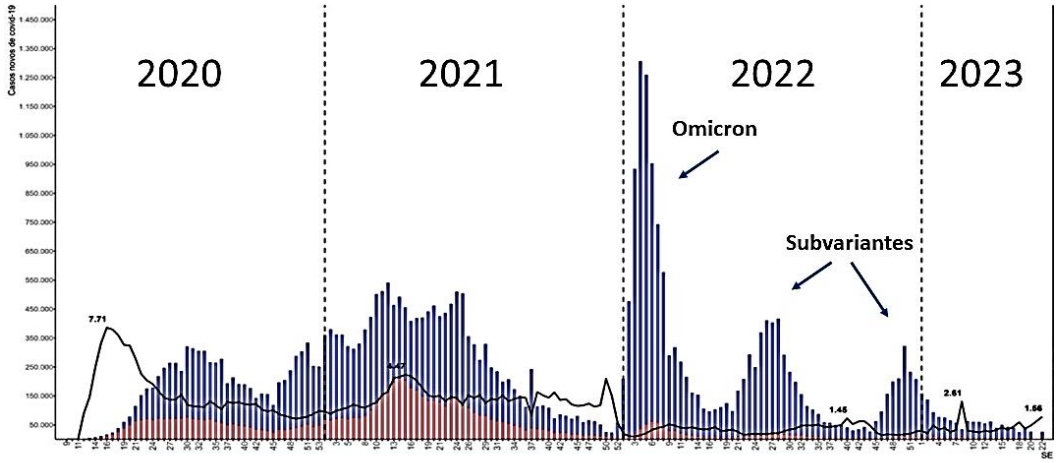


	2020	2021	2022	2023*
COVID-19 cases	7.716.405	14.575.102	14.039.774	1.294.635
SARS hospital admissions	700.565	1.214.520	235.568	22.706
COVID-19 deaths	195.725	423.380	74.748	9.438

The appearance of the Omicron variant of concern at the beginning of 2022 justifies the large number of COVID-19 cases in this period given its high transmissibility, but with lower hospitalization and death rates, due to the progressively greater number of vaccinated individuals.

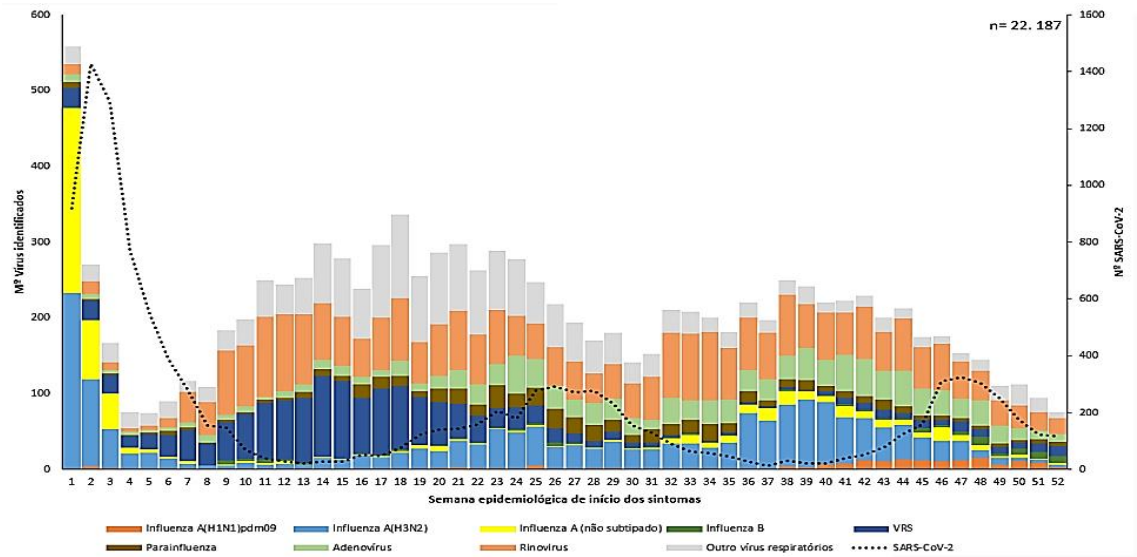
The great replication capacity of the Omicron variant has led to the rapid emergence of sub variants, leading to episodic increases in COVID-19 cases across the country (figure 2).

FIGURE 2. Cases, deaths and fatality rate from COVID-19 from 2020 to 2023[1]



It is very important to remember that the year 2022 also brought the return of other respiratory viruses (RV), which disappeared from the diagnosis scenario due to the high circulation activity of SARS CoV-2 and the containment measures implemented (use of masks, frequent hygiene of hands, use of alcohol gel, social distancing, etc.). With the reduction in the circulation of SARS CoV-2, other respiratory viruses began to circulate again. Figure 3 clearly shows the return of circulation of respiratory viruses throughout 2022[2].

FIGURE 3. Circulation of respiratory viruses in Brazil in 2022[3]



COVID-19 IN HCT RECIPIENTS PRE- AND POST-VACCINATION

Pre-vaccination data shows a high lethality of COVID-19 in allogeneic and autologous HCT recipients in Brazil and around the world (table 1).

TABEL 1. COVID-19 lethality in unvaccinated HCT recipients[4]

Author, year	N	Lethality	Risk factors for death
Sharma et al., 2020	318	32%	<50 years, masculine, 1º year CTH
Shah eet al., 2020	72	22%	-
Coll et al., 2020	85	20% alo; 24% auto	-
Varma et al., 2020	25	21%	Age, corticosteroid, 1º year CTH
Piñana et al., 2020	123	18% alo; 17% auto	Age, hypertension, PCR>20 mg/dL, lymphopenia
Ljungman et al., 2021	382	28,5% alo; 28% auto	Age, performance and ICU admission
Daudt et al., 2022*	86	15% alo; 36% auto	Age, performance and orotracheal intubation

In the pediatric population, SARS CoV-2 infection is often asymptomatic (30% to 40% of cases), and 47% of children have mild forms of COVID-19. However, approximately 10% of children can develop severe forms of the disease with fatality rates ranging from 3% to 8%[5,6].

Despite the intense circulation of the Omicron strain in 2022 and its subvariants, the morbidity and lethality of COVID-19 decreased with the progressive advancement of vaccination among HCT recipients as observed in the general population, demonstrating the capacity to respond to vaccination in this population.

A study carried out in a single Brazilian center including 174 cases of COVID-19 in HCT recipients showed a drop in COVID-19 lethality from 14.2% between May 2020 and May 2021, to 8% between June 2021 and May 2021. 2022. In this center, the lethality of COVID-19 was significantly higher in recipients of autologous HCT (23.5%) compared to allogeneic (4.7%)[7].

Meta-analyses of studies evaluating the humoral and cellular response to vaccination against COVID-19 showed a serological response in around 80% of recipients, slightly higher in autologous HCT compared to allogeneic[8,9]. Although the intensity of the antibody response was lower than that induced by COVID-19 vaccines in the general population, mass vaccination marked the easing of the pandemic and its impact on HCT centers.

It was three years of many sacrifices, hard work and a lot of sadness, but also of victories and achievements: better awareness of the importance of respiratory viruses and their transmission mechanisms, and greater adherence to control measures. Hand hygiene, use of masks, cough toilet, social distancing, etc., were measures incorporated into the daily routine not only of patients, but of the society as a whole. We gain access to systematic COVID-19 testing for candidates, recipients, donors, healthcare professionals, among others.

SYMPTOM SURVEILLANCE AND PRE-ADMISSION TESTING OF SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

It is important to remember that the recommendation for surveillance of respiratory symptoms and systematic testing of symptomatic candidates before admission for HCT precedes the COVID-19 pandemic[10]. This recommendation was initially justified by the high morbidity and mortality of respiratory syncytial virus (RSV) pneumonia in the first month of transplantation and the risk of transmission in the HCT unit. The opportunity to test asymptomatic patients can help the decision of postponing the transplantation in case of a positive test, since the risk of progression to RSV pneumonia is high if HCT is not postponed until symptoms resolution[11].

Subsequently, this recommendation was extended also to other respiratory viruses since they all present great morbidity, especially in the pre-grafting period[10,12,13]. Table 2 shows the incidence, frequency of pneumonia and mortality in hematological patients and HCT recipients, according to the respiratory virus diagnosed.

TABLE 2. Incidence, frequency of pneumonia and mortality from respiratory viruses[12]

Respiratory viruses	Incidence (%)	Pneumonia in diagnosis (%)	Mortality (%)
Influenza (INF) A/B	1.3-40	7-44	8-28
Parainfluenza (PIV)	3-27	7-50	10-50
Respiratory syncytial virus (RSV)	1-50	14-70	11-47
Human Metapneumovirus (HMPV)	2-11	5-41	6-40
Adenovirus (ADV)	1-30	14-42	14-73
Human Rhinovirus (HRV)	2-34	<5-27	<5-41
Human Coronavirus (HCoV)	3-23	<5	<5-54

Based on these data, some HCT centers in Brazil and many around the world have the testing of respiratory viruses in all candidates (symptomatic or not) before admission for transplantation as a standard of care.

The COVID-19 pandemic brought the opportunity to expand the testing recommendation also for asymptomatic candidates, due to the high transmissibility of SARS CoV-2 even in asymptomatic or pre-symptomatic cases. A systematic review and meta-analysis of 95 studies evaluating proven SARS CoV-2 infections showed a rate of 40.5% (95% CI; 33.5-47.5) of asymptomatic cases[14].

With the current decrease in COVID-19 cases in Brazil, several sectors (hospitals, transplant professionals, health plans, etc.) have been pushing to suspend the recommendation of pre-HCT testing for SARS CoV-2 in asymptomatic candidates.

However, we are still far from epidemiological stabilization of COVID-19. In August 2023, the World Health Organization (WHO) issued a statement about a new subvariant of interest (VOI) of the Omicron strain called EG.5, already identified in 51 countries. The EG.5 subvariant has new mutations that confer greater transmission capacity and immune escape, and is therefore capable of increasing the number of COVID-19 cases worldwide.

In light of this warning from the WHO, the Brazilian Society of Infectious Diseases published a technical note recommending to health authorities at the federal, state and municipal levels, measures to increase the collection of diagnostic tests and genomic surveillance of COVID-19 cases, aiming to early detection of the EG.5 subvariant[15].

In addition to the instability of the epidemiological situation of COVID-19 and the high frequency of asymptomatic infections caused by SARS CoV-2, other respiratory viruses circulate throughout the year in the community and data from Sivep-Gripe clearly show the increase in these agents when decreases the incidence of SARS CoV-2, possibly due to competition for the host. A recent epidemiological study demonstrated that the frequency of asymptomatic infections for most respiratory viruses in the general population is greater than 50%[16].

In HCT recipients, the frequency of asymptomatic infections with respiratory viruses other than SARS CoV-2 is about 23%, occurring in 14.5% of adults and more than 30% of the pediatric population[5,17,18].

Based on the above, the ideal recommendation for patient safety is not only to maintain the testing of asymptomatic patients, but also to expand the diagnostic capacity of the current assays targeting other respiratory viruses.

We understand that economic and/or logistical limitations interfere with the decision to test asymptomatic people. However, it is up to the SBTMO Infections Group to clarify the risks and define recommendations (even in an ideal scenario) that offer a greater probability of protection for patients and HCT Units. Likewise, it is up to HCT centers and Institutions to adjust these recommendations in the best possible way.

RECOMMENDATIONS FOR PREVENTION AND TESTING OF RESPIRATORY VIRUSES IN HCT UNITS

1. Healthcare professionals, HCT candidates, donors and recipients must be up to date with vaccinations against COVID-19 and influenza. Booster doses of the COVID-19 vaccine for this population must have been administered with the bivalent vaccine, and preferably less than 1 year ago. It is important to highlight that vaccines remain active in protecting severity and deaths for all circulating variants of SARS CoV-2, including EG.5[15].

2. Maintenance of non-pharmacological measures to control the transmission of respiratory viruses, that is, use of masks when indicated, social distancing, frequent hand hygiene with soap and water and/or alcohol gel, cough toilet, isolation of positive cases according to the recommended precautions, etc.

3. For the safety of HCT recipients and to reduce the risk of transmission of SARS CoV-2 and other respiratory viruses in HCT units, candidates, donors and companions must be tested for respiratory viruses before admission, regardless of the presence of respiratory symptoms.

4. Daily questioning of respiratory symptoms is mandatory for healthcare professionals, patients and companions throughout hospitalization, and during outpatient visits. Patients with symptoms should be removed from positive pressure rooms. All symptomatic patients should be tested for diagnosis of RV[13].

5. After HCT, testing of asymptomatic patients is only recommended for healthcare professionals, patients or companions who had contact in the previous week with a suspected or confirmed case of respiratory viruses.

6. The healthcare professional (symptomatic or asymptomatic) diagnosed with RV must be removed for a specified period of time in accordance with local recommendations.

7. Preferably, RV diagnosis should be made with PCR diagnostic platforms, including all respiratory viruses (multiplex). There are several multiplex PCR testing platforms available on the market. If it is impossible to use broad diagnostic platforms, customized solutions can be used, as long as they include the RVs that are known to pose a greater risk to the patient (RSV, Influenza A and B, Parainfluenza, Metapneumovirus, SARS CoV-2 and Adenovirus). ELISA tests and direct or indirect immunofluorescence tests (IFD or IFI) have good diagnostic sensitivity and specificity, although lower than molecular tests. The diagnostic targets of IF or ELISA tests are limited to include only RSV, INF A/B, PIV, and ADV.

8. Antigen tests for COVID-19 can be used in symptomatic patients, but not for screening asymptomatic individuals, as they have lower sensitivity compared to molecular tests[13]. Likewise, chromatography tests for RSV or INF A/B should not be used for diagnosis due to low sensitivity.

9. Donors who test positive for RV should be excluded from donating until full recovery from symptoms. There is no disease-free interval before transplantation considered optimal in the case of an infected donor[19]. In case of urgency for the transplant, the safest measure is to repeat the collection after 7 days and if the result is negative and the donor is asymptomatic, HCT can continue.

10. In candidates with a positive test for respiratory viruses, it is recommended to postpone the HCT. The decision to proceed with HCT must be balanced between the respiratory virus detected, the candidate's immunological status, the availability of antiviral and/or monoclonal drugs (in the case of COVID-19) that are effective in avoiding RV infection complications *versus* the risk of disease progression and the loss of remission status that will certainly affect the success of HCT. If the decision is to proceed with HCT, the candidate and/or guardian must be aware of the risks assumed by the team and authorize the transplant to be carried out.

11. In the case of candidates or recipients who have had COVID-19 and persist with a positive test for a prolonged period, the use of the PCR reaction CT above 30 cycles can be used to decide whether to admit the patient to the HCT unit (never in positive pressure rooms). In these cases, the risk of transmission is low, but not zero[13]. It is important to remember that CT >30 does not guarantee a lower risk of complications from COVID-19 after HCT.

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STUDY OF THE ASSOCIATION OF EXPOSURE TO GENOTOXIC AGENTS AND MYELODYSPLASTIC SYNDROME OR SECONDARY ACUTE MYELOID LEUKEMIA IN PATIENTS ATTENDED AT AN AMBULATORY REFERENCE SERVICE IN CEARÁ

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INTRODUCTION

Myelodysplastic syndromes (MDS) consist of a heterogeneous group of diseases with comprehensive clinical, laboratory characteristics and pathogenesis but have in common a clonal defect in hematopoietic progenitor cells[1]. MDS is characterized by cytopenia in peripheral blood with normocellular or hypocellular bone marrow with the presence of dysplastic changes (>10%) in one or more hematopoietic lineages. About a third of patients with MDS progress to myeloid leukemia[2,3]. The annual incidence of MDS occurs in 3 to 4/100,000 people in the United States[1]. Advanced age is one of the risk factors for the development of MDS, being rare in childhood[4], and it is more common in males[1]. Epidemiological studies have demonstrated the association between the occurrence of MDS and factors such as smoking, exposure to benzene and derivatives[2,5-12]. Pesticides, also commonly called pesticides and pesticides, are associated with the occurrence of leukemia, lymphoma and other hematological diseases[13-15], with a positive association between domestic exposure to pesticides and childhood leukemia[13].Poynter and colleagues [16] evaluated occupational and residential chemical exposures as risk factors for Acute Myeloid Leukemia (AML) and MDS using population-based data. Associations were verified between SMD and LMA and benzene and vinyl chloride. Exposure to soot, creosote, paints, dyes and tanning solutions, and coal dust have been associated with AML. Although chemical exposures have a clear role in the etiology of myeloid malignancy, these exposures do not represent the majority of cases, with exposures being reported in a small percentage of cases (≤ 10%)[16]. The issues of exposure of population groups to risk situations that cause myelotoxicity, which can trigger a hematological disease such as MDS or AML, justifies the relevance of the present study for public health. Understanding the epidemiological behavior of MDS and AML related to the environment and occupation is fundamental for prevention and the establishment of preventive measures. Therefore, the present study aims to associate the various health problems in patients with MDS and AML with the environmental/occupational risk conditions associated with them in a specialized hematology service.

OBJECTIVES

General

Associate exposure to genotoxic agents in patients with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia in a State reference hospital.

Specifics

• Determine the distribution of demographic and clinical characteristics of patients with MDS and AMLs treated at a reference outpatient service in the state of Ceará;

• Correlate personal and family history and occupational/environmental exposure to genotoxic agents with the occurrence and problems related to MDS and/or AMLs;

• Establish a causal relationship between exposure to environmental or occupational hematotoxic risk situations with the occurrence of MDS and AMLs

MATERIALS AND METHODS

This is an observational, prospective and retrospective study, through research in patient records. The study was carried out in the state's main hematology reference service, located in the onco-hematological diseases outpatient clinic of the Walter Cantídio University Hospital (HUWC), in Fortaleza, Ceará. The population of this study consisted of adults of both sexes, with a diagnosis of MDS and/or AML confirmed by the clinic and laboratory tests, undergoing outpatient follow-up care from July 2021 to July 2022, capturing a total of 50 patients. Those patients who did not reside in Ceará and who were diagnosed with another oncological disease were excluded from the study. HUWC is a reference in the care of people with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia located in the Rodolfo Teófilo neighborhood, Fortaleza-CE.

All procedures were carried out in accordance with the ethical guidelines established by resolution 466/12 of the National Health Council. To this end, immediately after the consultation, the patient was informed about the study and after reading and signing the informed consent form (TCLE), the study included the application of a pre-structured questionnaire lasting approximately 20 minutes. From then on, consultation of medical records was possible by signing a trust form. by the hospital superintendent. The data obtained in the study regarding hematological diseases were crossed with data from the literature, aiming to establish a causality criterion with environmental or occupational risk conditions.

The cases were distributed considering individual characteristics, personal, occupational and environmental history. For purposes of comparison between variables (dependent and independent), cases were grouped according to contingency tables. The data collected will be analyzed using the SPSS Program (Statistical Package for the Social Sciences) version 8.0. The study population characterization data were presented using absolute and relative frequencies and organized in simple tables. Differences were considered statistically significant when $p< 0.05$.

Inclusion criteria

Patients with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia treated at the HUWC outpatient clinic were invited to participate in the study consecutively. Informed consent was obtained prior to carrying out any study procedures.

Exclusion criteria

Patients who did not meet diagnostic criteria for MDS or AML were excluded from the research.

Risks and Benefits

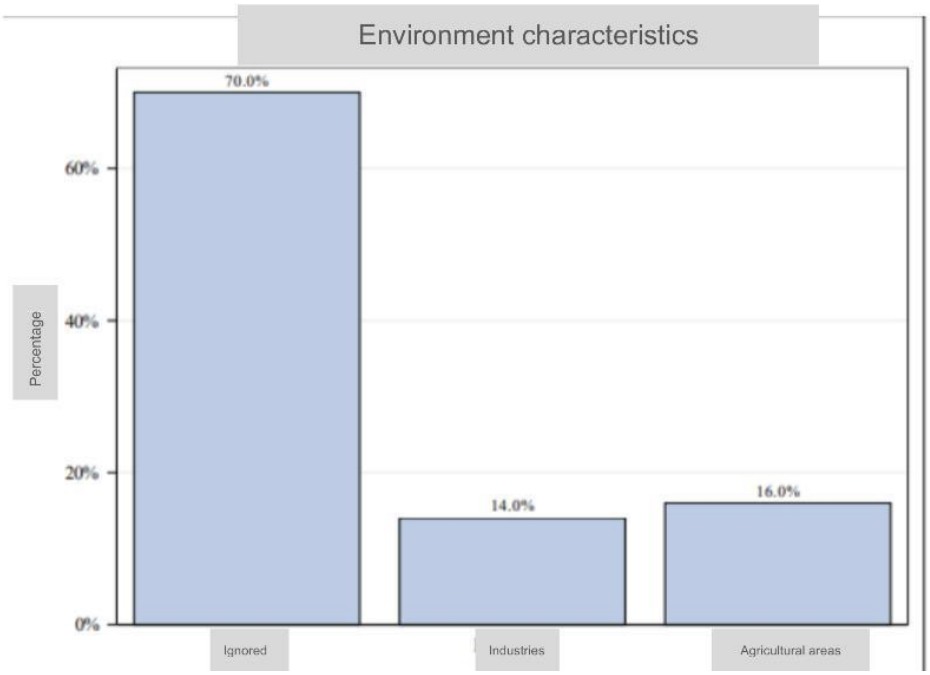
Risks: The questionnaires were administered before or after routine consultations at the unit. No extra travel was necessary. The assessment was carried out in the usual way. The risk of the present study was related to the confidentiality of the information and data of the research participants.

Benefits: The information collected in the questionnaire contributed to the understanding of the association between genotoxic agents and MDS and AMLs. Participation in the study is voluntary.

RESULTS

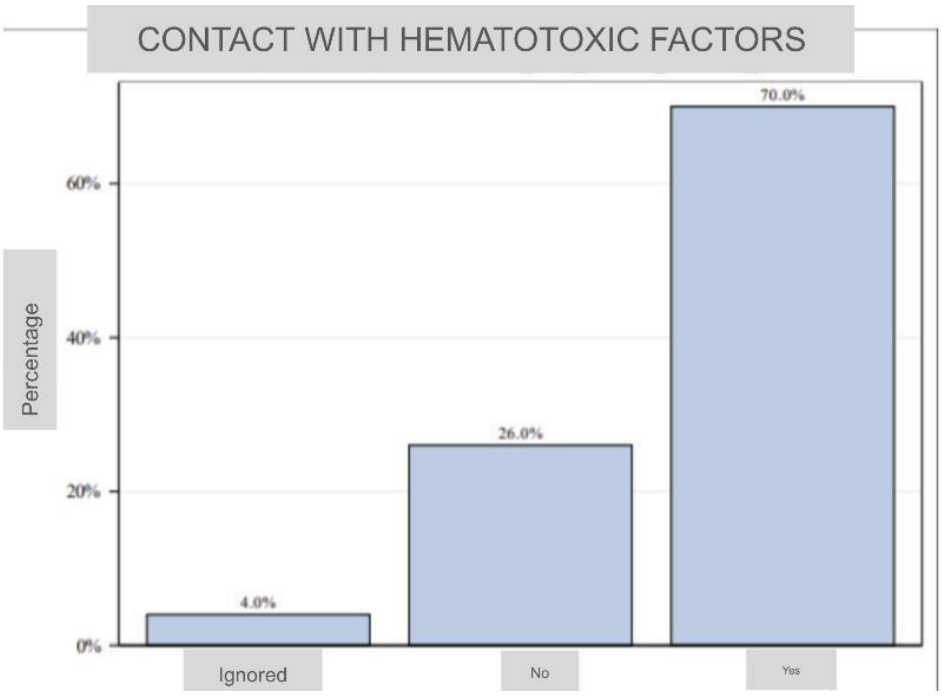
The sample collected consists of 50 patients who were undergoing therapeutic activities at the HUWC Hematology Service, with an average age of 67.8 years. Among these, 14 patients (28%) were male, while 36 patients (72%) were female. With regard to race, a numerical superiority was noted in mixed/brown indigenous individuals and Caucasian/white individuals; which, together, accounted for 90% of the patients interviewed. Regarding the patients' level of education, a diverse range was found, in which 7 patients (14%) were illiterate and 43 patients (86%) had some level of education. Regarding domicile situation, 6 patients (12%) live in rural areas, while 44 patients (88%) live in urban areas. In this sense, it was reported that 30% of these patients live in residences close to industries (14%) and agricultural areas (16%) (Figure 1).

FIGURE 1 – Environment characteristics



Of the patients interviewed, 47 were diagnosed with myelodysplastic syndrome; while 3 - have a diagnosis of acute myeloid leukemia. Of these, 11 patients reported having reports of similar hematological disease in the family. Of the 50 patients, 35 patients (70%) stated that they had contact with factors hematotoxic; of these: pesticides (30%), metals (6%), solvents (38%), paints and varnishes (38%) and ionizing radiation (40%) (Figure 2).

FIGURE 2 – Contact with hematotoxic factors



When it comes to lifestyle habits, it was reported that 42 patients (84%) were using medications, such as: antihypertensives (46%), antibiotics (5%), cardiotonics (6%), hypoglycemic drugs (15%), centrally acting drugs (26%), gastroprotectors (14%) or anti-inflammatory drugs (4%). In social history, 15% of patients reported smoking or having a previous history of smoking. With regard to alcohol consumption, 14% reported drinking or having a previous history of alcoholism. Regarding the consumption of illicit drugs, only 1 patient (2%) reported using or having a previous history of dependence.

DISCUSSION

In the present study, it is possible to observe a higher number of female patients (72%) compared to male patients (28%), one of the factors possibly related to the increased prevalence of MDS and AML would be the exposure of some women to hematotoxic products from dyes used in hair, as the female public is exposed in greater quantities to these factors compared to the male public. According to the study Hair Dye Ingredients and Potential Health Risks from Exposure to Hair Dyeing. In the American and European population, around 33% of women over 18 and around 10% of men over 40 dye their hair. Permanent hair dyes penetrate the hair to change the natural hair color, and are more often associated with adverse reactions and pose a greater risk to human health. Two population-based case-control studies related[3,17] that patients subjected to the use of hair dye had a higher prevalence of primary myelodysplastic syndrome when compared to individuals who did not have such exposure[18].

The predominance of patients living in urban locations (88%) in our study is notable, however patients living in rural locations (12%) may have been exposed to pesticides that are toxic to the bone marrow, especially pesticide agents. The relationship between occupational exposure to pesticides in high doses and the occurrence of several diseases is well established, notably in hematological malignancies, recently reported in AML[19,20].

According to the study Low-Dose Pesticides Alter Primary Human Bone Marrow Mesenchymal Stem/Stromal Cells through ALDH2 Inhibition[21], the risk of developing a myeloid disorder (MDS or AML) for individuals exposed to such components is increased compared to the general population, however the contribution of pesticide products to the development of such hematological disorders in the exposed individual is low, thus suggesting a multifactorial pathophysiology that may include environmental impact. This hypothesis is supported by the observation that there is an underexpression of aldehyde dehydrogenase 2 (ALDH2), with an increased concentration of acetaldehyde in the stromal and mesenchymal cells of patients exposed to pesticides who developed primary MDS[21].

(ALDH2) is known to be a cytosolic enzyme responsible for the intracellular oxidation of aldehydes, which is involved in the oxidation of retinol to retinoic acid during the initial stages of differentiation of hematopoietic stem cells (HSC). This enzyme is crucial for the protection of HSCs against endogenous and exogenous toxic aldehydes, as well as for the ability of these cells to differentiate into distinct lineages[21].

In the sample collected, it was seen that 11 patients (22%) had similar hematological diseases in the family. Currently, approximately 7 loci of a single gene are known that, when mutated, predispose to an increased risk of developing primary MDS and AML. Table 1 summarizes the 7 single-gene loci that predispose to hereditary MDS, as well as the two most common pediatric bone marrow failure diseases that increase the risk of adult incidence of MDS.[25]

Therefore, clinicians should be aware of the signs and symptoms of hereditary predisposition to hematologic malignancies and should obtain a family history and careful history in all patients with MDS and AML to identify patients who may be appropriate for additional genetic counseling and testing. Since, individuals with such inherited genes need additional consideration regarding the appropriate therapeutic choice, especially with regard to allogeneic stem cell transplantation[22]. In our study, there was a numerical predominance of mixed/brown individuals and Caucasian/white individuals; which, together, accounted for 90% of the patients interviewed. Findings from the study The incidence, risk factors, and survival of acute myeloid leukemia secondary to myelodysplastic syndrome: A population-based study indicate that race does not alone contribute to the increased risk of developing AML and/or MDS, but when other variables are attributed such as: Married marital status, female sex and black race demonstrated a better prognostic impact on survival when compared to single, white, male individuals who demonstrated a worse prognostic impact on survival[23].

In the sample of the present study, it was proven that 11 patients had contact with pesticide agents. In a 2021 study, Foucault et al evaluated exposure to pesticides and the relationship with changes in the mesenchymal stroma of the bone marrow, altering the production of cell activity. ALDH2 enzyme, which

TABLE 1 – Familial myelodysplastic syndromes (MDS)/acute leukemia (AL) prodisposition syndromes

Syndrome	Gene	Inheritance	Heme Malignancy	Other Associated Abnormalities	Reference
Familial platelet disorder with propensity to myeloid malignancies	*RUNX1*	AD	MDS/AML/T-cell ALL	Thrombocytopenia, bleeding propensity, aspirin-like platelet dysfunction	[3]
Thrombocytopenia 2	*ANKRD26*	AD	MDS/AML	Thrombocytopenia, bleeding propensity	[4]
Familial AML with mutated DDX41	*DDX41*	AD	MDS/AML, CMML	None	[5]
Thrombocytopenia 5	*ETV6*	AD	MDS/AML, CMML, B-cell ALL, multiple myeloma	Aplastic anemia	[6]
Familial MDS/AML with mutated GATA2	*GATA2*	AD	MDS/AML/CMML	Neutropenia, monocytopenia, MonoMAC syndrome, Emberger syndrome	[7]
Familial aplastic anemia with SRP72 mutation	*SRP72*	AD	MDS	Aplastic anemia	[8]
Familial AML with mutated CEBPA	*CEBPA*	AD	AML	None	[9]
Fanconi anemia	Complementation Groups	AR, X-linked	MDS, AML	Pancytopenia, macrocytic anemia, congenital malformations	[10]
Telomeropathies (dyskeratosis congenita)	*TERC, TERT,* others	AD, AR	MDS/AML	Macrocytosis, aplastic anemia, oral leukoplakia, dysplastic nails, lacy skin rash	[11]

AD, Autosomal dominant; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CMML, chronic myelomonocytic leukemia; AR, autosomal recessive.

induces accumulation of acetaldehyde and damage to DNA, causing defects in primitive hematopoiesis. Therefore, the genotoxicity of these components and the need for appropriate preventive measures are reaffirmed.

In a study carried out in 2016 involving exposure to polycyclic aromatic hydrocarbons and other metals[24], 41 studies were analyzed, in which, in 4, significance was seen between aluminum, iron and steel smelting industries and the occurrence of leukemias and lymphomas not hodgkin. In the present study, an association of 6% with metals and 38% with solvents was seen, lacking more relevant studies.

In a systematic review carried out in 2022, it is reported that 2 population studies determined that the use of hair dye is a risk factor for MDS[3,17], although a large number of studies have found no significant association between hair dye and an overall increased risk for leukemias, NHLs or myelomas. Therefore, given the presence of conflicting data, further studies are necessary.

In a study that evaluated radiation exposure in children in 2012[25] an association was seen between brain tumors and leukemia in children who underwent more CT scans. In addition to this finding, 40% of the patients studied had some exposure to radiation.

Tobacco remains an important risk factor associated with neoplasms, despite a reduction due to awareness campaigns over the years, in a 2021 study, it was proven that leukemias still constitute 13% of malignancies caused by smoking.mar[26]. We observed in our sample an exposure of 15% of patients among smokers and ex-smokers.

CONCLUSION

The biases in the study were the number of patients, as it is a rare disease, and the failure to monitor patients longitudinally, which makes an analysis of cause and consequence impossible.

Lack of knowledge about this pathology combined with its low incidence makes early diagnosis

difficult, increasing morbidity and mortality, making it necessary to focus more on this disease in the training of primary care doctors. Knowing the main risk factors can help in the screening and diagnostic suspicion of myelodysplastic syndrome, mitigating its complications, such as acute myeloid leukemia.

In short, it has been demonstrated that the main factors involved in the genesis of Myelodysplastic Syndrome are family history and exposure to hepatotoxic factors, such as pesticides, paints, varnishes and radiation. Demonstrating the need for guidance from the health system to the population with the aim of primary prevention of a disease with a high rate of morbidity and mortality and treatments that are difficult to access.

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USE OF INFLAMMADRY® FOR MMP-9 DETECTION IN OCULAR GRAFT VERSUS HOST DISEASE

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ABSTRACT

Background: InflammaDry® is a point-of-care test that can detect matrix metalloproteinase-9 (MMP-9), an inflammatory biomarker that is elevated in ocular surface stress and desiccation, such as in ocular graft-versus-host disease (oGVHD).

Objectives: To characterize MMP-9 levels in patients diagnosed with oGVHD and to assess InflammaDry® ability to detect ocular surface disease in patients diagnosed with oGVHD.

Methods: A retrospective chart review was completed on 74 patients who have undergone a hematopoietic stem cell transplantation (HSCT) and have been diagnosed with oGVHD. Date of chronic GVHD diagnosis; date of ocular symptoms onset; oGVHD NIH grade on day of InflammaDry® testing; InflammaDry® results; and interventions used to treat ocular symptoms were collected on each patient. Percent positivity, positivity rate and accuracy of InflammaDry® was calculated.

Results: The positivity rate of InflammaDry® showed an increasing trend in relation to increasing oGVHD severity as well as an overall percent positivity of 87.16% and accuracy of 88.36%.

Conclusion: InflammaDry® has demonstrated to be a promising tool that may be used as a screening tool to detect the development of oGVHD onset. However, before InflammaDry® can be implemented into Hematology/Oncology clinics, the rate of positivity of InflammaDry® in patients pre-HSCT must first be determined.

Keywords: Matrix Metalloproteinase 9. Graft-versus-host disease.

INTRODUCTION

Graft-versus-host disease (GVHD), which can be defined as either acute or chronic, is a complication following allogeneic hematopoietic stem cell transplant (HSCT) that is a major contributing factor to patient morbidity and mortality[1]. Acute GVHD was defined as symptoms manifesting before day 100 following HSCT, and chronic GVHD was defined as symptoms continuing or manifesting after one hundred days following HSCT[2]. However, new guidelines suggest that the difference between acute GVHD and chronic GVHD diagnosis should be based on the manifesting symptoms of the patient. While some organs, such as the skin, mouth, gastrointestinal tract, liver, and lungs, can be involved in both acute and chronic GVHD; organs such as the eyes, muscles, genitalia, and nails are typically only impacted in chronic GVHD[3]. Specifically, between 40-60% of patients who develop chronic GVHD will develop ocular complications, also known as ocular graft versus host disease (oGVHD)[4]. Symptoms of oGVHD

include photophobia, redness, pain, excessive tearing, blurred vision, grittiness, or foreign-body sensation[5,6]. Common clinical ocular manifestations include the ocular surface, resulting in keratoconjunctivitis sicca, cicatricial conjunctival fibrosis, corneal perforation, and filamentary keratitis[5, 7-9]. However, oGVHD can additionally affect all tissues of the eye, including the retina and optic nerve[10]. Therefore, oGVHD can negatively affect patient quality of life and cause sight-threatening vision loss[5, 7-10]. The severity of oGVHD is graded on a scale developed by the NIH, ranging from 0-3. A grade of zero represents a patient with no symptoms of oGVHD, whereas a grade of three represents a patient with severe symptoms, which significantly affect their activities of daily living (Table 1)[11].

TABLE 1. National Institute of Health grading scale on severity of ocular graft-versus-host disease. Adapted from Inamoto et al. (2012).

Grade	Findings
0	Asymptomatic
1	Mild dry eye symptoms not affecting ADLs (requiring artificial tears ≤ 3x per day) OR asymptomatic + findings of keratoconjunctivitis sicca
2	Moderate dry eye symptoms partially affecting ADLs (requiring eye drops > 3x per day or punctal plugs) without vision impairment
3	Severe dry eye symptoms significantly affecting ADLs (requiring special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca

While the pathogenesis of oGVHD is not completely understood, using murine models has allowed for an improved understanding of the disease process[12]. Concepts regarding the disease process of oGVHD include an increase in IL-6 followed by Treg cell suppression and increased host Th17 cells, corneal infiltration of graft and host mature T-cells, and infiltration of donor-derived fibroblasts leading to immune-mediated fibrosis causing lacrimal gland dysfunction[13-15]. Overall, despite the unclear pathogenesis of oGVHD, it is well accepted that oGVHD is caused by autoimmune destruction of corneal and conjunctival epithelium along with lacrimal gland destruction leading to tear film deficiency. This destruction leads to loss of tissue function, vascularization, and fibrosis resulting in impaired vision or blindness and ocular discomfort or pain[10]. The decreasing morbidity of oGVHD is pertinent and can be achieved by earlier diagnosis and earlier treatment.

InflammaDry® is a point-of-care test that can detect matrix metalloproteinase-9 (MMP-9), an inflammatory biomarker that is elevated in ocular surface stress and desiccation, such as symptoms seen in oGVHD[16-19]. InflammaDry® has an 85% sensitivity and 94% specificity in detecting MMP-9 at a threshold of 40 ng/ml[20]. MMP-9 is a protease that plays a role in many biological processes, such as wound healing. MMP-9 functions via the degradation of many extracellular matrix proteins, altering cell-to-cell interactions and basement membrane degradation[21]. While overexpression of MMP-9 in ocular surface disease may be necessary for wound healing, this molecular marker may also cause collagenous filaments, tissue remodeling and vascular proliferation[19]. Additionally, MMP-9 has been shown to induce proinflammatory molecules including IL-1, TNF-alpha and NF-kB[19]. Given MMP-9 overexpression to allow for wound healing, this marker has provided a diagnostic marker of ocular surface disease[19], and has been shown to be significantly elevated in oGVHD as compared to other dry eye disease causes[22]. The purpose of this study is to determine if InflammaDry® is able to detect MMP-9 in the tear film of patients diagnosed with oGVHD.

METHODS

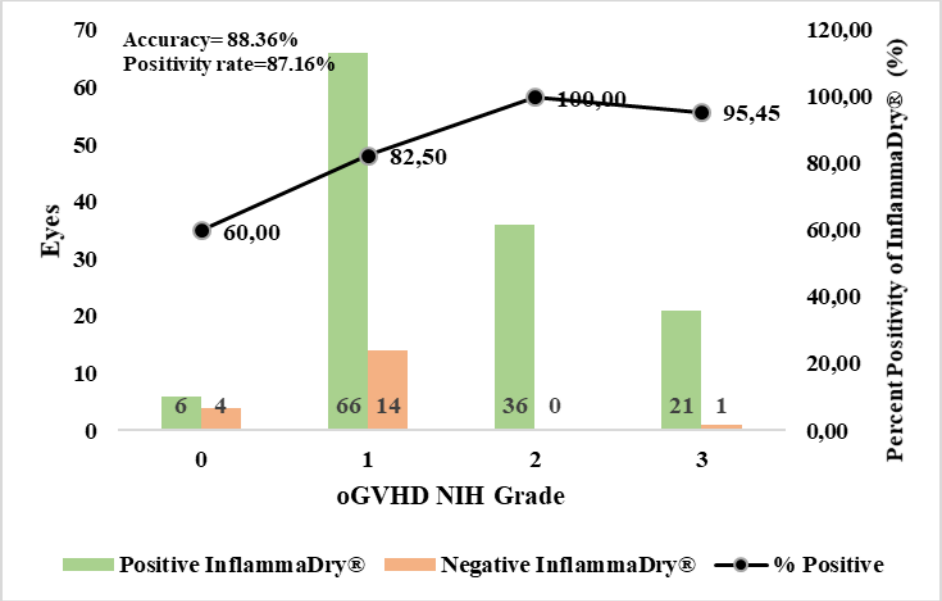
A retrospective chart review was completed on 74 patients who have undergone a hematopoietic stem cell transplantation (HSCT) and have been diagnosed with oGVHD. Demographic data (MRN, age, gender, ethnicity); oncologic diagnosis; date of HSCT; date of chronic GVHD diagnosis; date of ocular symptoms onset; date of referral to ocular surface disease (OSD) clinic; date of

initial appointment at the OSD clinic; oGVHD NIH grade on day of InflammaDry® testing; InflammaDry® test date; InflammaDry® results; and interventions used to treat ocular symptoms were collected on each patient. InflammaDry® results were marked as either positive or negative. To analyze these data, InflammaDry® test results were plotted against oGVHD NIH grading (Grade 0, 1, 2 or 3). The percentage of positive InflammaDry® tests per NIH grade was also plotted on the same graph, which was calculated with the equation [% Positivity Rate= # Positive Tests in NIH grade/ Total Tests for NIH grade]. The overall positivity rate of InflammaDry® was calculated with the equation [Total Positive Tests/ Total Tests Collected]. Accuracy of InflammaDry® was analyzed with the equation [Accuracy= (# True Positive tests/ (# True Positive + # True Negative))*100]. The number of days it took for a patient to receive InflammaDry® testing from an eye care provider following cGVHD diagnosis was determined by subtracting the date of InflammaDry® testing from the date of cGVHD diagnosis. The average, median and range of number of days was calculated based off data from all 100 patients from which this study collected data from. Additionally, the number of days it took for a patient to receive InflammaDry® testing from an eye care provider following ocular symptom onset was calculated with the question [Number of days= Date of InflammaDry® testing – Date of ocular symptom onset]. The average, median and range was calculated from all 100 patients from which this study collected data from. Lastly, to analyze which ocular treatments patients were using at the time of InflammaDry® testing, the total number of patients on any given ocular treatment was collected. The number of patients were placed into a table under the category of treatment they were using. Patients may have been using multiple concurrent treatments at the time of InflammaDry® testing. Therefore, some patients had multiple treatments and were duplicated to account for each modality they were using. Treatments used prior to InflammaDry® testing were not collected in this analysis.

RESULTS

The positivity rate for oGVHD NIH Grade 0, 1, 2 and 3 were 60%, 82.50%, 100% and 95.45%, respectively. An example calculation for percent positivity for NIH grade 0 [(%)= (6/10) * 100 = 60% positivity]. The overall percent positivity of InflammaDry® was 87.19% (Figure 1).

FIGURE 1. Positivity rate of InflammaDry® in patients diagnosed with ocular graft versus host. Primary axis: Number of eyes that resulted positive or negative using InflammaDry® at a given diagnosed ocular graft versus house NIH grade (0-3). Secondary axis: Positivity rate of InflammaDry® at each ocular GVHD NIH grade. N= 148 eyes (74 patients).



Overall percent positivity of InflammaDry® was calculated using the equation [(129/ (129 + 19)) * 100 = 87.16% positivity]. The positivity rate showed an overall increasing trend that correlated with increasing oGVHD symptom severity. However, while 100% of InflammaDry® tests were positive at oGVHD Grade 2, only 95.45% of InflammaDry® tests were positive at oGVHD Grade 3 (Figure 1). The singular InflammaDry® test that resulted negative in a patient with oGVHD Grade 3 was a false negative, because a repeat InflammaDry® test resulted positive in both eyes. Upon further analysis of data, it was determined that there was another false negative in the category of oGVHD Grade 1. Again, the rationale behind this is because a repeat InflammaDry® test resulted positive in both eyes. False negatives could have been due to inadequate tear collection using InflammaDry®. Given the two false negatives, accuracy of InflammaDry® was calculated to be 88.36% (Figure 1). Accuracy was calculated using the follow equation: (129/ (129 + 17)) *100 = 88.36% accuracy.

The impact of the length of time the patient had oGVHD and treatments for ocular symptoms on InflammaDry® testing was also analyzed. The median number of days from the time a patient was diagnosed with cGVHD to when the InflammaDry ® test was completed was 953 days (Table 2).

TABLE 2. Analysis of the number of days between the date of chronic graft versus host disease diagnosis and date of InflammaDry® testing. Number of days= Date of InflammaDry® testing- Date of chronic GVHD diagnosis. Number of days was collected from 74 patients. Average number of days, median number of days and range of number of days were determined.

Average (Days)	Median (Days)	Range (Days)
1255.87	953	-64-5903

Additionally, the median number of days between the time a patient presented with ocular symptoms, as documented at their oncology appointments, from when an InflammaDry ® test was completed was 834 days (Table 3).

TABLE 3. Analysis of the number of days between the date of ocular symptom onset and date of InflammaDry® testing. Number of days= Date of InflammaDry® testing- Date of ocular symptom onset. Number of days was collected from 74 patients. Average number of days, median number of days and range of number of days were determined.

Average (Days)	Median (Days)	Range (Days)
1166.03	834	7-5079

Furthermore, 78.38% of patients were on symptomatic treatment for oGVHD on the same day of InflammaDry® testing using artificial tears. Additionally, 22.97% of patients were using warm compress, 18.92% were using Cyclosporine and 16.22% were using topical steroid drops (Table 4).

TABLE 4. Therapies used on the day of InflammaDry ® testing. Categories of therapies which patients were using on the same day of InflammaDry ® testing were collected. For each category of treatment, the total number of patients on that given treatment was determined from a population of N=74 patients. The relative percentage of patients on each given treatment was calculated [% of patients on X therapy= (Number of patients on X therapy/ Total number of patients) *100]. N= 74 patients.

Current treatment on day of InflammaDry ® test	Number of patients	Percentage of patients on therapy (%)
Cyclosporine	14	18.92
Artificial tears	58	78.38
Lubricating ointment	4	5.41
Warm compress	17	22.97
Cold compress	1	1.35
Punctal plugs	3	4.05
Punctal cautery	1	1.35
Topical steroid	12	16.22
Lifitegrast	7	9.46
Lid scrubs	14	18.92
Autologous serum drops	9	12.61
Topical antibiotics	3	4.05
Oral antibiotics	6	8.11
Albumin drops	2	2.70
Scleral lenses	1	1.35
Fish oil	1	1.35
Red eye drops	4	5.41
Allergy drops	4	5.41
None	8	10.81

DISCUSSION

The positivity rate of InflammaDry® showed an increasing trend in relation to increasing oGVHD severity as well as an overall percent positivity of 87.16% and accuracy of 88.36% (Figure 1). On the day of InflammaDry® testing, patients had been experiencing symptoms of cGVHD for a median of 953 days (Table 2) and symptoms of oGVHD for a median of 834 days (Table 3) prior to InflammaDry® testing. Additionally, 78.38% of patients had been on symptomatic treatment for oGVHD on the day of InflammaDry® testing. This suggests that while patients were being treated for oGHVD, InflammaDry ® testing and therefore MMP-9 production was minimally impacted given an 87.16% overall positivity rate of InflammaDry ® over all oGVHD grades (Figure 1).

Research has shown that treatments such as doxycycline and methylprednisolone lead to a decrease in MMP-9 expression and, furthermore, prevention of recurrent epithelial erosion[23], suggesting that treatment targeting MMP-9 may be beneficial in improving patient's symptoms of ocular surface disease[19]. However, despite patients being on treatment, there was still an 87.16% overall positivity rate of InflammaDry®. On reviewing the types of treatment used by patients, only 16.22% of patients were using topical corticosteroids and only 8.11% were using oral antibiotics, such as doxycycline (Table 4). Treatments with topical corticosteroids and oral antibiotics may have played a role in decreasing MMP-9 production and therefore impacted the overall positivity rate of InflammaDry®. However, given that length of treat-

ment was not considered, nor was InflammaDry® collected before and after initiating treatments, this study cannot draw conclusions on which treatments may have resulted in a decrease in MMP-9 production. Furthermore, it can be inferred that treatment minimally impacted InflammaDry® results, given that patients with more severe oGVHD symptoms (NIH Grade 2 and 3) were likely on a more intensive treatment regimen; however, InflammaDry® positivity rates were improved in these patients as compared NIH Grade 0 and 1.

Given the positivity rate (87.16%) and accuracy (88.36%) of InflammaDry® in detecting MMP-9 in patients with oGVHD, InflammaDry® could be used as a screening tool for oGVHD onset. The importance of a screening tool for oGVHD is to earlier detect the onset of oGVHD prior to symptom onset, allowing for earlier treatment initiation. Research suggests that earlier treatment is necessary to decrease morbidity in patients with oGVHD[5], therefore improving their quality of life. However, further investigation needs to be pursued to determine whether MMP-9 is present in patients prior to undergoing an allogeneic HSCT. It has already been demonstrated that dry eye disease has been detected in patients with hematological diseases before HSCT[24]. Therefore, in order to determine whether InflammaDry® can be used as a screening tool for oGVHD, it needs to first be determined whether MMP-9 is elevated in patients who will be undergoing an allogeneic HSCT. Should MMP-9 be elevated in patients before HSCT, prophylactic treatment for oGVHD, even prior to HSCT, may be warranted.

CONCLUSION

Given the high positivity rate (87.16%) and accuracy (88.36%) in detecting MMP-9 in patients with known oGVHD, InflammaDry® has been demonstrated as a viable screening tool to determine if a patient has oGVHD. Therefore, InflammaDry® can be used: 1) by oncology providers at patient appointments following HSCT to quickly and accurately determine if a patient is developing oGVHD disease, 2) to initiate treatment, and refer a patient to an eye care practitioner sooner. Due to this, implementing the use of InflammaDry® during oncology clinic appointments may help reduce ocular morbidity caused by GVHD. However, before implementing InflammaDry® as a screening tool in Hematology/Oncology clinics, the positivity rate of InflammaDry® pre-hematopoietic stem cell transplant must be determined. If InflammaDry® results positive prior to receiving HSCT, this would suggest candidates have ocular surface inflammation due to a cause other than oGVHD, and therefore InflammaDry® would not be a good screening tool to detect oGVHD onset.

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REPOSITIONING AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE MANAGEMENT OF NEWLY DIAGNOSED MULTIPLE MYELOMA

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High-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) has been a cornerstone of treatment for patients with newly diagnosed multiple myeloma (NDMM) for the last three decades. The essence of this treatment is the powerful anti-myeloma effect of melphalan when administered at standardized high doses that require rescue with autologous hematopoietic stem cell transplantation for optimal safety. This procedure is considered mainstream therapy for patients up to the age of 70 (and older patients in some contexts), is available worldwide and has demonstrated progression-free survival advantage over a strategy of deferred transplantation in multiple historical and recent randomized trial, including in the context of modern, triplet therapy (Table 1).

Autologous transplantation, however, carries substantial inconvenience and toxicity. It causes universal alopecia, pancytopenia exposing patients to the risk of infections, potentially serious gastrointestinal toxicity and transient yet pronounced impairment in quality of life[1]. ASCT also likely contributes to the long-term risk of second malignant neoplasms in patients with multiple myeloma[2]. It is therefore a genuine pursuit to identify circumstances when autologous stem cell transplant may not be necessary. Here we provide a critical review of the most recent available data appraising the role of autologous transplantation in newly diagnosed myeloma, discuss existing challenges with current evidence an ongoing research effort that might lead to a more refined use of this therapy in the future.

PROGRESSION-FREE SURVIVAL, BUT NO OVERALL SURVIVAL ADVANTAGE

There has not been a randomized clinical trial in the last two decades that compares ASCT vs. no-ASCT in NDMM[1,3-6]. Every single one compares a strategy of upfront vs. deferred ASCT, with transplant being offered at time of first progression. Every one of these trials were designed and powered to test impact of upfront ASCT in progression-free survival (PFS), and showed that deferring ASCT jeopardizes PFS. Strictly speaking, all those trials were "positive" and demonstrated an improvement in PFS, the primary endpoint, for upfront ASCT even in the setting of triplet therapy with a proteasome inhibitor (PI) and immunomodulatory agent (IMiD) and dexamethasone.

While these trials often reported overall survival (OS) as a secondary endpoint, none reported difference in OS favoring either arm generating the hypothesis, and often the narrative, that ASCT might be dispensed from the initial therapy without affecting OS. There are, however, several limitations to this extrapolation.

First, all these trials included ASCT at the time of initial progression. Therefore, by trial design, patients eventually paid the "penalty" of the ASCT toxicity since progression in the deferred transplant arm seems unavoidable. So if the objective is to avoid to harm from ASCT while preserving OS, this strategy is flaw. Rate of ASCT at the time of progression varies substantially across trial, and was reportedly < 30% in the recent DETERMINATION trial, however that

trial was affected by substantial early censoring and post progression therapy not fully described.

Secondly, randomized clinical trials are planed rigorously around a central hypothesis that guides the statistical design. None of these trials were planned around an OS hypothesis, therefore did not have the proper number of participants and duration of follow up to test an OS benefit of upfront ASCT. That is particularly important as the median OS of patients treated with triplet therapy and ASCT seem to exceed 10 years. Therefore, OS comparisons in these trials are plagued by a very high risk of type 2 error.

Thirdly, and most importantly, OS may just be an unfeasible and unreasonable endpoint to appraise therapies in transplant-eligible, NDMM. In current era, patients often experience deeper and prolonged responses during second line therapy and beyond. In a condition with OS now exceeding 10 years, the therapies available at time of recurrence are often different and superior to the therapies available at the time of trial design. Since these trials do not control post-progression therapy, the heterogeneity introduced makes post progression data extremely challenging to interpret. This is true not only for ASCT. In fact, drugs that are pivotal in the management of younger patients with NDMM, such as lenalidomide and bortezomib, have not been shown to improve OS in transplant-eligible NDMM (exception for lenalidomide in the maintenance setting). In fact, all evidence for OS impact of PI, IMiD and, most recently, anti-CD38 monoclonal antibodies in NDMM comes from trials of non-transplant-eligible patients with NDMM, a population with much higher rate of events and more limited post-progression survivorship. If we were to reject upfront ASCT on the basis of lack of OS advantage despite PFS benefit, we would have to reject bortezomib, lenalidomide and daratumumab as part of upfront therapy in order to stay consistent.

ASCT AND RISK STRATA

NDMM is a notoriously heterogenous condition in terms of clinical presentation and, most importantly, clinical outcome. Such heterogeneity is recognized by multiple prognostic system based on clinical characteristics and presence of certain chromosome abnormalities. More recently, the presence of gene expression signatures and single-gene mutations were demonstrated to affect long term prognosis. However, with very few exceptions, randomized clinical trials in NDMM define population by age and organ function, not by disease characteristics. While the overall result of the trial captures the typical effect of the intervention, it may miss nuances in particular disease subsets.

Cytogenetic risk, for instance, appears to modulate the impact of upfront ASCT in NDMM. In the EMN-02 trial, a pronounced impact of upfront ASCT on PFS (HR 0.63, 95% CI 0.46-0.88) and OS (HR 0.66, 95% C.I. 0.45-0.99) was seen in patients with high-risk chromosome abnormalities, either del17p, t(4;14) or t(14;16). In fact, patients with high risk cytogenetics appear to benefit from tandem vs. single ASCT in terms of PFS (HR 0.59, 95% C.I. 0.34-1.03)[5]. In the more recent DETERMINATION trial, high-risk patients treated with triplet induction and consolidation therapy and ASCT had median PFS of 55.5 months vs. 17.1 months in those who deferred transplantationl[1].

To further characterize the interaction of cytogenetic risk and ASCT, Bal and colleagues quantified the MM clone using next generation sequencing before and after ASCT, in a cohort of patients homogenously treated with quadruplet induction. Patients with one or more high-risk chromosome abnormalities had greater reduction in disease burden and a higher conversion to minimal residual disease (MRD) negativity[7].

In aggregate, the literature indicates that although ASCT prolongs PFS for patients across the risk spectrum, higher impact is afforded to those with high-risk disease, a fact that can influence the risk-benefit discussion for individual patients.

ASCT IN THE SETTING OF QUADRUPLET THERAPY

Anti-CD 38 monoclonal antibodies daratumumab and isatuximab increase the frequency and depth of response when added to other MM drugs in various settings, including transplant-eligible patients with NDMM. In the CASSIOPEIA trial, patients who received daratumumab in addition to bortezomib, thalidomide and dexamethasone (Dara-VTd) for induction and post ASCT consolidation had longer PFS than patients who received VTd alone[8]. In the randomized phase 2 GRIFFIN study, the addition of daratumumab to bortezomib, lenalidomide and dexamethasone (VRd) induction, VRd consolidation and lenalidomide maintenance also increased the frequency of patients reaching stringent complete response, MRD negativity and improved PFS[9]. More recently, in the GMMG-HD7 trial, Isatuximab added to VRd also improved the proportion of patients achieving MRD negativity prior to ASCT[10]. However, no trial has directly compared upfront ASCT vs. deferred or no ASCT in the setting of quadruplet induction therapy.

In principle, the improvement in conventional therapy, demonstrated by higher proportion of patients achieving MRD negativity even before ASCT, strengthens the case for deferral of transplantation. A lesson learned from prior trials however is that benefit of transplant is not homogenous in the population with NDMM. A transplant vs. non-transplant trial in the setting of quadruplets is unlikely to happen. Instead, we should challenge transplant in risk and response-defined favorable subsets.

ASCT IN PATIENTS WITH DEEP RESPONSE TO INDUCTION THERAPY

Among patients with NDMM exposed to the same therapy, the achievement of deep response, characterized by minimal residual disease < 10^{-5} or even <10^{-6} by next generation flow cytometry or next-generation sequencing is a strong predictor of long term PFS and OS and at least partially mitigate the impact of staging and cytogenetic abnormalities on long term prognosis. Both IFM-2009[11] and DETERMINATION[1] trials indicate that patients achieving MRD negativity with and without ASCT have similar long-term prognosis, leading to an interest in deferring ASCT in patients who achieve MRD negativity post induction. This approach, while logical, has a few caveats. None of these trials systematically evaluated MRD post induction and pre ASCT. The comparisons presented related to MRD pre-maintenance, therefore after multiple cycles of induction/consolidation, and past the decision for ASCT. If one looks at the control arm of GRIFFIN, only 5.8 % of patients achieve MRD negativity after 4 cycles of RVd[12]. With improvement in induction strategies, particularly with assimilation of anti-CD38 antibodies, a higher proportion of patients reach MRD negativity post induction. In GRIFFIN, 21.2% achieved MRD negativity after 4 cycles of Dara-RVd and in MASTER[13] 38% achieved MRD negativity after 4 cycles of daratumumab, carfilzomib, lenalidomide and dexamethasone. The question of transplant deferral in patients achieving MRD negativity in the setting of quadruplet induction is currently being answered in prospective randomized trials (NCT04934475, NCT05231629).

TREATMENT ACCESS AND ASCT

Despite being available worldwide, access to ASCT is still not universal, limited by number of centers offering the therapy and center capacity. This reality is certain to have a negative impact on clinical outcomes. In a recent publication, it was identified that the waiting period for allogeneic transplantation has an independent negative impact on patient survival[14]. This is a reflection of the limited transplant capacity in developing countries.

Despite the development of new drugs and technologies for the treatment of patients with multiple myeloma, the availability of such technologies is still limited for a large proportion of these patients. Therefore, access to early ASCT gains even more importance, and remains one of the main therapeutic choices, particularly in low- and middle-income countries.

FUTURE DIRECTIONS

Multiple myeloma therapy continues to rapidly evolve. Broader use of anti-CD38 monoclonal antibodies in the newly diagnosed setting, provides the perspective of a large proportion of patients achieving MRD negative responses even without ASCT. Innovations recently introduced in the relapsed and refractory setting, particularly chimeric antigen receptor T (CAR-T)[15,16] cells and bispecific T-cell engagers[17-19], are expected to quickly arrive at the newly diagnosed setting in the context of well-designed clinical trials. It will be crucial to answer whether improvements in induction regimens will be able to provide similar outcomes with deferral of ASCT, particularly among patients achieving MRD negativity. It is also expected that CAR-T cell therapies and even bispecific T-cell engagers will challenge ASCT as best consolidative strategy after modern induction regimens. While we would welcome the opportunity to provide similar or improved outcomes to our patients without the toxicity of ASCT, we should expect the future comparators match or exceed its efficacy, but without compromising safety, access, and affordability. Until them, ASCT remains a dependable, safe, and available strategy to reach deep and prolong responses in a large proportion of our patients.

TABLE 1 – Modern trials comparing upfront vs. deferred ASCT for patients with newly diagnosed multiple myeloma

	N	Induction Regimen	Median PFS (months) (ASCT vs control)	Median OS (months) (ASCT vs control)
RV-MM-PI-2093	273	RD	41.9 vs. 21.6 (HR 0.47, 0.33-0.65)	N.R. vs. N.R. (HR 0.64, 0.36-1.15)
IFM-20094	700	RVD x 3 cycles	50 vs 36 (HR 0.65, 0.53-0.80)	N.R. vs. N.R. (HR 1.16, 0.80-1.68)
EMN-025	1197	VCD x 3-4 cycles	56.7 vs. 41.9 (HR 0.73, 0.62-0.85)	N.R. vs. N.R. (HR 0.90, 0.71–1.13)
FORTE6	315	KRD*	N.R. vs. N.R. (HR 0.61, 0.43-0.88)	N.R. vs. N.R. (HR 0.94, 0.54–1.63)
Determination1	722	RVD x 3 cycles	67.5 vs. 46.2 (HR 0.65, 0.52-0.81)	N.R. vs. N.R. (HR 0.90, 0.61–1.37)

RD= lenalidomide, dexamethasone; VCD= bortezomib, cyclophosphamide and dexamethasone; RVD= lenalidomide, bortezomib and dexamethasone; KRD= carfilzomib, lenalidomide, dexamethasone, *Carfilzomib, cyclophosphamide, dexamethasone arm not represented

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A RETROSPECTIVE STUDY OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW IN MULTIPLE MYELOMA PATIENTS

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ABSTRACT

Background: Multiple myeloma is a malignant hematological neoplasm, whose treatment involves the use of bisphosphonates and monoclonal antibodies, which may be related to medication-related osteonecrosis.

Objective: The present study aims to verify the presence of medication-related osteonecrosis of the jaws in patients undergoing treatment for multiple myeloma who used chemotherapy associated or not with bisphosphonates and/or monoclonal antibodies. Beyond this, to trace the epidemiological profile of patients who developed medication-related osteonecrosis.

Methods: This 15-year retrospective observational study consisted of evaluating 461 medical records of patients diagnosed with multiple myeloma from the oncology referral hospital in Paraná state, Erasto Gaertner Hospital.

Results: It was observed inthat both groups, which s (the one in which patients developed and did not developed osteonecrosis), had no statistically significant difference when evaluated separately regarding sex, bone marrow transplant and ethnicity. However, the group with osteonecrosis showed a higher frequency in the use of bisphosphonates, did not progress to death, were non-smokers, the jaw was the most affected anatomical site, and the type of bone exposure spontaneously was the most observed.

Conclusions: The combined use of pentoxifylline and tocopherol was responsible for the successful resolution of cases of medication-related osteonecrosis. Isolating the underlying disease allowed for greater control and knowledge regarding the medications used for the treatment of medication-related osteonecrosis.

Keywords: Osteonecrosis; Hematologic neoplasms; Multiple myeloma; Pentoxifylline; Tocopherols.

INTRODUCTION

In Brazil, approximately seven thousand patients are diagnosed with multiple myeloma per year[1]. This disease represents 10% of hematological malignancies, in addition to being considered the second most common type of blood-related cancer, followed by leukemias[2, 3]. With a prevalence in males, it affects twice as many melanoderma and its diagnosis occurs, in most cases, around the sixth decade of life[3]. In myeloma multiple, there is an uncontrolled proliferation of type B cells in the bone marrow, which

is responsible for the increase in the production of plasma paraproteins and immunoglobulins, mainly IgG, IgA and, more discreetly, IgM[4]. The abnormal proliferation of plasma cells results in suppression of the bone marrow and can cause bone resorption due to the high level of calcium in the blood, resulting in hypercalcemia[5]. Estimated as one of the most effective forms of treatment, autogenous bone marrow transplantation (BMT) can assist in the treatment of this neoplasm, as well as the inclusion of drugs such as bisphosphonates and monoclonal antibodies, which also help in the patient's survival[6].

Bisphosphonates are also prescribed for patients with hypercalcemia, osteoporosis and, also in Paget's disease of bone[7]. They are classified according to their side chain to the carbon atom and can be considered as nitrogenous (alendronate, ibandronate, pamidronate, risedronate and zoledronate) and non-nitrogen (clodronate and etidronate)[8].

One of the most observed adverse effects in the use of bisphosphonates is bone necrosis, since this medication has a high affinity for binding with hydroxyapatite, which makes it difficult for osteoclasts adhesion to the bone surface, in addition to promoting their cell death[9]. These drugs are synthetic analogues of pyrophosphates, whose mechanism of action occurs through the inhibition of bone resorption, being released locally and absorbed by osteoclasts, which inhibit their maturation and lead to apoptosis[10].

Monoclonal antibodies have been used, associated or not with bisphosphonates, for the treatment of multiple myeloma and can also cause bone necrosis[11]. Monoclonal antibodies are developed in the laboratory, present a specific antigen as a specific target[12] and are classified as anti-resorptive and anti-angiogenic[7]. Anti-resorptive monoclonal antibodies can cause bone necrosis because they act against the receptor activator of nuclear factor kappa-B (RANKL), which prevents the osteoclasts differentiation, promoting apoptosis and resulting in bone resorption inhibition, by depletion of mature osteoclasts[13]. On the other hand, anti-angiogenic monoclonal antibodies are antagonists of vascular endothelial growth factor (VEGF) and can neutralize the biological effects of growth factor activity or block the VEGF receptor and its signaling pathways, thus, there is no vascular neoformation, which will result in necrosis[14].

As bisphosphonates and monoclonal antibodies can cause osteonecrosis, in 2014 the diagnosis of drug osteonecrosis was established and it is made when there is current or previous treatment with antiresorptive or antiangiogenic agents; the bone, exposed or not, can be probed through an intraoral or extraoral fistula in the maxillofacial region, which persists for more than eight weeks, and when there is no history of radiotherapy in the head and neck region or obvious metastatic disease in the gnathic bones[15].

The treatment performed for medication-related osteonecrosis consists in a surgical resection associated or not with antimicrobial therapy or with the use of platelet-rich fibrin[16]. However, till this moment, few studies have demonstrated the effectiveness of using pentoxifylline and tocopherol (pento protocol) for the treatment of medication-related osteonecrosis[17, 18].

Previous studies demonstrate the follow-up of medication-related osteonecrosis caused by either bisphosphonate or monoclonal antibody for a period of no more than ten years and the studied population is composed of cancer patients diagnosed with breast cancer, prostate cancer, lung cancer, multiple myeloma, bone metastases and patients with osteoporosis[17, 19]. To our knowledge, there are no studies evaluating only one underlying disease isolated from other malignant neoplasms, as well as an evaluation for a period of 15 years where patients had used bisphosphonates and / or monoclonal antibodies.

Thus, the present study aims to verify the presence of medication-related osteonecrosis in the jaws of patients undergoing treatment for multiple myeloma who used chemotherapy associated or not with bisphosphonates and / or monoclonal antibodies. Beyond this, to trace the epidemiological profile of patients who developed medication-related osteonecrosis in relation to patients who did not develop it, to verify the anatomical site of greatest involvement, the most efficient form of treatment and the type of bone exposure.

METHODS AND MATERIALS

This is a retrospective observational study, with a quantitative basis of secondary data from three sources, which are from the medical records from the Medical and Statistical Archive Service (SAME) of the referral oncology hospital in Brazil (Hospital Erasto Gaertner - HEG, Curitiba-PR), from the book of bone marrow transplant records, from the HEG Hemotherapy Service and from the HEG Oral and Maxillofacial Surgery Service record book, between the years 2004 and 2018, which included patients diagnosed with multiple myeloma as a base disease and who

were not previously submitted to an antineoplastic treatment. The data were collected by an appropriately trained and qualified professional specialized in oral and maxillofacial surgery, since he worked at the present oncological institution working directly in the Service of Oral and Maxillofacial Surgery. This study was approved by the Ethics and Research Committee of HEG under Opinion N°. 3,198,509.

Of the 114,158 patients seen over 15 years, 541 (0,47%) had the diagnosis of multiple myeloma as the underlying disease. After applying the eligibility criteria, there were 461 (0,40%) records that could be included in the study.

The exclusion criteria were in cases when the patient had undergone previous radiotherapy in the head and neck and / or palliative radiotherapy; evolved to death before treatment and / or before confirmation of the anatomopathological result; when the anatomopathological results were inconclusive or absent for multiple myeloma; other tumors; loss of follow-up; abandonment of treatment; chemotherapy performed at another hospital and incomplete information. Eighty patient records were excluded, of which: 7 had undergone prior radiotherapy in the head and neck region; 10 received palliative radiotherapy; 10 died before treatment; 7 passed away before the confirmation of the anatomopathological result; 2 had inconclusive anatomopathological findings; 13 had no anatomopathological evidence of multiple myeloma; 12 had other tumors; 13 cases had loss of follow-up; 1 discontinued treatment; 2 underwent chemotherapy at another hospital, and 3 had incomplete information.

The variables analyzed were: sex, age, smoking, death, type of bone marrow transplant performed, medication used in chemotherapy, presence or absence of bone necrosis, anatomical location (maxilla, mandible or maxilla and mandible affected concomitantly), medication used (bisphosphonates, monoclonal antibody or a combination of both), type of exposure to osteonecrosis (spontaneous or provoked), form of treatment and evolution time for the onset of osteonecrosis, all contained in the data collection form. Bisphosphonates, monoclonal antibody or both were prescribed by doctors at the HEG Hemotherapy Service.

Cases that presented osteonecrosis of the jaws associated with medications were identified in patients undergoing multiple myeloma treatment according to the classification of medication-related osteonecrosis defined in the Position Paper of the American Association of Oral and Maxillofacial Surgery[20], which took into account only the presence or absence of necrosis bone and the site of involvement, without considering its extension.

The data were entered into a database in the Microsoft® Excel 2010 program, being processed and analyzed with the aid of the Statistical Package for the Social Sciences (SPSS), version 25.0.

As the sample size for the group that did not develop medication-related osteonecrosis was greater than 30 (n = 447), the sample distribution of means tended to be normal, therefore, parametric tests were chosen. The sample size of the group that developed drug osteonecrosis was less than 30 (n = 14) and the Kolmogorov-Smirnov and Shapiro-Wilk normality tests indicated normal distribution for the age variable in this group. Student's parametric t test for independent samples was used to compare the average age of the two groups.

In the Levene homogeneity test of variances, it was shown that the age variable is homogeneous. Pearson's Chi-Square test was performed for the other dichotomous or polytomous nominal variables. When the minimum expected count was less than 1, the value of the Chi-Square test with correction of likelihood ratio was used. After the Chi-Square test indicated dependence between dependent variable and group ($p < 0.05$), the Z-test of difference between two proportions was applied, aiming to identify which categories of dependent variable showed differences between groups.

RESULTS

It was observed that, over the 15 years of study, 3% (14/461) developed medication-related osteonecrosis (MON) and 97% (447/461) did not develop. The mean age of patients without osteonecrosis (58.80 ± 11.181) was similar to the age of patients with osteonecrosis (58.36 ± 6.122), $p = 0.800$.

The percentage of patients who used bisphosphonates was higher in the group with osteonecrosis when compared to the group without osteonecrosis. The Z-test power of difference between two proportions when rejecting H0 was 94.1%. A higher frequency of chemotherapy not associated with bisphosphonates or monoclonal antibody was found in the group without osteonecrosis when compared to osteonecrosis. For the other variables, there was no statistically significant difference (Table 1).

TABLE 1 - Patients with Multiple Myeloma stratified according to the absence or presence of osteonecrosis.

Z test of differences between two proportions: different lowercase letters on lines indicates differences between groups ($p < 0.05$).

Different capital letters in a column indicates statistically significant differences ($p < 0.05$).

Variable	Patients without osteonecrose	Patients with osteonecrose	Chi-square test P value
SEX			0,928
Man	250 (55,9%)Aa	8 (57,1%)Aa	
Woman	197 (44,1%)Aa	6 (42,9%)Aa	
BMT*			0,197
Autologous	180 (40,3%)Aa	9 (64,3%)Aa	
Allogenous	1 (0,2%)Aa	0 (0,0%)Aa	
No	266 (59,5%)Aa	5 (35,7%)Aa	
DEATH			0,164
Yes (underlying disease)	212 (47,4%)Aa	4 (28,6%)Aa	
No	235 (52,6%)Aa	10 71,4%)Ba	
SMOKING			0,143
Yes	183 (40,9%)Aa	3 (21,4%)Aa	
No	264 (59,1%)Aa	11 (78,6%)Ba	
MEDICATION			0,009
Bisphosphonate	259 (57,9%)Aa	12 (85,7%)Ab	
Monoclonal antibody	5 (1,1%)Aa	1 (7,1%)Ba	
Combined	13 (2,9%)Aa	1 (7,1%)Ba	
Chemotherapy not associated with bisphosphonates or monoclonal antibody **	170 (38%)Aa	0 (0,0%)Bb	

differences between groups ($p < 0.05$).
Different capital letters in a column indicate statistically significant differences ($p < 0.05$).
*Bone Marrow Transplantation (BMT).
**Chemotherapy not associated with bisphosphonates or monoclonal antibody: Melfalan, Thalidomide, Vincristine, Doxorubicin, Cyclophosphamide, Cisplatin, Bortezomib, Velcade, Alkeran, Methotrexate and Etoposide.

In the group of patients without osteonecrosis, it was observed that: men and women had the same frequency, there was no statistically significant difference between bone marrow transplantation, deaths and non-deaths, smoking and medications used. For the group of patients with osteonecrosis, there were also no statistically significant differences between sexes and bone marrow transplantation, but a higher frequency was identified in patients who did not progress to death, were non-smokers and used bisphosphonates.

The jaw was the site most affected by medication-related osteonecrosis. Bisolphosphonate zoledronic acid, used alone or administered in conjunction with another type of bisphosphonate, pamidronate, were the most frequent treatments for multiple myeloma in cases of MON. A higher frequency of spontaneous bone exposure was observed. Four patients belonging to the group that developed drug osteonecrosis evolved to death due to multiple myeloma. The pento protocol was the most frequent treatment for osteonecrosis, followed by its association with sequestrectomy (Table 2).

TABLE 2. Patients with Multiple Myeloma with osteonecrosis stratified according to the affected anatomical site, the medications responsible for osteonecrosis, the type of osteonecrosis exposure and the form of treatment.

Variable	Frequency
OSTEONECROSIS SITE	
MANDIBLE	09 (64,3%)a
MAXILLA	03 (21,4%)b
BOTH	02 (14,3%)b
TREATMENT OF MULTIPLE MYELOMA	
BISPHOSPHONATE Zoledronic acid	05 (35,7%)a
BISPHOSPHONATE Pamidronate	02 (14,3%)a
BISPHOSPHONATE Zoledronic acid + Pamidronate	05 (35,7%)a
MONOCLONAL ANTIBODY Daratumumab	01 (7,1%)b
COMBINED Bisphosphonate + Monoclonal Antibody	01 (7,1%)b
TYPES OF OSTEONECROSIS EXPOSURE	
SPONTANEOUS	9 (64,3%)a
INDUCED after tooth extraction	2 (14,3%)b
INDUCED after implant installation	1 (7,1%)b
SPONTANEOUS AND INDUCED *	2 (14,3%)b
TREATMENT	
PENTO PROTOCOL	05 (35,7%)a
SEQUESTRECTOMY	01 (7,1%)b
PENTO PROTOCOL + SEQUESTRECTOMY	03 (21,4%)a
PENTO PROTOCOL + HEMIMANDIBULECTOMY	01 (7,1%)b

Z test of difference between two proportions: different lowercase letters indicate differences between groups ($p < 0.05$).
* In one of the dental arches, the exposure was spontaneous and in the other, caused by post-extraction.

Among the patients undergoing the proposed treatment, eight had complete resolution of osteonecreosis exposure, while one patient developed pathological fracture and the other presented resolution of osteonecrosis in the mandible, but the bone exposure remained in the maxilla. These patients who did not resolve remained in treatment after completing this study.

It was observed that, in three isolated cases with the use of bisphosphonates, patients developed drug osteonecrosis in less than one year of administration of the drug. The patient who used a monoclonal antibody developed osteonecrosis 10 years after its administration.

From 461 records included in the study, 96% (443/461) belonged to white patients, 2.4% (11/461) belonged to browns, 0.65% (3/461) belonged to blacks and, in 0, 9% (4/461) had no information regarding ethnicity. The ethnicity variable did not indicate statistically significant differences when compared to the variables gender, bone marrow transplantation, death, smoking and medication.

DISCUSSION

The present study first isolated an underlying disease in patients who developed drug osteonecrosis and a frequency of 3% was observed. The literature shows that the frequency of MON is 37.6%[19, 21]. This index is much higher than the one shown in this study, as the patients that make up the other works belong to different oncological areas and, in some cases, multicenter studies have been carried out[7]. However, the present study was carried out only at the oncology referral hospital in the Paraná state. The frequency of medication osteonecrosis in this study proved to be a rare event.

Studies show that groups of patients who used bisphosphonates were higher in the group with os-

teonecrosis when compared to the group without osteonecrosis[21]. The present study corroborates the presented fact. On the other hand, in a study by Wazzan et al (2018)[19], patients who did not develop MON had a higher frequency of use of bisphosphonates compared to the group with osteonecrosis, since patients had a higher quality of oral health[19]. In this study, the quality of the patient's oral health was not evaluated, only the presence or absence of medication-related osteonecrosis. Therefore, it cannot be said whether patients who developed medication-related osteonecrosis had a lower oral health condition compared to patients who did not develop osteonecrosis.

The epidemiological profile of the patient without osteonecrosis has a slight predilection for the female gender, non-smokers, with a mean age between 57 and 61 years and with greater frequency in the use of bisphosphonates[17, 19]. This study showed that there are no statistically significant differences involving the variables gender, smoking and medication used, and the mean age is similar to that reported in the literature (58.8 years). On the other hand, the profile of patients with osteonecrosis is more frequent as: men, jaw as the most affected site, non-smokers, the use of bisphosphonates as medication and the average age is 62 years[17, 19]. The present study corroborates the literature regarding the variables smoking, bisphosphonates and most affected site. However, there are no statistically significant differences between the sexes and the average age is slightly inferior, being 58.3 years old.

In the present study, it was observed that multiple myeloma was diagnosed in a population composed of 96% of white patients. Perhaps this fact is observed due to the region where the oncological Hospital had the data collected. Since, according to the last census conducted by the Brazilian Institute of Geography and Statistics (IBGE), the southern region is made up of more than 20 million whites, while the rest of the population, together, total almost 6 million people[21]. All patients who developed medication-related osteonecrosis were white.

Pentoxifylline is a phosphodiesterase inhibitor derived from methylxanthine and has an anti-TNF-α effect, increases the flexibility of blood cell membranes, improves microcirculation and peripheral blood flow, in addition to tissue oxygenation[18, 22]. Tocopherol, also called vitamin E, is an antioxidant agent that protects the phospholipid membrane from oxidative damage and the cell membrane against lipid peroxidation[23]. It decreases reactive oxygen species, resulting in the healing of injured tissue[24]. When combined, pentoxifylline and tocopherol are effective in reducing radiation-induced fibrosis and decrease the protein expression of the transforming growth factor (TGF-β) molecule more effectively than any medication alone[25].

A study carried out by Bohn et. al. (2016)[26], involving irradiated patients from the same institution as the present study, demonstrated success in the resolution of osteoradionecrosis (ORN) when the pento protocol was used[26]. In 2018, Kolokythas et al, published in a systematic and meta-analytical review that the pento protocol showed successful results in advanced cases of ORN[27]. When the exposure of necrotic bone is caused by the use of drugs such as bisphosphonates, the literature also shows success with the use of the pento protocol[17, 28], the present study corroborates this fact.

In 2012, Mcleod et. al.[29] demonstrated that the proposed treatment for ORN with the pento protocol consisted of ingesting 400mg of pentoxifylline twice a day and 1000UI of tocopherol once a day[29]. Thus, based on the conduct in front of the ORN, the HEG Oral and Maxillofacial Surgery Service implemented the pento protocol, using the same dosage, for the treatment of MON, which led to the resolution of clinical cases. As far as is known, the pento protocol is only proposed for the treatment of ORN[30]. However, the present study sought to demonstrate the effectiveness of the pento protocol for the treatment of MON, as well as the few previous studies[28].

The differences found in the resolution of the MON can possibly be attributed to the protocol used, since authors performed control of the local infection through hygiene, antibiotic therapy and, in cases of non-resolution, surgical debridement, bone resection and use of platelet-rich plasma[31, 32]. In addition, some studies did not have exclusively cancer patients with multiple myeloma and / or who also used monoclonal antibodies as a study population[33]. In the present study, patients with MON were submitted to treatment involving the pento protocol with or without sequestrectomy and hemimandibulectomy. It became evident that the use of the pento protocol in the treatment of drug-induced bone necrosis has been successful, as well as in cases of osteoradionecrosis (ORN) in which the same protocol is employed.

Studies suggest that the exact location of MON is in the mandible, and bone exposure occurs more frequently in a provoked way[17, 30]. In the present study, it was observed that the most affected site was the mandible. However, in three cases the maxilla was

affected, and in two other cases, both the mandible and the maxilla were affected concurrently. It was also analyzed that the spontaneous form of exposure to osteonecrosis was the one with the highest frequency. The use of bisphosphonates alone or the combination of two types of bisphosphonates also resulted in a higher frequency of MON cases, converging with studies where bisphosphonate administered alone was responsible for a higher frequency in the development of MON[22, 34].

When Marx demonstrated the appearance of bone necrosis caused by the use of bisphosphonates, in 78% of the cases (28 patients), the exposure of necrotic bone occurred after surgical intervention[35]. In the year following the first report of osteonecrosis caused by drugs, Ruggiero et al (2004)[36] identified medical records of patients with various oncological diagnoses (56 patients, 88.9%), including seven cases (11.1%) of treatment for osteoporosis, where everyone used pamidronate and / or zoledronate. In only nine cases, osteonecrosis exposure was spontaneous[36]. This study differs from the ones mentioned above, since only medical records of patients who had multiple myeloma as the underlying disease were evaluated, where nine cases presented spontaneous bone necrosis.

In the present study, three patients who used only bisphosphonate presented the development of medication-related osteonecrosis in periods of less than one year; they were six, seven and eight months, respectively. Among these cases, two patients presented spontaneous osteonecrosis and one case after extraction of the right upper canine. It was observed in this study that the isolated use of monoclonal antibody (Daratumumab™) was responsible for the spontaneous exposure of necrotic bone after 10 years of use. The case presented by Neuprez et al (2014)[37] demonstrated that, in just nine months of using Denosumab™, the region submitted to surgical removal of the third molar did not heal and resulted in the presence of necrotic bone[37]. It is believed that subsequent multicenter studies involving oncology referral hospitals are necessary to elucidate and increase knowledge about the time of MON emergence due to the use of monoclonal antibodies.

The pathophysiology of MON is still unknown, as it is considered a multifactorial disease[30, 38]. Hypotheses suggest that there is a change in bone remodeling, inhibition of angiogenesis, soft tissue toxicity, infection, and suppression of immunity[38]. The diagnosis is based on the patients' medical and medication history, as well as on the clinical and radiographic characteristics of the exposed or not exposed necrotic bone[39]. Pharmacogenetic studies are being developed to determine whether genetic differences influence the variability of the patient's response to these drugs[40]. In this study, the diagnosis occurred according to the definition of the American Association of Oral and Maxillofacial Surgeons and further studies may be developed to assess the confirmation or not of the genetic influence of the patient using bisphosphonates and / or monoclonal antibodies[40].

The literature demonstrates that nicotine has an adverse effect on bone healing and regeneration, since it acts on small blood vessels, producing peripheral vasoconstriction, systemic venoconstriction and increased coronary vascular resistance, in addition to inhibiting the gene expression of bone morphogenetic protein in osteoblasts[40].

Nicotine results in the accumulation of hypoxia-inducing factors and impairs healing, as it causes a decrease in the proliferation of fibroblasts and a decrease in the production of collagen[41]. Benzopyrene, in addition to being a carcinogen found in cigarette smoke, is responsible for decreasing osteoclastic formation, since it inhibits the kappa-B binding factor (RANKL) receptor activator[42]. It was shown that both nicotine and benzopyrene affect, but do not prevent bone healing[43]. In the present study, only three patients who had MON were smokers, however, it is not known whether bone healing was delayed or not because, once treatment with the pento protocol was proposed, there was complete resolution of the clinical conditions. The association between cigarette components and medications that cause osteonecrosis is a subject that can be analyzed in later studies.

CONCLUSION

It was observed that, even though it is a rare event, osteonecrosis associated with medications in the head and neck region can be observed in patients with multiple myeloma. Obtaining the epidemiological profile of the patient with MON makes it possible, through this retrospective study, to assist in diagnosis and treatment, which will provide greater comfort regarding the quality of oral life.

DISCLOSURE STATEMENT

All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication, as well as have no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR ALL SESSION SBTMO 2023 ACCESS TO HEMATOPOIETIC STEM CELL TRANSPLANTATION: FACING OUR CHALLENGES

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There are major challenges for HSCT in Brazil. The access to the transplant due to an insufficient number of active beds for adults and even less for pediatric patients and lack of access to some critical medications such as antiviral drugs and GVHD therapies were discussed with SBTMO associates and the coordinator of the Government National Transplant System (SNT), in order to improve this scenario.

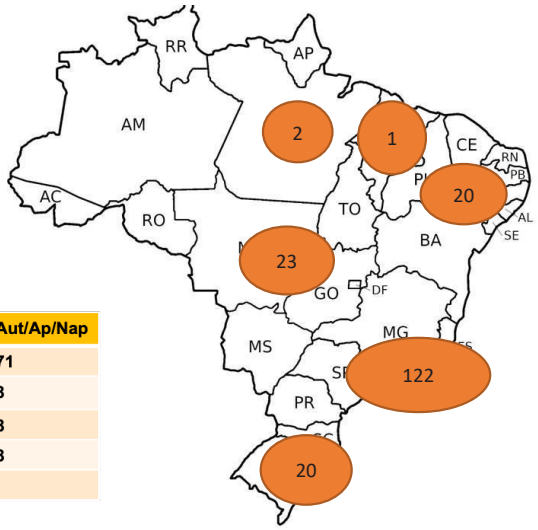
HSCT IN BRAZIL: WHERE ARE WE?

Brazil has one of the biggest transplant programs in the world. In the HSCT scenario, 70% of the HSCT is performed by our Public Health System (SUS) and about 30% is performed at private Hospitals.

Currently, Brazil has 261 transplant centers in 124 establishments, being 247 public: 124 for autologous only, 80 for auto and allogeneic related, and 57 for autologous, allogeneic related and unrelated HSCT. Most centers are concentrated in Southeast and South Brazil (figure 1). [1]

Furthermore, Brazil has the third donor registry in the world: REDOME has more than five million donors registered. [2]

FIGURE 1. Transplant Centers in Brazil

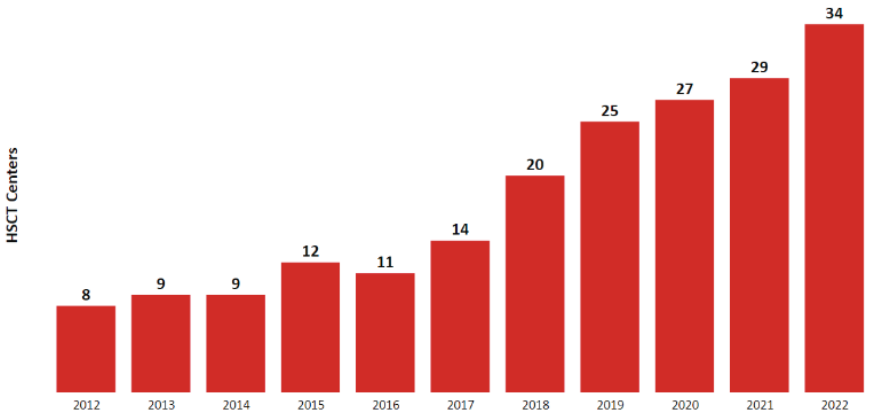


Região	Aut	Aut/Ap	Aut/Ap/Nap
Sudeste	33	18	71
Centro Oeste	9	6	8
Sul	6	6	8
Nordeste	8	4	8
Norte	2		

We have very few centers in the north, northeast and central regions of Brazil. This concentration generates a higher cost to the public system to take the patients to centers far away from their cities of origin. Family support, essential to these patient's quality of life, is also often limited when they are far from their cities.[1]

Nevertheless, thirteen new centers were authorized in 2023 and we can see that the number of active centers has been increasing through the last few years, as well as the proportion of allogeneic transplants (Figure 2)[1]

FIGURE 2. Brazilian Active Centers in the CIBMTR by year[1]



However, with a population of 200 millions of inhabitants, in 2022, Brazil performed only 2840 transplants by SUS, being 1745 autologous, 866 related and 229 unrelated transplants. We estimate only 160 beds for HSCT in SUS. Therefore, we can see long lines of unattended patients either waiting for autologous (myeloma, lymphomas, and germ cell tumors) or allogeneic HSCT (especially acute leukemia, bone marrow failure, myelodysplastic syndrome, myeloproliferative disorders and falciform anemia).

Even with a limited number of unrelated HSCT performed, there is great difficulty in finding centers for marrow harvest or peripheral blood collection. For autologous transplants, strategies for simplifying the requirements can be discussed (perform autologous transplants in hematology units, for example). Despite many achievements in recent years, Brazilian centers still have problems to registering these transplants. When collected and sent to regional state transplant coordination, these data seem not to reach SNT, which claims to have insufficient information about HSCT around the country. There is also no monitoring, to make sure the data is collected, by the government. Besides, the lack of data manager staff at the centers limits their ability to register their results.

Another important difficulty in HSCT in Brazil is the lack of access to important tests and medications. With the increment of unrelated and particularly haploidentical transplants in Brazil, we had an increment of infection, which is the leading cause of death for our patients.[1] Viral infections are frequent in this scenario. However, there is no reimbursement for viral identification by PCR, which is the recommended method for monitorization. Diagnosis by PCR for CMV, EBV, adenovirus and respiratory virus are crucial to HSCT. Besides, specific evaluations of engraftment by chimerism (STR analysis) are not reimbursed. This is very important to guide immunosuppressive drugs management and the requirement of strategies, like donor lymphocyte infusions, which is not reimbursed either. The absence of viral monitorization and therapy is a matter of great concern given Brazil's remarkable increment of haploidentical transplants.

Regarding the drugs important to HSCT we have diverse difficulties. Some of them are no longer produced by pharmaceutical companies without any advice or time to be substituted. It was the case for melphalan and busulfan, which are essential to the conditioning phase of HSCT. Other medications are not reimbursed by the public health system. It is the case of some immunosuppressive agents which are available for other types of transplants (solid organs) but not for HSCT, such as tacrolimus, mycophenolate mofetil and sirolimus. It is also the case of important antiviral drugs like cidofovir and foscarnet, which are not available in our country. Some other new drugs or new developments which would be very important for conditioning (treosulfan, thiotepa), GVHD therapy (ruxolitinib, ibrutinib or extracorporeal photopheresis) or for CMV prophylaxis (letermovir) and

therapy (maribavir) are not available.[3,4] It usually takes too long for new medications or procedures to be incorporated into our regulatory system, which can certainly impact the results. There are many established indications for HSCT that are not included in the regulation either for public or private scenarios, and this is an urgent matter. There is also no financial support from the government for clinical research protocols in this field.[5]

Total body irradiation is not available in many centers, which can compromise the results of the HSCT for Acute Lymphoblastic Leukemia (ALL).

PEDIATRIC HSCT IN BRAZIL

One important unattended need is the pediatric transplant. SBTMO Pediatric Group estimates that around 400 kids would need transplants for a year only because of leukemia. Besides acute leukemia, taking into consideration many other diagnoses (SCID, falciform anemia, inherited disorders), there is a clear need for an increment in pediatric transplants in the country. Amplifying screening measures for inherited disorders will tend to worsen this situation. 400 hundred pediatric transplants were performed in 2022 in Brazil. Transplants have also been centralized in a few centers in the southeast and south of the country. Infection is the main cause of death, suggesting that these children have been referred late to the transplant centers. Acute Lymphoblastic leukemia is the main diagnosis among pediatric transplants performed in our country.[1]

MAIN ACHIEVEMENTS

Since its foundation on April 15th, 1996, the Brazilian Society of Transplant and Cellular Therapy (SBTMO) has had great development. With 1171 associates, SBTMO has an important online journal (the first transplant journal in Latin America), and has established partnerships with other societies in the field (EBMT, ASBMT, LABMT, WBMT). SBTMO Consensus guidelines have been important to guide current practices in the country and in the Latin American Continent. With the partnership with CIBMTR, there are an increasing number of centers which report their data to this platform, currently more than 86 centers, with the important coordination of SBTMO data managers group. Reporting centers are certified by SNT. Through the data back to center tool, these data could come back to SBTMO and establish the Brazilian HSCT Registry (RBTMO), which captures data from both HSCT and Car-T cell infusions.[2]

Summary slides with general results of HSCT in Brazil are then published at JBMTCT annually.[1] Aside from the information, many educational initiatives have been taken as regional and national meetings, meetings with FACT and "Young Transplanter Program", which has been an important source of education for our residents and young staff. GEDECO, the scientific working group of SBTMO, has published in the last years many collaborative trials in important peer review journals.[2]

As a result of this robust society and a government disposition to discuss and solve current problems we also have some regulatory achievements at the public health system such as the increment of age of transplant and a recent improvement in the reimbursement according to the qualification of the center.

PROPOSALS AND PERSPECTIVES

During the discussion, many proposals were discussed and can therefore be summarized to guide future efforts of improvement of HSCT in Brazil:

- Increment of active beds for both adult and pediatric HSCT;
- Expansion of centers in North, Northeast and Central Region of Brazil, with the proposal of Tutorials and continuous educational programs;
- Improvement and expansion of RBTMO through mandatory hiring of data managers and mandatory registry of data;
- Reporting data to SNT for adequate diagnosis and working in collaboration with the government to solve the problems identified;
- Discuss strategies of implementation of cellular therapy programs;
- Establish a special group for discussing the autologous transplant regulation in Brazil
- Partnership with Anvisa to discuss notification of industries which do not respect the required time to discontinuation of products;
- Partnership with Anvisa and MS to stimulate other industries for production of critical drugs;
- Revision of transplant indications and continuous actualization;
- Discussion about incorporation of drugs and procedures.
- Establishment/ funding for clinical research national protocols.

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CHALLENGES TO ACHIEVING BMT IN THE TREATMENT OF AML IN BRAZIL: BAHIA UNIVERSITY HEMATOLOGY CENTER EXPERIENCE

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ABSTRACT

Introduction: Acute myeloid leukemia is a heterogeneous aggressive leukemia with a poor prognosis. The standard remission induction regimen for medically eligible patients consists of a backbone of cytarabine & anthracycline.

Objective: This study assessed the efficacy and safety of cytarabine and anthracycline in a public health center in Salvador, Brazil.

Methods: It is a retrospective analysis of 45 non-promyelocytic AML patients diagnosed between 2018 and 2022. Subgroups analyzed included patients having FTL3 and NPM1 mutations, leukocyte count (>10,000 or <10,000), platelets count (>20,000 or <20,000), and transplanted patients. Kaplan-Meier methods were used to determine overall survival (OS) and progression-free survival (PFS).

Results: The median age at diagnosis was 43 years (16-69 years), and 62% were females. FLT3-ITD and NPM1 mutations were found for 17.8% and 13.3% of patients, respectively. 85% of the patients had a normal karyotype. For efficacy, 52% of patients were eligible for the next treatment after complete remission. Refractory patients were 20%. Early mortality was 28.8%. Median values of PFS and OS were 3.6 and 8.2 months, respectively. Patients presenting FLT3 mutation and stem cell transplantation had PFS and OS of 20 and 43 months, respectively.

Conclusion: The outcomes were consistent with the literature. Waiting time was not critical for treatment outcomes.

Keywords: Leukemia, Myeloid, Acute. Survival rate. Progression-Free Survival.

INTRODUCTION

Acute myeloid leukemia (AML) is characterized by infiltration of bone marrow, blood, and other tissues by proliferative and undifferentiated cells of the hematopoietic system[1,2]. Although the treatment of AML significantly improves outcomes for younger patients, the prognosis for the elderly remains poor: approximately 70% of patients aged 65 years and older die within one year of diagnosis. The National Cancer Institute (INCA) estimates that for the 2023-2025 triennium, 11,540 new cases of leukemia will be diagnosed, corresponding to 5,33 per 100,000 inhabitants in Brazil [3–5].

The disease prognosis is fundamental for its management. Prognostic factors are improved by stratifying patients according to treatment risk resistance or treatment-related mortality (TRM), in addition to the therapeutic decision, whether to use induction, consolidation or stem cell transplantation. Among clinical factors, increasing age and poor performance status are related to lower complete remission rates (CR) and decreased overall survival (OS) [2,3].

The first stage of AML treatment involves the concept of eligibility for intensive induction chemotherapy and aims for complete remission (CR). Furthermore, three therapeutic modalities can be administered to AML patients in post-remission: conventional-dose chemotherapy, high-dose chemotherapy (consolidation) followed by salvage with autologous hematopoietic stem cells, and allogeneic hematopoietic stem cell transplantation [2,5,6]. Therapies have remained essentially the same for 40 years. The therapeutic regimen, known as "7+3", is performed during the induction period of treatment for eligible patients [1,2]. However, most patients achieving CR with a 7+3 regimen eventually relapse[1].

This study aims to evaluate the efficacy and safety of treatment induction with anthracycline and cytarabine (7+3 regimen) in patients diagnosed with Acute Myeloid Leukemia in a public hospital unit in Salvador/Bahia for five years. In addition, we plan to correlate efficacy and early mortality with treatment waiting time, which is unprecedented in Brazil.

METHODS

The present work was submitted to the Research Ethics Committee of the Hospital Universitário Edgar Santos (HUPES). Retrospective patient data were analyzed up to 01/19/2023.

This is a retrospective hospital-based cohort study evaluating the efficacy and safety of 7+3 chemotherapy treatment (anthracycline + cytarabine) in patients diagnosed with non-promyelocytic Acute Myeloid Leukemia between 2018 and 2022 at the University Hospital Professor Edgar Santos - HUPES, in the city of Salvador/Bahia. Data collection was performed from physical and electronic medical records.

HUPES is a reference university hospital in the North/Northeast region of Brazil, encompassing a Bone Marrow Transplantation unit and offering, in partnership with scientific research, hematological tests not provided by the Unified Health System in Brazil (SUS). The hematological tests performed include FLT3 and NPM1 mutations, in addition to karyotype.

To analyze the efficacy of AML induction using anthracycline and cytarabine regimen, the following parameters were followed: (1) overall survival (OS - period between the initiation of therapy with 7+3 regimen and the date of possible death); (2) progression-free survival (PFS - period between the date of initiation of 7+3 therapy and the date of evidence of possible disease progression); (3) eligible for the next treatment (patients achieving complete remission after induction with 7+3 regimen and who underwent subsequent bone marrow transplant or consolidation therapy within 60 days). PFS and OS were analyzed through the Kaplan-Meier methodology, using the R project version 2.13.1 program for Windows.

The subgroups to evaluate the efficacy and safety of the 7+3 regimen were defined as (1) FLT3 or NPM1 patients mutation status; (2) total leukocytes at the time of diagnosis (less than/equal to or above 10,000); (3) total platelets at the time of diagnosis (less than/equal to or above 20,000); (4) patients who underwent bone marrow transplantation or not.

The p-value with a 90% confidence interval ($p = 0.01$) was adopted for statistical analysis between subgroups. Early mortality was defined as death occurring within four weeks after the first day of treatment. Waiting time was defined as the number of days patients diagnosed with AML had to wait until admission to HUPES.

RESULTS

Between 2018 and 2022, 45 patients underwent induction therapy with a 7+3 regimen at HUPES. The majority were female (62%), from the city of Salvador (26%), and brown-skinned (60%). The mean age was 43 years (16-69 years). The search for FLT3 mutation status was carried out in 30 (66.7%) patients; the majority belonged to the non-mutated group (48.9%;

Table 1). The NPM1 mutation search was performed in 25 (55.5%) patients; the rest were from the non-mutated group (42.2%). A Karyotype exam (85% had a normal karyotype) was performed in 14 patients. The characteristics of the patients are shown in Table 1.

TABLE 1. Characteristics of patients treated with 7+3 regimen in HUPES (N=45).

	Number of patients (%)
AGE > 60 years < 60 years	 5 (11.1) 40 (88.9)
GENDER Female Male	 26 (62.2) 17 (37.8)
RACE White Black Brown	 11 (24.5) 7 (15.5) 27 (60)
Nationality Salvador Bahia State Other	 12 (26.7) 30 (66.7) 3 (6.6)
FLT3 Status Mutation No-Mutation Unknown	 8 (17.8) 22 (48.9) 15 (33.3)
NPM1 Status Mutation No-Mutation Unknown	 6 (13.3) 19 (42.2) 20 (44.5)
Leukocytes* > 10 x 109L < 10 x 109L	 30 (66.7) 15 (33.3)
Platelets* > 20 x 109L < 20 x 109L	 32 (71.2) 13 (28.8)
Transplantation** Yes No	 8 (17.8) 37 (82.2)

*At the time of diagnosis, **Allogeneic related/unrelated (7) and haploidentical (1) bone marrow transplantation.

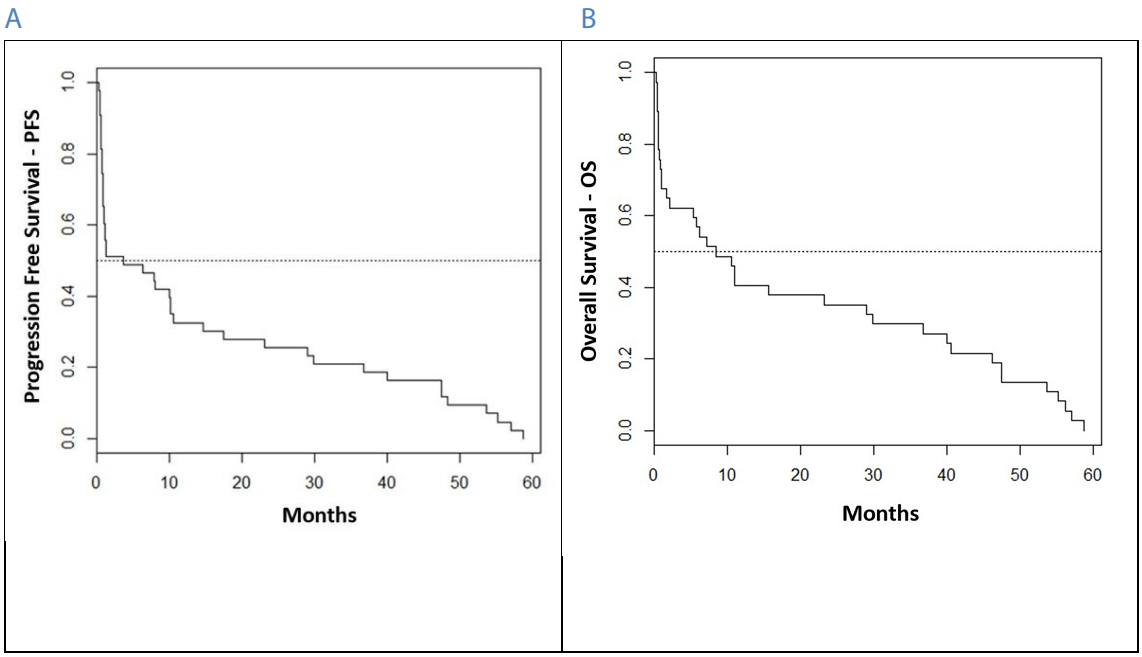
The mean waiting time for those patients who required hospitalization to start treatment with 7+3 regimen was 12.3 days (Table 2). There was no difference in the mortality for patients waiting less than 12.3 days or more. Five patients out of 38 died irrespective of waiting time (Table 2).

TABLE 2. Early mortality according to waiting time for treatment initiation.

Less than 12.3 days (%)	More than 12.3 days (%)
5 (38)	5 (38)

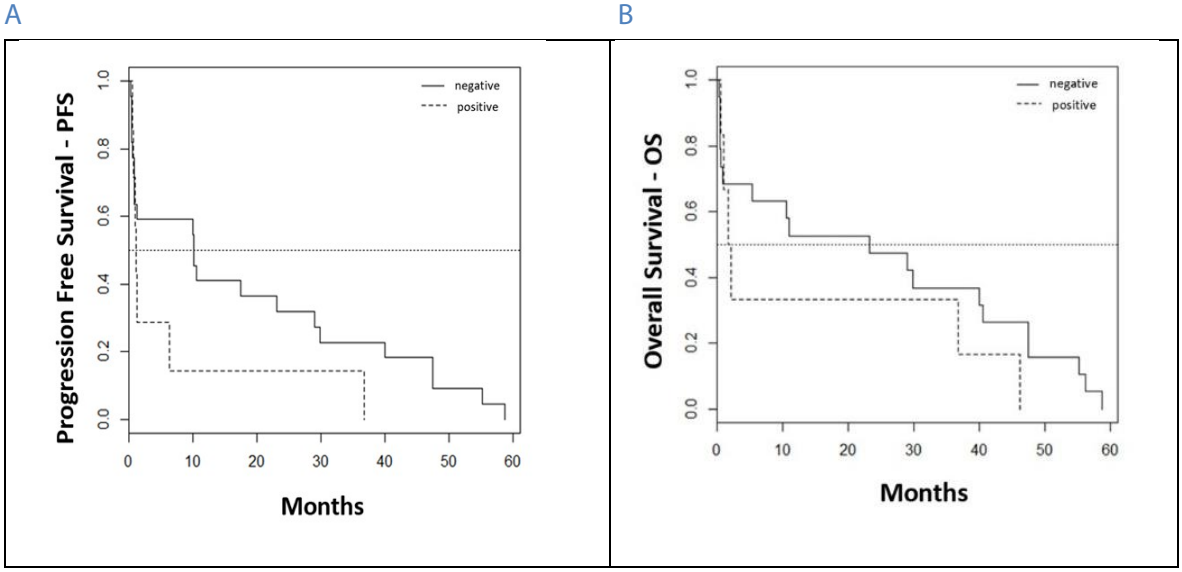
Regarding efficacy, 52% of the patients were eligible for the next therapy after complete remission (consolidation or stem cell transplant), and 20% did not respond to treatment. Early mortality (within four weeks) was 28.8%, and the causes of death were septicemia (8), alveolar hemorrhage (2), tension pneumothorax (1), acute respiratory infection (1), and COVID-19 (1). Median PFS and OS were 3.6 and 8.2 months, respectively. Early mortality was not affected by waiting time for treatment initiation (Figure 1 and Table 2).

FIGURE 1. Kaplan-Meyer curve for progression-free survival (A) and overall survival (B) in AML Patients treated with a 7+3 chemotherapy regimen.



FLT3 mutation-free patients had a median PFS of 10.1 months versus 1.1 months for FLT3 patients with mutation (HR 0.84; p=0.330; Figure 2A). The prognosis for OS was worse for FLT3 patients having the mutation, with a median of 1.9 months versus 23.3 months for those with no mutation, marginally significant (HR 0.63; p =0.077: Figure 2B).

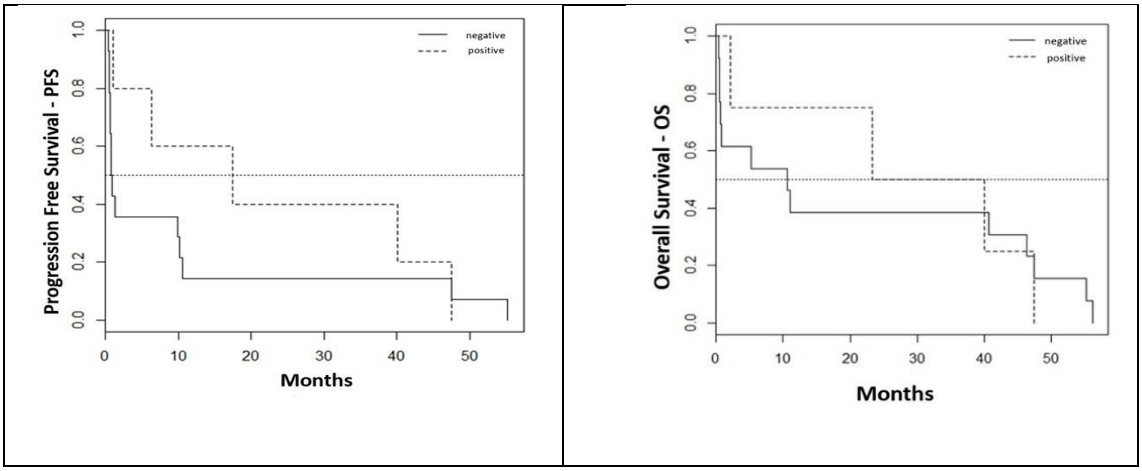
FIGURE 2. Progression-Free Survival (A) and Overall Survival (B) for FLT3 mutation in AML patients treated with 7+3 chemotherapy regimen.



Median PFS for NPM1-patients with mutation was 17.4 vs. 0.9 months for those with no mutation (Figure 3A). OS for NPM1 patients with mutation against those without mutation was 31.7 vs. 10.6 months (HR 0.99; p = 1.00). See Figure 3B.

FIGURE 3. Progression-Free Survival (A) and Overall Survival (B) for NPM1 patients with an AML mutation treated with a 7+3 chemotherapy regimen.

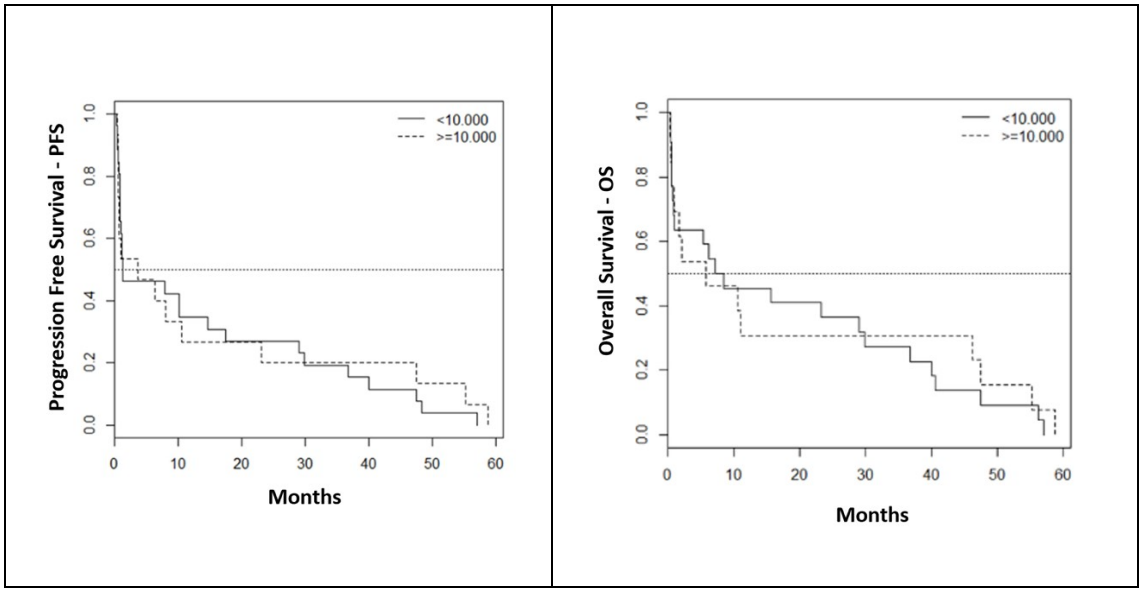
A B



The median for PFS was higher in the group of patients who had leukocytes above 10,000 at the time of diagnosis compared to the group of leukocytes below 10,000 (3.64 vs 1.24; HR 0.91; p = 0.78). There was also a better prognosis regarding OS (7.8 vs. 5.7; HR 0.85. p = 0.67). See Figure 4A and B.

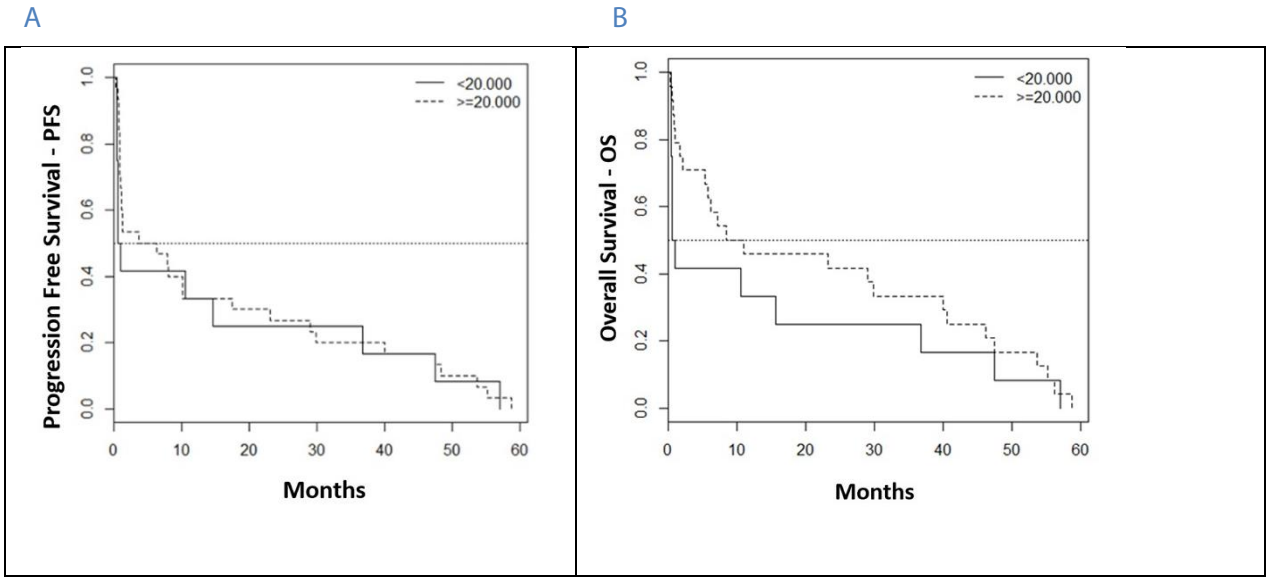
FIGURE 4. PFS (A) and OS (B) related to the number of leukocytes at AML diagnosis in patients treated with a 7+3 chemotherapy regimen.

A B



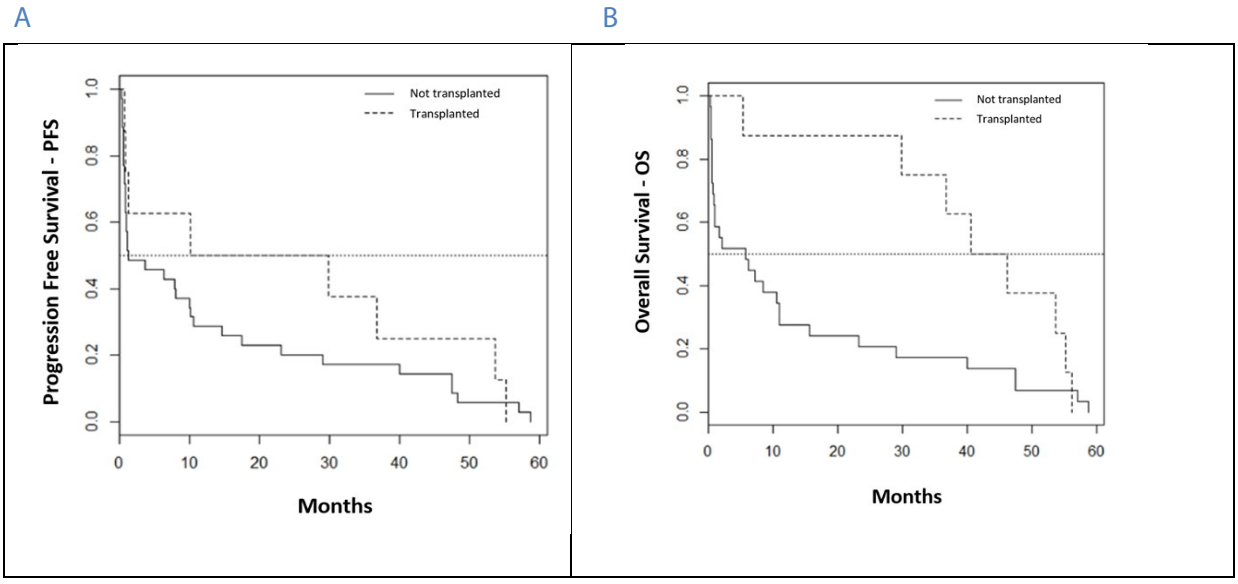
Regarding the number of platelets at the time of diagnosis, a better prognosis was observed for the group that had platelets greater than 20,000, both for median PFS (5.0 vs. 0.6 months; HR 0.81; p = 0.540) and median OS (9.7 vs. 0.9 months; HR 0.68; p = 0.27). See Figure 5A and B.

FIGURE 5. PFS (A) and OS (B) related to the number of platelets at AML diagnosis in patients treated with a 7+3 chemotherapy regimen.



Patients eligible for the next treatment and who underwent bone marrow transplantation had a higher PFS (20.0 vs. 1.2 months; HR 0.67; p = 0.310) and a statistically significant OS (43.5 vs. 5.7 months; HR 0.47; p = 0.065), as seen in Figure 6A and B.

FIGURE 6. Patients PFS (A) and OS (B) for AML treated with 7+3 chemotherapy regimen in relation to bone marrow transplantation.



DISCUSSION

The efficacy and safety outcomes of this study using a 7+3 chemotherapy regimen demonstrated that 52% of the patients were eligible for the next treatment (complete remission), the median progression-free survival was 3.6 months, and overall survival 8.2 months, including early mortality of 28% (61% due to septicemia). Significant treatment efficacy among the groups studied included higher OS (85%) for transplanted versus non-transplanted patients, and patients having an FLT3 mutation had significantly worse OS (90% higher). The mean waiting period to start treatment (12 days) was not a critical factor for clinical outcomes.

Our results are consistent with other real-life studies in Brazil involving AML. A 10-year study observed a complete remission rate of 53% and an early mortality of 20% for treated patients. The median OS was 7 months[7]. A retrospective study at a public service in Minas Gerais[8] found a median OS of 3.7 months and early mortality of 37%. In São Paulo, two similar studies in different public institutions reported complete remission of 49.5% and early mortality of 25.8%[9], including a median overall survival of 4.6 months[10]. Another multicentric retrospective study in Brazil found a median OS of 12.4 months[11]. A complete remission of 62% involved another study, and 15% of patients were alive at an estimated time of 13 years[9,12].

Bone marrow transplantation (BMT) is indicated as standard post-induction treatment after a 7+3 regimen for patients with intermediate or unfavorable cytogenetic risk. BMT is the most effective post-remission therapy for AML and is particularly highly recommended worldwide for patients aged 45 to 59 years and/or with high-risk cytogenetics. The efficacy and safety results of HUPES transplanted patients converge with data published for other real-life studies [3,7,11,13].

The 2022 ELN and the NCCN (version 3.2023) describe that FLT3-ITD mutations represent an unfavorable prognosis in patients with AML. The literature describes that patients with FLT3-ITD mutations have a poor prognosis, with an increased risk of recurrence and lower overall survival compared to patients without the mutation, similar to our study[13–15].

Leukocyte counts below 10,000 and platelet counts below 20,000, together with the absence of NPM1 mutation, had a worse prognosis for PFS and OS. However, they were not statistically significant in the present study. However, the European LeukemiaNet (2022) states that low leukocyte and platelet counts are associated with a higher mortality risk due to bleeding events and tumor lysis. In the same context, it is known that patients with NPM1 mutations (56%) have higher complete remission rates and higher disease-free and overall survival than wild-type NPM1 patients. NPM1 mutation (without FLT3 mutation) has a favorable prognostic factor in the context of AML [14,16].

Patients with hematologic malignancies are at increased risk of infection, associated with high morbidity and mortality. Patients with AML have qualitative and quantitative deficits in granulocytes, predisposing to bacterial and fungal infections [17]. Our real-life study for a developing country, involving socio-economic differences compared to developed countries, demonstrated that mortality data due to infections was the leading cause of death during induction with 7+3 chemotherapy.

HUPES patients waited, on average, 12 days to start treatment. To date, no Brazilian studies related the time to start AML treatment to clinical outcomes. However, a retrospective Swedish study found that patients aged up to 60 years waited between 11 and 15 days to start induction therapy and did not show significant disease remission, mortality up to 30 and 60 days, and overall survival at two years compared to those patients waiting between 0 and 5 days [18].

The combination chemotherapy regimen with anthracycline and cytarabine in eligible patients is standard for national and international guidelines. The National Comprehensive Cancer Network (NCCN), the European LeukemiaNet (ELN), and the Manual de Oncologia Clínica do Brasil (MOC) [19] recommend the induction of AML with the 7+3 regimen for eligible patients. The institutional protocol by the Hospital das Clínicas to treat patients with this type of leukemia is consistent with the leading global recommendations. However, for patients with the FLT3-ITD mutation, it is indicated (in Brazil – supplementary health, and in other international guidelines) the addition of midostaurin target therapy to the 7+3 regimen due to improved survival. However, SUS does not cover this treatment, and HUPES does not perform it. It is a high-cost therapy, and discussions of its incorporation into health services in Brazil are necessary. It is also observed that in some international protocols, such as NCCN, venetoclax treatment (BCL2 inhibitor) can be added for patients in AML induction therapy. This is not an approved indication in Brazil and is not performed at HUPES either [4,15,20] .

The study's advantages were the correlation of efficacy and early mortality with waiting time for treatment initiation in a public hospital in Brazil. Furthermore, it is the first time that data was collected in northeastern Brazil. The limitations include the statistical relevance of between-group comparisons, given that it was a retrospective study with a total population of 45 patients. For the statistical analysis between subgroups, the p-value with a 90% confidence interval ($p = 0.01$) was adopted, which is different from other studies with a higher population and p-value ($p = 0.05$).

Acute Myelocytic Leukemia is a disease with limited therapeutic options. Induction followed by consolidation therapy remains standard in the main therapeutic guides in onco-hematology settings. The efficacy and safety demonstrated in this work are consistent with the national and international literature. The waiting period for treatment does not seem to be a determining factor in clinical outcomes compared to other studies. Improvements in diagnostic processes, prevention of opportunistic infections, and developing new technologies for treating AML are vital.

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CONFRONTING DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN VIRAL REACTIVATION AFTER ALLOGENEIC TRANSPLANTATION: EXPERIENCE OF A BRAZILIAN PUBLIC CENTER

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ABSTRACT

BACKGROUND. Despite recent advances of allogeneic hematopoietic stem cell transplantation (HSCT), viral infections are still a significant complication and remain a frequent cause of morbidity.

OBJECTIVE. To evaluate the profile of viral infection in patients undergoing HSCT in a Brazilian reference hospital.

STUDY DESIGN. This is a retrospective, descriptive, analytical and quantitative study. Allogeneic transplants performed in the last 5 years, in patients aged 16 years or older, were analyzed.

RESULTS. A total of 117 allo-HCT recipients were included. Of these, 50.43% were women and 49.57% were men, with a median age of 36 years. Acute myeloid leukemia was the most frequent underlying disease (27,35%). 88,33% of the patients had some virus detected (in any value) during the post-BMT period. There was a prevalence of viral reactivation in haploidenticals, with 90.91% of detection. CMV reactivation was the most frequent. We found a prevalence of CMV infection after allo-HSCT (70.94%) with 62 patients (52.99%) above the cut-off of 1,000 IU/mL and 21 (17.95%) below this value. EBV was the second virus with the highest reactivation rate.

CONCLUSIONS. CMV remains in the first place among viral reactivations. CMV and EBV were predominant in unrelated transplants, while BKV and HHV6 predominated in haploidentical.

Keywords. Hematopoietic Stem Cell Transplantation. Transplantation, Homologous. Virus Activation.

BACKGROUND

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for numerous hematological diseases. Conditioning regimens used to reduce the risk of allograft rejection increase considerably the risk of viral infections.[1] As consequence, viral infections remain a leading cause of morbidity and mortality after transplant, including DNA viruses such as cytomegalovirus (CMV), BK polyomavirus (BKV), Epstein Barr virus (EBV) and human herpesvirus-6 (HHV-6).[2]

Effective screening and early preemptive therapy are essential for minimizing unfavorable outcomes, however they still represent a challenge in several Brazilian transplant centers, especially in the public health system. Part of this challenge is to draw the

reactivation profile of each region, as it can vary intensely, according to access to appropriate screening methods, GVHD incidence, and standardized types of conditioning, prophylaxis and immunosuppression in each center.

Current literature lacks clinical-epidemiological studies with cohorts of Brazilian population, especially northeastern, which has socioeconomic peculiarities reflected in unequal access to infrastructure and health services. Therefore, the key force of the present study was to draw a viral reactivation profile in a public transplant center, in order to guide our screening and treatment preemptive strategies. We also hope to encourage other northeastern centers to do the same.

METHODS

We retrospectively analyzed patients who underwent a allogeneic HSCT from January 2017 through December 2021 at the Walter Cantídio University Hospital, Fortaleza, Brazil. The minimum age was 16 years. Only patients with at least 100 days of follow-up were included, unless the reason of death was our endpoint. Second allogeneic transplants were also included, but no patient underwent both within the study period.

The local ethics committee approved the study protocol and the analyses were based on medical records and tests results only, with anonymity guaranteed for patients. Data were anonymized before analysis. Demographics, transplant characteristics, and viral events are presented as absolute numbers, percentages or medians and range, according to the type of transplant.

Conditioning regimens varied according to the indication for transplantation and the donor type. Patients diagnosed with aplastic anemia received anti-thymocyte globulin. Most patients received GVHD prophylaxis with cyclosporine combined with methotrexate or cyclophosphamide.

Before starting the conditioning regimen, all patients underwent serology for HIV, hepatitis virus, syphilis, chagas disease, toxoplasmosis, HTLV, CMV, and EBV. Conditioning regimens varied according to the indication for transplantation and the donor type. All patients received standard prophylaxis with trimethoprim-sulfamethoxazole, acyclovir and antifungal (fluconazole, micafungin or voriconazole).

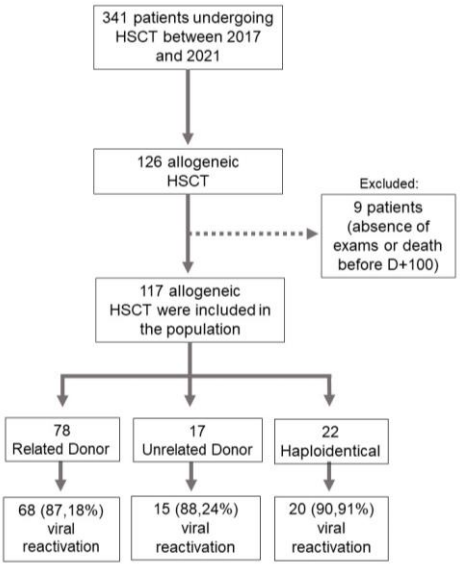
Reactivation was monitored weekly, by real-time quantitative PCR in plasma (for CMV, EBV and HHV-6) and in urine (for BKV). Viral reactivation was defined by detection of virus by PCR technique. Time to reactivation was calculated from the day of transplantation until the date of detectable PCR. The diagnosis of CMV infection was established by the detection of a viral load >1.000 UI/mL. The cut-off is not consensual in the literature and diversify among transplantation centers and according to the laboratory technique used. Recurrent CMV infection was defined as new CMV infection in a patient with previous evidence of CMV infection without the virus detected for 4 weeks during active surveillance.

Patients were treated preemptively for CMV and EBV. In the case of CMV infection, ganciclovir was the first-line therapy. Valganciclovir, Letermovir and Foscarnet are currently unavailability in the Brazilian Public Health System. In EBV infection, rituximab treatment was initiated. Preemptive treatment was performed for patients above the cut-off and individualized according to the assessment of risk factors, type of transplant, presence of GVHD and immunosuppression for those below the cut-off.

RESULTS AND DISCUSSION

Between January 2017 and December 2021, 341 patients underwent HSCT at the Walter Cantídio University Hospital. Of these, 126 were allogeneic. Nine patients (5 related and 4 unrelated) were excluded due to lack of viral screening records or death before D+100. A total of 117 allo-HCT recipients were included in the final study cohort, as detailed in figure 1.

FIGURE 1. Flow chart of patients included in the study.



The patients age at the time of transplant ranged from 17 to 70 years (median = 36 years) and was similar in all groups. 50.43% were women and 49.57% were men. Baseline clinical features are presented in Table 1.

Acute myeloid leukemia was the most frequent underlying disease (27,35%), followed by Acute Lymphoblastic Leukemia (23,93%), Aplastic Anemia (16,24%), Chronic Myeloid Leukemia (10,26%) and Myelodysplasia (8,55%). Other diagnoses represented 13,67% of patients.

Myeloablative conditioning was the most utilized (82,91%; n=97). Graft source was peripheral blood (83,76%; n=98) or bone marrow (16,24%; n=19). No patient underwent cord blood transplantation.

Studies find that 90% of alloHCT recipients have at least 1 DNA virus infection.[1]

TABLE 1. Overall demographics and clinical characteristics of patients undergoing Allogeneic Stem Cell Transplantation.

Characteristic	Total (n=117)	Haploidentical (n=22)	Unrelated Donor (n=17)	Related Donor (n=78)
Patient's Age (years)	36	36	36	36
Median				
Range	(16-70)	(17-64)	(17-58)	(17-70)
Donor's Age (median, in years)	35	35	35	35
Sex of patient	58 (49,47%)	12 (54,55%)	8 (47%)	38 (48,72%)
Male				
Female	59 (50,43%)	10 (45,45%)	9 (53%)	40 (51,28%)
Diagnosis				
Acute myeloid leukemia	32 (27,35%)	9 (40,91%)	1 (5,88%)	22 (28,21%)
Acute lymphocytic leukemia	28 (23,93%)	6 (27,27%)	8 (47,06%)	14 (17,95%)
Myelodysplastic syndrome	10 (8,55%)	1 (4,55%)	3 (17,65%)	6 (7,69%)
Aplastic anemia	19 (16,24%)	2 (9,09%)	1 (5,88%)	16 (20,51%)
Chronic myeloid leukemia	12 (10,26%)	2 (9,09%)	3 (17,65%)	7 (8,97%)
Other disease	16 (13,67%)	2 (9,09%)	1 (5,88%)	13 (16,67%)
ABO compatibility				
Major ABO Incompatibility	17 (14,53%)	3 (13,64%)	4 (23,53%)	10 (12,82%)
Minor ABO Incompatibility	20 (17,1%)	4 (18,18%)	3 (17,65%)	13 (16,67%)
Bidirectional	3 (2,56%)	0	2 (11,76%)	1 (1,28%)
Isogroup	77 (65,81)	15 (68,18%)	8 (47,06%)	54 (69,23%)

Our findings are consistent with those reported, with some virus being detected in 88,33% of the population, equivalent to 103 patients. These numbers correspond to 68 related donor (87.18%), 15 unrelated donor (88.24%) and 20 haploidentical (90.91%) transplantations. The distribution pattern of viral reactivations is specified in Table 2.

TABLE 2. Distribution of viral reactivation by type of HSCT

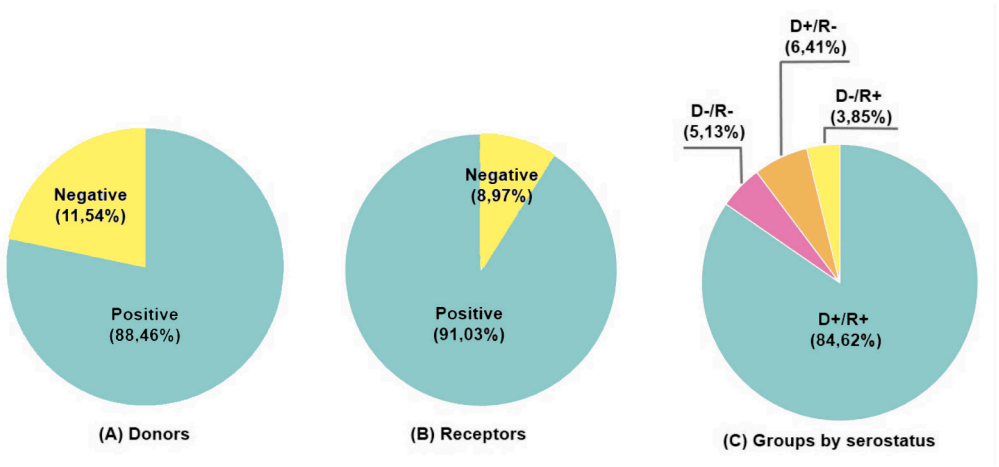
Type of HSCT	CMV (117 tested)			EBV (90 tested)			BKV (64 tested)		HHV6 (58 tested)	
	Indetectable	Detectable		Indetectable	Detectable		Indetectable	Detectable	Indetectable	Detectable
		<1000 UI/mL	>1000 UI/mL		<1000 UI/mL	>1000 UI/mL				
Allogeneic HSCT	34 (29,06%)	21 (17,95%)	62 (52,99%)	30 (33,33%)	24 (26,67%)	36 (40%)	39 (60,94%)	25 (39,06%)	34 (58,62%)	24 (41,38%)
Related Donor	26 (33,33%)	12 (15,38%)	40 (51,28%)	21 (41,18%)	16 (31,37%)	14 (27,45%)	26 (74,29%)	9 (25,71%)	23 (71,43%)	11 (28,57%)
Unrelated Donor	4 (23,53%)	3 (17,65%)	10 (58,82%)	2 (11,76%)	3 (17,65%)	12 (70,59%)	6 (50%)	6 (50%)	6 (66,67%)	3 (33,33%)
Haploidentical	4 (18,18%)	6 (27,27%)	12 (54,55%)	7 (31,82%)	5 (22,73%)	10 (45,45%)	7 (41,18%)	10 (58,82%)	5 (33,33%)	10 (66,67%)

A substantial proportion of patients (67.52%) reactivated more than one virus during follow-up, respectively: 50.43% with 2 viruses (the most frequent association was between CMV and EBV, with 40.17% of cases), 10.24% with 3 viruses and 6.84% with 4 viruses. It is reported that multiviral infections are frequently encountered. The number of post-HSCT patients with more than one virus is described in the literature as 60%, which is similar to our study, and numerous studies have demonstrated a dose-response relationship between the cumulative burden of virus exposure and mortality.[1]

CMV reactivation remains one of the most common infectious complications after allogeneic HSCT.[3] This was maintained in our study. Consistent with literature, we found a prevalence of CMV infection after allo-HSCT (70.94%) with 62 patients (52.99%) above the cut-off of 1,000 IU/mL and 21 (17.95%) below this value. A similarly high incidence of CMV infection was reported by Diaz and collaborators, who describe a total of 59%.[4] That is also consistent with previous literature, that fluctuate between 34% and 90% of incidence. This wide range is attributable to diversity of populational pre transplant CMV serostatus and laboratory techniques used in the diagnosis. A report from Latin America showed an incidence of 69%.[4,5] Other factors may influence this incidence. Goldsmith and collaborators published a CIBMTR analysis whose findings strongly suggest that PTCy contributes significantly to the development of CMV infection, regardless of donor source.[6]

Recipient and donor serologic status is a critical risk factor for CMV infection and disease.[2] Therefore, knowing the serological profile of the transplant center is essential to plan screening strategies. An overall CMV seroprevalence of 83% is estimated in the general population, varying among nationalities, with 90% in the Eastern Mediterranean region and 66% in the European region.[7] In Brazil, seroprevalence is historically high. Data from the Brazilian registry of SBTMO/CIBMTR evaluating 5697 patients between 2008 and 2021 demonstrate 78% positivity among recipients and 88% among donors.[8] In our population, 88.46% of donors and 91.03% of recipients had positive pre-transplantation serology for CMV. The relatively smaller *n* in our study may explain this lower proportion of seroprevalence compared to the national.

FIGURE 2. Subdivision based on the serological status of the donor (A), recipient (B), and their relationship (C).



CMV infection usually occurs within the first 100 days, related to an immunosuppressed state.[4] In particular, we found that time to CMV reactivation ranged from 11 to 182 days (median = 32); duration of DNAemia ranged from 7 to 70 days (median = 14); viral load at reactivation ranged from 1.037 to 32.250 UI/mL (median 2.644) and maximal viral load ranged from <500 to 114.177 UI/mL (median 3.066). Recurrent CMV infection range 1 from 5 episodes per patient (median 1).

High initial viral load (>20.000 copies/mL) would be related with the likelihood of CMV disease, as does the presence of leukopenia (white blood cell count < 3.000/mL) at diagnosis.[9] When we consider each type of transplant separately, our data suggest that the unrelated and haploidentical transplantations reactivate slightly earlier and present more recurrence, longer duration of viremia and higher viral loads (initial and maximum). Table 3 exposes these findings.

TABLE 3. CMV reactivation characteristics by transplantation type

CMV features	Total	Related Donor	Unrelated Donor	Haploidentical
Viremia Frequency Median (in number of episodes) Range	 1 (1-5)	 1 (1-4)	 1 (1-4)	 2 (1-5)
Reactivation date Median (in days post HSCT) Range	 32 (11-182)	 34 (15-182)	 32 (13-59)	 32 (11-42)
Duration of viremia Median (in days) Range	 14 (7-70)	 14 (7-49)	 18 (7-70)	 21 (7-70)
Viral load at reactivation Median (in UI/mL) Range	 2.644 (1.037 - 32.250)	 2.429 (1.037 - 13.369)	 3.490 (1.049 - 32.205)	 2.684 (1.202 - 10.112)
Largest viral load Median (in UI/mL) Range	 3.066 (<500 - 114.177)	 3.030 (<500 - 114.177)	 3.486 (<500 - 105.582)	 3.486 (<500 - 10.112)

Preemptive therapy based on CMV viremia has become the standard prevention of CMV diseases after transplantation.[14] The first line used for the treatment of CMV reactivation in our study was ganciclovir 5mg/kg intravenously every 12h, with a minimum duration of 2 weeks. Accordingly Chan and Logan[9], when treated with pre-emptive antiviral therapies, <5% of cases with CMV reactivation progress to CMV disease. In our study, 20.97% of patients had viremia above the cutoff point after the second week of treatment. In the Literature, this occurs in half (50.6%) of patients experiencing CMV viremia, and is associated with increased risk for CMV disease and treatment-related mortality when it occurs within the first 100 days. In this setting, the toxicities of prolonged treatment may contribute to myelosuppression and renal impairment.[9]

Accordingly Wei et al[10], the infection EBV rate exceeds 90% worldwide. Regarding the pre-transplant serological status, the profile of our population is 96.1% positivity for recipients and 97.4% for donors. Reactivation is a common complication post alloHSCT, which has increased significantly with the development of haploid, unrelated donor transplantation, and the application of antithymocyte globulin (ATG) in pretreatment. The reported incidence post HSCT ranges from 0.1 to 63% according to different GVHD prevention, conditioning regimens and monitoring techniques.[10]

Ru and collaborators conducted a retrospective study that enrolled 890 allo-HCT recipients. Independent risk factors for EBV reactivation were use of ATG, haploidentical donor, and the presence of chronic GVHD. The cumulative incidence of EBV reactivation for patients with 0, 1, 2, and 3 risk factors was 2.9%, 11.7%, 27.3%, and 41.9%, respectively.[11]

These findings are consistent with our study: EBV was the second virus with the highest reactivation rate (40% of patients had more than 1.000UI/mL), as described in table 2. Thirty-four (29.06%) patients used ATG. Of these, 29 (85.29%) reactivated some virus and 14 (56%) reactivated EBV.

Kerbauy et al[2] observed higher rates of EBV reactivation in the UD group in comparison with haploidentical, and occurring earlier in UD. In our results, EBV reactivation was predominant in patients undergoing unrelated HSCT, followed by haploidentical patients. The median time reactivation was 48 days (ranging from 15-159), but 12 patients had later reactivation (after D+180). Unrelated HSCT reactivated earlier and had higher viral loads. Table 4 details the characteristics of EBV reactivation.

TABLE 4. EBV reactivation characteristics by transplantation type.

EBV features	Total	Related Donor	Unrelated Donor	Haploidentical
Reactivation date (until D+180 follow up) Median (in days post HSCT) Range	48 (15-159)	48 (15-159)	38 (21-126)	42 (20-127)
Viral load at reactivation Median (in UI/mL) Range	7.220 (1.060 - 1.078.290)	6.913 (1.060 – 1.078.290)	10.520 (1.270 – 108.301)	2.973 (1.669 - 79.124)
Largest viral load Median (in UI/mL) Range	7.373 (1.060 – 108.301)	7.391 (1.060 – 1.078.290)	10.520 (5.459 – 108.301)	5.972 (1.669 – 79.124)
Reactivations after d+180 (in nº of cases)	12	9	2	1

After HSCT, loss of immune surveillance promotes opportunistic growth of EBV-infected cells, causing EBV reactivation, which can progress to post-transplant lymphoproliferative disorder (PTLD).[12] Therefore, adequate screening and preventive treatment is essential to prevent this feared condition. At our transplant center, preemptive treatment with rituximab was given according to EBV-DNAemia, risk factors and clinical assessment of each patient.

Reactivation of HHV-6 is common after HSCT, especially cord blood transplantation. Like other herpesviruses, HHV-6 establishes chronic latency, and its reactivation can cause a range of central nervous system symptoms, like post-transplant acute limbic encephalitis-PALE, in severely immunocompromised hosts.[13,19] In our cohort, HHV6 had a general detection rate of 41.38% among allogenes, predominantly haploidentical and unrelated (66.67% and 33.33%, respectively), as shown in Table 2. This is consistent with reported in the studies: approximately 30% to 50% of recipients with HHV-6 reactivation after transplantation.[13,14,15] It was the virus with the earliest reactivation (median of 26 days; ranging from 11 to 98). No sample of cerebrospinal fluid was positive in the studied population.

BK polyomavirus infection results in significant morbidity in post TCTH, mainly due to hemorrhagic cystitis. This complication can occur early, after conditioning, or later, approximately from the tenth day to six months after HSCT. The consequences can be tubulointerstitial nephritis and even renal failure.[16] Studies evaluating a BKV viral load cut-off for the development of hemorrhagic cystitis suggest the value above 10^7 copies/mL in urine.[17] Second ECIL guidelines for BK polyomavirus, the observed incidence of BKV is 8%–25% and 7%–54% in paediatric and adult patients, respectively, being higher after allogeneic than after autologous HSCT and particularly after haploidentical HSCT with post-transplant exposure to cyclophosphamide as prophylaxis for graft versus host disease (GVHD).[18] In our study, similarly, BKV reactivation was found in 39.06% of patients, with a predominance of haploidentical patients, followed by unrelated patients. Median reactivation was 45 days. The median of the highest viral load was 2.166.085, with a predominance of unrelated (median 36.048.373) and haploidentical (median 2.166.085).

CONCLUSION

Allogeneic HSCT is associated with substantial rates of viral reactivation resulting in the need for prolonged antiviral therapy and considerable morbidity as well. Optimal management of viral infections is a essencial objective in every HSCT strategy in order to limit virus-related morbidity and mortality. Therefore, strategies to prevent viral infection are strongly warranted.

In our study, CMV remains in the first place among viral reactivations. CMV and EBV were predominant in unrelated transplants, while BKV and HHV6 predominated in haploidentical. The earliest reactivation was HHV6, with a median of 26 days.

There are limitations to our study related to retrospective characteristic and difficult to access the information collected in the medical records.

Despite access and infrastructure challenges of the public health system, it is possible to develop adequate screening and timely preemptive treatment in the alogenic transplantation.

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BARRIERS TO ACCESS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: AN INTEGRATIVE REVIEW

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ABSTRACT

Introduction: Hematopoietic stem cell transplantation is a therapy for which even countries with universal health systems face challenges to ensure its access to the population. Barriers to access can be characterized as geographic, organizational, socioeconomic and of information.

Objective: To conduct an integrative review of barriers to access of hematopoietic stem cell transplantation. Methods: Databases chosen were BVS, PubMed and Scopus. Population and phenomenon were established, respectively as "hematopoietic stem cell transplantation" and "barriers to access" with descriptors in Portuguese and English. 22 articles, published between 2012 and 2022, were selected.

Results: Access was hampered by the distance to transplant center, in more populous regions, with high demand for services and transportation difficulties. There was better access in countries with higher GDP per capita, more installed transplant centers and for the population with higher income. Insurance coverage, support by public policies, assistance in academic centers, organized regulation and prioritization of emergencies facilitated access. The understanding of the diseases, the adherence to the treatments, the perception of survival by the patients and the skills of the professionals improved the access.

Conclusion: All categories of access barriers were addressed, with multifactorial and interrelated origins, with the vulnerable population being the most affected.

Keywords: Health services accessibility. Bone marrow transplantation. Hematopoietic stem cell transplantation.

INTRODUCTION

Bone marrow transplantation or hematopoietic stem cell transplantation (HSCT) is a form of cell therapy used to treat various hematological and onco-hematological diseases. When the patient happens to be his/her own donor, this transplant is characterized as autologous, with control or cure of the underlying disease being dependent on high doses of chemotherapy. To the contrary, when we have another compatible individual donating to the patient, whether a family member or not, this characterizes the allogeneic transplant - a process in which immunological modulation plays a role, and in which the cure is dependent on the graft versus tumor process or on the recovery of effective hematopoiesis [1].

Both HSCT modalities are successfully used worldwide, with the main indications for autologous transplantation being multiple myeloma and lymphomas, and the main indications for allogeneic transplanta-

tion being acute leukemias[2,3]. The number of transplants has progressively increased in recent decades, because of technological advances and better understanding of clinical management, thereby allowing better survival of this group of patients, despite the considerable morbidity and mortality still associated with the treatment. Furthermore, due to the increase in the incidence and prevalence of onco-hematological diseases in the elderly population, combined with improvements in the health conditions of this group, indications and procedures for transplantation are being performed with increasing frequency in patients of advanced age, guided by status adequate performance and geriatric clinical evaluation [4].

Access to health services is a complex multidimensional concept that involves several determinants. There is a better understanding when the concept is related to health planning in accordance with data on population needs, which help to shape the characteristics of the provision of services in that health system. The epidemiological profile and health conditions of the population are related to the social inequalities prevailing in that society, and the differences in access to health services are reflections of the characteristics of health systems and the value attributed to public policies by decision makers[5]. Even in populations whose health care is provided by universal systems there is no uniformity in access and each country has its own dilemmas regarding the barriers faced which can be subdivided into four main types of interrelated categories: geographic, financial/socioeconomic, organizational and information/cultural[5].

Geographical barriers are those imposed by space, which can hinder movement/ transportation of the population to health services [5]. These barriers mainly arise in the case of treatments that involve high complexity of health technologies with high costs and health systems must structure reference centers. Other factors, such as income, can minimize the impact of geographic barriers by mechanisms facilitating transport, by the private disbursement of transport costs, for example.

Even developed countries suffer the impact of rising health costs and some adopt the strategy of sharing the costs of these services with users[6]. The greatest impacts occur on the population with the lowest income, leading to further deepening of social inequalities, a fact that can be minimized with strategies enabling universal access [5].

The way health services are organized generates facilities or limitations for gaining access. This impact occurs not only on an initial attendance, but also has repercussions on the continuity of care. This may involve parameters such as collaborative models, methodological and cultural diversity of professionals, communication problems, differences in management models, issues related to socioeconomic diversity and the present legislation[7].

Cultural aspects and the level of information of the population can also affect access to transplantation since it is a procedure involving considerable morbidity and mortality. Religion, for example, can be an important barrier to access by Jehovah's Witnesses, with autologous HSCT being the only possible modality for selected cases[8]. Whereas well-informed patients can make more conscious decisions, such as undergoing transplantation in cases of those who perceive worsening of their clinical condition, even during the pandemic[9].

Given the complexity of the spectrum of access due to the organizational variables of health systems and the socioeconomic and geographic aspects involved in the concept, this study becomes relevant. Its aim was to analyze the barriers that hinder access to HSCT, identify the types of barriers found into a discussion on determination of these barriers and the challenges for improving access to HSCT.

MATERIAL AND METHODS

This study was an integrative systematized review of the literature with the objective of searching the databases to identify knowledge about the barriers to access to HSCT. Descriptors were chosen and search strategies were defined to answer the research question: "What does the scientific literature present about the Barriers to access to hematopoietic stem cell transplantation?". The databases chosen for searches were BVS, PubMed and Scopus.

Based on the research question, the poles of population and phenomenon were established as being "hematopoietic stem cell transplantation" and "barriers to access", respectively. Descriptors in Portuguese were used, according to "DeCS - Descritores em Ciências da Saúde" for the search in the BVS and according to MeSH for PubMed and Scopus.

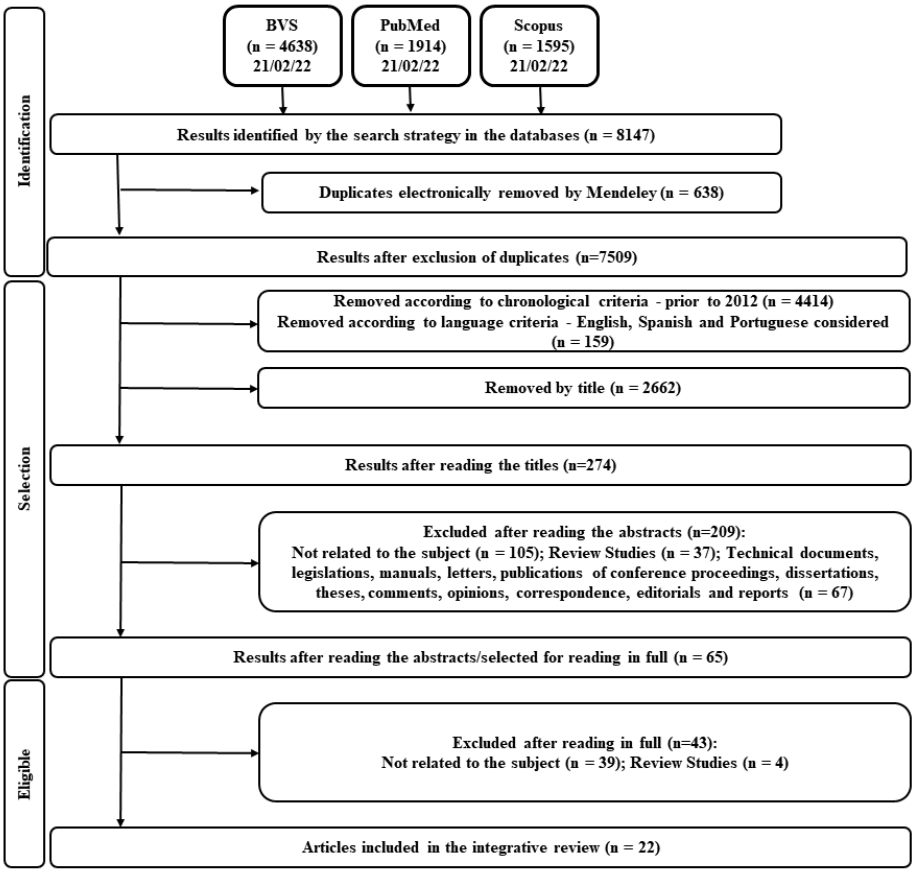
The inclusion and exclusion criteria adopted were scientific articles that discussed barriers to access to bone marrow transplantation; studies in Portuguese, English and Spanish and publications from January 2012 to February 2022. Scientific articles that were unrelated to the subject studied were excluded from the study, and so were technical documents, legislation, manuals, letters, publications of conference proceedings, dissertations, theses, comments, opin-

ions, correspondence, editorials, reports, articles not available for reading and review studies.

The final syntax for the database of BVS was (mh:("acesso a medicamentos essenciais e tecnologias em saude" OR "acesso universal aos servicos de saude" OR "barreiras ao acesso aos cuidados de saude" OR "cobertura universal de saude" OR "equidade no acesso aos servicos de saude" OR "judicializacao da saude" OR "qualidade, acesso e avaliacao da assistencia a saude" OR "acesso aos servicos de saude" OR "acesso efetivo aos servicos de saude" OR "controle de acesso" OR "decisoes judiciais" OR "jurisprudencia" OR "custos de medicamentos" OR "imunossupressores" OR "uso de medicamentos")) AND (mh:("hematologia" OR "transplante de medula ossea" OR "transplante de celulas-tronco hematopoeticas" OR "transplante de celulas-tronco de sangue periferico")). For Pubmed the following terms were used (((Hematology[MeSH Terms]) OR (Bone Marrow Transplantation[MeSH Terms])) OR (Hematopoietic Stem Cell Transplantation[MeSH Terms])) AND (((((Delivery of health care[MeSH Terms]) OR (Social Deprivation[MeSH Terms])) OR (Jurisprudence[MeSH Terms])) OR (Referral and consultation[MeSH Terms])) OR (Health care costs[MeSH Terms])), and for Scopus (KEY ("Hematology") OR KEY ("Bone Marrow Transplantation") OR KEY ("Hematopoietic Stem Cell Transplantation")) AND (KEY ("Delivery of health care") OR KEY ("Social Deprivation") OR KEY ("Jurisprudence") OR KEY ("Referral and consultation") OR KEY ("Health care costs")).

The syntaxes were used for database searches on February 21, 2022, with the result being 4638 documents obtained in BVS, 1914 documents in PubMed and 1595 documents in Scopus, totaling a survey of 8147 results. This dataset was imported into the Mendeley, and 638 items were electronically excluded because they were duplicates. After this, the list of documents was imported into the Rayyan application, then the chronological and language criteria were applied, resulting in the exclusion of 4414 and 159 documents, respectively. The next filter procedure involved reading the titles; this resulted in the exclusion of 2662 items. After applying these processes, 274 results remained for reading the abstracts. According to the exclusion criteria, after reading the abstracts, 65 articles were selected for reading in full with 22 articles being retained, as shown in the flowchart below based on PRISMA (Figure 1) [10].

FIGURE 1. Flowchart of the article selection process



RESULTS

The documents selected for the integrative review are listed below according to main author, year, title, and journal of publication (Table 1).

TABLE 1. Articles included in the integrative review, according to author, year of publication, title and periodical.

ID	Main Author	Year	Title	Journal
1	Gramajo, P	2012	Accesibilidad al trasplante de células progenitoras hematopoyéticas según entidades financiadoras de salud en Argentina, 2000-2010.	Rev Argent Salud Pública
2	Bierenbaum, J	2012	Racial differences in presentation, referral and treatment patterns and survival in adult patients with acute myeloid leukemia: a single-institution experience.	Leukemia Research
3	Urbano-Ispizua, A	2012	Hematopoietic stem cell transplantation in Europe. Differences between Eastern and Western countries.	Hematology
4	Omondi, N	2013	Barriers to hematopoietic cell transplantation clinical trial participation of african american and black youth with sickle cell disease and their parents.	J Pediatr Hematol Oncol
5	Moore, H	2013	Barriers to accessing health care for hematopoietic cell transplantation recipients living in rural areas: perspectives from healthcare providers.	Clin J Oncol Nurs
6	Pidala, J	2013	Practice variation in physician referral for allogeneic hematopoietic cell transplantation.	Bone Marrow Transplantation
7	Thompson, A	2013	An educational symposium for patients with sickle cell disease and their families: results from surveys of knowledge and factors influencing decisions about hematopoietic stem cell transplant.	Pediatr Blood Cancer
8	Maeda, T	2014	Regional differences in performance of bone marrow transplantation, care-resource use and outcome for adult T-cell leukaemia in Japan.	BMC Health Services Research
9	Mikles, B	2014	Pediatric hematology providers on referral for transplant evaluation for sickle cell disease: a regional perspective.	J Pediatr Hematol Oncol
10	Besse, KL	2015	Estimating demand and unmet need for allogeneic hematopoietic cell transplantation in the United States using geographic information systems.	Health Care Delivery
11	Mitchell, J	2015	Factors affecting receipt of expensive cancer treatments and mortality: evidence from stem cell transplantation for leukemia and lymphoma.	Health Services Research
12	Patel, MI	2015	How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia?	Cancer Epidemiol Biomarkers Prev
13	Alsultan, A	2016	Demands and challenges for patients with sickle-cell disease requiring hematopoietic stem cell transplantation in Saudi Arabia.	Pediatr Transplantation
14	Delamater, P	2016	Geographic access to hematopoietic cell transplantation services in the United States.	Bone Marrow Transplantation
15	Schriber, JR	2017	Hispanics have the lowest stem cell transplant utilization rate for autologous hematopoietic cell transplantation for multiple myeloma in the United States: a CIBMTR report.	Cancer
16	Umakanthan, JM	2018	Factors associated with receipt of hematopoietic cell transplantation for acute lymphoblastic leukemia.	Future Oncology

17	Ailawadhi, S	2019	Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis.	Blood Advances
18	Mupfudze, TG	2020	A qualitative analysis of state Medicaid coverage benefits for allogeneic hematopoietic cell transplantation (alloHCT) for patients with sickle cell disease (SCD).	Transplantation and Cellular Therapy
19	Truong, T	2020	Regional differences in access to hematopoietic stem cell transplantation among pediatric patients with acute myeloid leukemia.	Pediatr Blood Cancer
20	Leuthold, N	2021	Patient preferences for allogeneic hematopoietic stem cell transplantation: how much benefit is worthwhile from the patient´s perspective?	Supportive Care in Cancer
21	Worel, N	2021	Changes in hematopoietic cell transplantation practices in response to COVID-19: A survey from the Worldwide Network for Blood & Marrow Transplantation.	Transplantation and Cellular Therapy
22	Pan, D	2021	Evaluating race and time to transplantation in multiple myeloma: The Mount Sinai Hospital Experience.	Clinical lymphoma, myeloma & leukemia

Data were summarized in a summary spreadsheet with the following parameters: main author, study design, study participants, type of transplant involved, type of access barrier discussed, main results and conclusions (Table 2).

TABLE 2. Summary of articles selected for the integrative review

Main Author	Study Design	Study Participants	Type of Transplant involved	Barriers to Access	Main Results	Conclusion of Study
Gramajo (2012)	Retrospective	Population submitted to transplant with procedure financed by different entities, in Argentina, between 2000 and 2010.	Not discriminated	Organizational and Geographic	Patients with health insurance had higher rates of transplantation compared with patients without insurance, considering all insurance entities in the country. There were differences in access among the insured population depending on geographic localization. Better access in the province of Buenos Aires for patients without health insurance because it has its own financing entity.	There was vertical inequality in access to transplants in Argentina, which should motivate further studies on the issue of financing these procedures and, in the analysis of only the group with health insurance, there was horizontal inequality that needs organizational discussion.
Bierenbaum (2012)	Retrospective	Patients with acute myeloid leukemia, white versus black, treated from 2000 to 2009 at a tertiary university hospital in Baltimore (United States).	Allogeneic	Socioeconomic and cultural	Fewer black patients had access to transplants compared with whites, especially males, and these findings may also reflect lower access to clinical studies. The income of the black families assisted was lower than that of the white patients.	The authors were unable to explain the disparities, but it was speculated that there were socioeconomic and cultural factors involved.

Urbano-Ispizua(2012)	Retrospective	Transplant candidate population in Western and Eastern Europe based on registry data since 1990.	Autologous and allogeneic	Financial	Countries with higher GDP per capita and higher density of transplant teams had higher transplant rates.	Macroeconomic factors influenced access to transplantation, with higher rates in countries in Western Europe compared with Eastern Europe, since the number of teams also depended on the economic and financial power of the country
Omondi (2013)	Cross-sectional	Parents of young patients (<16 years) and young Black patients with sickle cell disease in the United States.	Allogenic	Information	The lack of information about the disease and understanding of the treatment, mainly by the parents responsible for the patients, suggested difficulties in gaining access to transplantation by clinical trials.	Identifying barriers to information could help healthcare professionals and managers to perform interventions to improve access to transplantation for patients with sickle cell disease in the United States.
Moore (2013)	Cross-sectional	In 2009, Health professionals questioned about access to post-transplant care for patients living in rural areas far from a transplant center (over two hours of traveling by car) in the United States.	Not discriminated	Geographic	Limitations of transport to the transplant center, lack of expertise in assistance at the place of residence and the distance from the transplant center restricted access to post-transplant care.	There was a need for education of health providers in locations close to the patients' homes to ensure continuity of care and these objectives must be worked on at an organizational level.
Pidala (2013)	Cross-sectional	Medical specialists questioned about referring onco-hematological patients for transplantation in the United States in 2011.	Allogeneic	Information and organizational	Lack of transplant coverage by insurers, lack of social support, non-adherence to treatment and lack of understanding of treatment by the patients were factors associated with lack of referral to transplant centers.	Improvements in coverage, investment in education and social support for patients were necessary to enable decision-making that would allow better access to transplantation.
Thompson (2013)	Cross-sectional	Patients with sickle cell disease and their caregivers were questioned about factors that influenced their decision on whether or not to undergo a transplant, in Washington (United States) in the years 2011 and 2012.	Allogeneic	Information	The factors with the greatest impact on the decision were the risk of death from the procedure, complications of the underlying disease, risk of transplant complications, trust in the medical team, risk of transplant failure and the emotional impact caused by the transplant.	It was not possible to generalize the findings to a larger population of patients with sickle cell disease and their families, however, the expectation was that the dissemination of information would increase the search for transplantation to cure this disease and improve the quality of life of patients.

Maeda (2014)	Cross-sectional	Patients with adult T-cell leukemia treated in different regions of Japan in 2010.	Allogeneic	Organizational	Although there were no apparent differences in per capita health expenditure between regions, Kanto and Kansai had higher transplant rates.	There were regional differences in access to transplantation related to local factors, with better efficiency in the use of resources.
Mikles (2014)	Cross-sectional	Healthcare Providers for Pediatric Patients with Sickle Cell Disease on the Perspective of Transplant Referral in the Northeastern United States in 2011.	Allogeneic	Information, geographic and organizational	Professionals who received training less than 20 years ago and those who worked in centers that performed transplants tended to refer a larger number of patients for the procedure. The phenotype of the disease had an impact on the rate of referrals. There were variations in the rates of transplants by teams. The degree of risk of death perceived relative to the procedure also affected referral rates.	There was a need to develop national guidelines to achieve greater uniformity of professional conduct in relation to the indication and referral of patients with sickle cell disease for transplantation.
Besse (2015)	Cross-sectional	Population that underwent transplantation in the United States in 2012.	Allogeneic	Geographic and organizational	There was difficulty with meeting the demand in areas with a larger population, with New York and California being the regions with the highest demand and the fewest needs of the adult and pediatric population being met, respectively.	The study revealed the need to build and expand transplant centers to cover unmet needs based on the perspective of analyzing geographic information.
Mitchell (2015)	Retrospective	Patients with leukemia and lymphoma treated in California (United States) in 2002 and 2003.	Not discriminated	Organizational, Socioeconomic and Geographic	The population of patients with private insurance and white men were more likely to undergo a transplant, and so were patients who lived closer to treatment centers and had higher incomes.	There were multiple variables involved in gaining access to transplantation, seen as a high-cost therapy for the health system, and the financing model could affect both access and clinical outcomes.
Patel (2015)	Cross-sectional	Population with acute myeloid leukemia diagnosed in California (United States) in the period between 2008 and 2018.	Not discriminated	Socioeconomic	In the population analyzed, Black patients were less likely to receive chemotherapy and transplantation than white patients. Patients of Latin origin had less access to transplants than white patients.	Further studies are needed, which correlate the differences in access to treatments among different ethnic groups with socioeconomic differences.

Alsultan (2016)	Cross-sectional	Patients with sickle cell anemia under follow-up in Saudi Arabia in the period from 2009 to 2014.	Allogeneic	Geographic and financial	The number of centers and teams that perform transplants was insufficient to meet the local demand, and some patients left the country to undergo the procedure.	The article recommended that greater funding (should be provided) for transplant programs, which would allow new centers to be opened and more teams to be trained.
Delamater (2016)	Cross-sectional	Total adult and pediatric population based on the number of transplant centers in the United States in 2015.	Not discriminated	Geographic	The adult population had better geographic access than the pediatric population. The white population had worse geographical access than ethnic minorities, and this data could reflect the predominance of the white population in rural areas.	Despite variations in terms of distance from transplant centers, approximately 94% of the population had geographic access to these centers, within 3 hours. Further studies were needed to assess clinical outcomes in relation to patients' distance from transplant centers.
Schriber (2017)	Cross-sectional	Patients with multiple myeloma (of Latino, Black, and white origin) undergoing autologous transplantation in the United States in the period between 2008 and 2014.	Autologous	Socioeconomic	Although the rate of using transplantation increased in the three groups from 2008 to 2013, fewer Latino and black patients over 60 years of ag underwent transplantation compared with whites. The white population had faster access to transplantation, from the time of diagnosis through to the procedure,	There are differences in access to transplantation for multiple myeloma among ethnic groups and new strategies are needed to minimize this disparity. Moreover, further studies are needed to better elucidate the factors that determine these differences.
Umakanthan (2018)	Retrospective	Patients with acute lymphoblastic leukemia, adults diagnosed in the United States in the period between 2003 and 2012.	Allogeneic	Socioeconomic and organizational	The factors related to a lower chance of undergoing a transplant were treatment at a non-academic center, low educational level, being a Medicare/ Medicaid user or one without health insurance coverage, and male gender.	The data found suggested that socioeconomic differences and differences in coverage of the procedure by the health system can affect access to transplantation. The reason why female patients had more access in this study, was not clear.

Ailawadhi (2019)	Retrospective	Black, white, and Latino patients with multiple myeloma covered by Medicare in the United States in the period from 2007 to 2014.	Autologous	Socioeconomic	Black and Latino patients experienced more delay in gaining access to new treatments and Latino patients were less likely to undergo transplantation within a year of diagnosis compared with white and Black patients.	Disparities in access to more modern treatments and transplantation between different ethnic groups involved socioeconomic variables that needed to be overcome to achieve equity of health in the group studied.
Mupfudze (2020)	Cross-sectional	Population with sickle cell disease covered by Medicaid in eight states in the United States.	Allogeneic	Organizational	All states reported that children with a fully matched related donor were covered, however, in clinical trials, only two states reported policies covering costs. Accommodation and travel expenses were not covered in most states. Funding did not cover the costs of the procedures, and the transplant center paid the difference. The different Medicaid plans led to differences in the process of obtaining authorization for the transplant.	The study pointed out the need for discussions concerning the legislation so that there could be greater uniformity in patients' access to transplantation for sickle cell disease. This referred especially to the issue of financing clinical studies for transplants with alternative donors, and to public policies that made it feasible for patients and caregivers to obtain accommodation and transport.
Truong (2020)	Retrospective	Pediatric population with acute myeloid leukemia diagnosed in different regions of Canada in the period between 2001 and 2015.	Allogeneic	Geographic	Patients with an indication for transplantation before the first relapse had better access when diagnosed in the East of the country compared with the Center and West. Patients with indication for transplantation after the first relapse had faster access if the leukemia treatment was carried out at a center that performed transplantation.	Although other variables such as distance from home to the hospital, income and ethnicity did not have an impact on access to transplantation in this study, the data found may help in the formulation of public policies and guide other studies that clarify the geographic and socioeconomic impact on the treatment of the condition in this population.

Leuthold (2021)	Cross-sectional	Adult patients submitted to bone marrow transplantation up to October 2018, were asked about the benefits in terms of survival and cure they considered receiving when accepting the procedure in a university hospital in Switzerland.	Allogeneic	Information	Approximately 95% of the patients considered a gain in survival of one-year as being acceptable to undergo the procedure, and 85% of the study population considered a minimum of 5 years justifiable. Most patients considered at least a 50% cure rate as being acceptable.	Further studies were needed to understand the gains in survival and cure from the perspective of patients, since there may have been selection bias and the younger population tended to accept more risks with fewer benefits.
Worel (2021)	Cross-sectional	Members of several international transplant societies asked online about changes in the handling of allogeneic and autologous donor products during the COVID-19 pandemic in 2020.	Allogeneic and autologous	Organizational	Most centers changed the criteria for cell collection and mobilization during the pandemic, in accordance with the recommendations of international societies. Some centers only performed urgent transplants and some even completely stopped performing autologous collections.	The pandemic imposed changes in conduct on transplant centers, with the need to postpone transplants considered non-urgent due to the risk of SARS-CoV-2 infection of donors, patients, and health professionals.
Pan (2021)	Retrospective	Both white and Black multiple myeloma patients, transplanted at a center in New York (United States) in the period from 2011 to 2016.	Autologous	Socioeconomic	No difference in time between diagnosis and collection of cells was demonstrated between white and black patients, but socioeconomic status based on difference in income had an impact on access to transplantation.	Although there was no statistical significance, the transplant center recognized the elapse of a longer time from diagnosis to collection of cells for black people, which may have been related to the socioeconomic situation of this population, which must be improved for then to gain faster access to cell therapy.

Eight retrospective studies and 14 cross-sectional studies with an approach to transplantation modalities were identified. There were 12 studies on allogeneic transplantation, 3 on autologous transplantation, 2 discussed both modalities and 5 studies did not discriminate the type of HSCT. Most of the studies found were conducted in the United States, with 15 of these corresponding to 68% of the total articles analyzed. The other articles found, one for each location, were carried out in Argentina, Saudi Arabia, Canada, Japan, Switzerland, in addition to one involving European countries and one with a global perspective. Six studies addressed the context of barriers to access in cases of leukemia, 5 in sickle cell disease and 3 in multiple myeloma.

Some of them involved the entire population residing in the country, with an indication for undergoing the procedure, when the issues discussed involved financing modalities or geographic distance. The studies with health professionals raised questions about geographic difficulties, regulation of access and changes in behavior in the COVID-19 pandemic. All categories of barriers to access were discussed. For geographic, organizational and culture/information barriers there were 3 articles to discuss each

of the topics and 5 studies relative to financial/ socioeconomic barriers. Eight articles discussed more than one barrier.

DISCUSSION

Access to health care is a complex concept that involves factors that are intermediaries between demand, access to health services, possible therapeutic interventions, and clinical follow-up. Following the proposal of the flow of events proposed by Frenk cited by Travassos & Castro, for the discussion and planning of access to health care, it is necessary to start from a population health need[5]. Through this flow, health systems should be based on reaching the broad domain of access, which involves everything from educational and cultural aspects that pertain to the way in which the population wants to obtain health care, through to the continuity of health care, whether preventive or curative. Even in universal health systems, planning and guaranteeing access to the broad domain are constant challenges. If only the aspects of seeking and entering health services were to be considered, this would generate public policies that would not consider aspects of prevention and would not guarantee continuity of care[5].

There are many factors involved in determining access that will help characterize the population's ability to use services within health systems. According to Rocha et al., the factors associated with access to allogeneic HSCT are availability donor, socioeconomic factors, aspects of health systems, actions related to health care providers and geographic determinants[11]. Adequate knowledge of these factors will help plan the type of access that health systems will offer, with the possibility of eliminating or reducing barriers, thereby promoting health of the population. This study was designed by grouping barriers to access into four categories that will be discussed: geographic, financial/socioeconomic, organizational, and information/cultural types.

Relative to the donor, with technological advances in the understanding of immunogenetics and advanced mechanisms for unrelated search, in addition to the advent of the use of high doses of cyclophosphamide as prophylaxis for graft-versus-host disease, most patients who need transplantation have donors. Therefore, despite the donor being a determining factor for HSCT to occur, this parameter was not considered in the searches of this study because of the wide donor availability in the current technical-scientific context.

CONCERNING THE SOCIOECONOMIC AND FINANCIAL BARRIERS

Socioeconomic and financial factors impact all levels of health care and characterize the barrier to access to HSCT found in this review [13–21]. Income is a parameter known to be an important factor in determining the health condition of populations whereas ethnic and socioeconomic issues are complex and require careful analysis of other factors, including clinical outcomes, which may influence them[22]. Furthermore, in recent decades, rising costs have had a significant impact on health systems around the world and pose, especially in underdeveloped countries, challenges for innovation in care models so that they are sustainable [23]. Human freedom to generate health is dependent on choices in the economic sphere and formulations of public policies for social well-being, mediated by the interests of the government around the world [24].

The results of this study reveal both micro and macroeconomic data that refer to differences in wealth among certain ethnic groups and even groups of countries. There was a significant finding of lower access to HSCT in groups of black people with lower income than white people[15,17,18]. Although other studies did not directly report results resulting from income discrepancies, there was a finding of difference in access between different racial and ethnic groups, with blacks and latinos also arriving later at HSCT centers [13,19,20] and in some situations had less access to chemotherapy for treatment prior to transplantation [19].

The GDP of countries affects health systems, and consequently access, however there are countries that, despite having a GDP per capita lower than developed countries, manage to organize themselves in a way that their population has a high life expectancy, which suggests that it is more important to know what to do with the resources available to be allocated than just their quantity[24]. Urbano-Ispizua et al. demonstrated that on the European continent, patients residing in countries with a higher GDP per capita, located predominantly in Western Europe had better access to HSCT[21]. In this same study, there was a positive impact in places with a higher density of health teams. There probably were more centers due to the availability of financial resources that allowed sustainability of a larger number of programs, and the findings of the study were interrelated. Alsultan et al. pointed out that there were cases such as Saudi Arabia, in which the offer of HSCT services

for sickle cell disease was insufficient to meet the demand to the extent that people left the country to receive treatment elsewhere [14].

In this review, not all countries found had universal health systems, which would have helped to minimize financial barriers by the group of individuals who did not have health insurance, which was a significant factor reported in some studies to achieve improvements in access [16,17,25]. Some countries can include patients in clinical studies, which allows them to use technological innovations in their treatment, especially when treated in academic centers [15,16].

CONCERNING THE GEOGRAPHIC BARRIERS

Geographical barriers involve the spatial challenges imposed, from transportation difficulties to the lack of specialized teams for the procedure. Gramajo et al. reported that in Argentina there is better access to HSCT in the province of Buenos Aires, even for those who do not have health insurance, as this region has its own financing entity that minimizes the lack of coverage by insurance companies [25]. This same study also reports that even among the insured population, there is a difference in access depending on the region of residence in the country.

Moore et al. point out that, in addition to issues related to difficulty in transportation, there is no adequate support in rural areas further away from HSCT centers in the United States due to the lack of training of local teams, making post-transplant follow-up difficult [26]. In contrast, Besse et al. argue that in urban centers with large populations there is a lack of infrastructure to meet demand and population needs are not met [27]. In the first case, the organization of care networks with education and qualification programs for professionals could minimize possible clinical harm to patients due to the lack of specialized care. Telehealth systems could be of great benefit in minimizing distances. As for locations with high demographic density, management depends on financial and organizational factors for the solution, with an increase in the installed capacity of HSCT beds or logistical agreements for referral to other regions.

Many of the solutions to geographic barriers are at the organizational level: if there is no way to change the geography, there is a need to increase the number of transplant centers, with the need for better financing or improving the logistics of transporting the poorest patients, as income also affects the geographic mobility of people[14,28].

Delamater et al., when studying the impact that geography had on transplants in the United States, found that the adult population would have more access than the pediatric population due to the presence of more centers that perform transplants in adults [29]. This finding is compatible with the epidemiology of the main indications for HSCT, with a higher prevalence in adults [30]. However, this same study raises the curious question that the white population residing in rural areas, generally with a more favorable economic situation than ethnic minorities in large centers, would have worse geographic access to transplantation. Even with the variable distance within the country, most of the population has access to some service within a few hours of travel, which suggests that other factors are interrelated determinants [29].

Truong et al. found better access to HSCT, in first remission, for children with acute leukemia in Canada who lived in the east of the country [31]. As should happen anywhere in the world, in patients with more urgent conditions, access is faster and more agile if the treatment takes place in an academic center that performs transplants [16,31].

CONCERNING THE ORGANIZATIONAL BARRIERS

The various health systems are organized to balance policies taking into account the interests of the State, the population and the market. Organizational issues affect equity in similar population groups with comparable per capita health expenditure [32], as well as in the case of patients with health insurance living in the same country, but who have differences in access to HSCT [25].

There is no uniformity in the coverage of HSCT procedures in the world [16,17,25,33,34], which interferes with decision-making by professionals [33], with the possibility of generating unfavorable outcomes. Furthermore, the lack of therapeutic guidelines makes regulating access and referral an additional challenge for the teams [35]. Locations with better efficiency in the use of resources have better access to HSCT [32], including covering the need to increase the number of centers and trained teams for some areas [27].

The COVID-19 pandemic led to an additional challenge with the need to change clinical protocols so that patients with an indication for transplantation could be treated according to their risk of exposure to SARS-CoV-2 and the risk of death from the underlying disease [36]. Most centers postponed HSCT for patients with chronic diseases, such as multiple myeloma, and there could have been an unmeasurable harm to the survival of those who did not have access to new pharmacological technologies for their treatment, deepening previously reported inequities [36,37].

CONCERNING THE CULTURAL AND INFORMATION BARRIERS

HSCT procedures bring with them the hope of curing diseases, but the therapeutic process imposes biopsychosocial challenges on patients, which includes a very considerable risk of death due to complications in some cases [38,39]. Transplant candidates and their families, in addition to the information provided by professionals, consider cultural and religious aspects and the emotional impact [40]. These parameters must be adequately understood and worked on by health teams, so that they are not barriers to access, but become tools that help in autonomous decision-making by the people involved.

Due to the multifactorial aspects involved in access to HSCT, it can be quite complex to infer the weight of cultural issues in decision-making. Bierenbaum et al. discussed the issue of access between white and black people with acute myeloid leukemia from the perspective of a single center in the United States, concluding that there was a difference in access between the groups, but without a significant explanation, suggesting that cultural factors may be involved [15].

Both for patients with chronic conditions, such as sickle cell disease, and for candidates for HSCT due to indications of onco-hematological diseases, adequate education and provision of information has an impact on the decision-making autonomy of patients and their families. Thompson et al. reported that the decision to undergo HSCT weighs not only on the perception of the complications of the underlying disease itself and of the HSCT, but also on trust in the medical team [40]. This is a complex decision for this group of patients, because they generally have no perception of the severity of their disease and lack technical-scientific alignment for uniform conduct in relation to indication and referral [35]. On the other hand, the onco-hematological patient with an indication for HSCT desires the transplant but needs information that brings security to their choice in terms of survival gains, as many would not accept the risks inherent to the transplant without the perception of a potential gain in survival [41].

Guiding patients and families about the entire HSCT process, its benefits, and complications, can even make a difference in access to clinical studies for this population, enabling the use of innovative therapeutic technologies[42]. It is important, therefore, to highlight that not only the level of information of the target population, but also the level of technical knowledge, the ability to disseminate guidance and the health teams' own perception of the HSCT process, its outcomes and the adherence to treatment may influence the regulation of access to transplantation [33,35].

FINAL CONSIDERATIONS

It is noteworthy that most of the studies found in this review were carried out in the United States, the country with the largest increase in health spending, but with questionable gains in survival and quality of life for the population[43]. As one of the highest-cost procedures, economic studies on HSCT should be of interest to society, especially for chronic diseases such as sickle cell anemia, which can be cured and generate social benefits for patients' families and gains in efficiency in health spending, avoiding treating late complications. Hong and Majhail proposed a model for studies that can better elucidate racial, socioeconomic, and geographic barriers, with factors that interfere in the patient's line of care, from social policies and interventions, through regulation of access and education of health professionals[44]. The factors that act in determining access to treatment are as complex as transplantation.

This study has some limitations. The fact that it is an integrative review refers to a methodology that covers part of the knowledge and that may fail to find and discuss all aspects involved in barriers to access to HSCT and be limited to the perspectives of the studies found.

CONCLUSION

The issues surrounding access to HSCT are complex and interrelated, considering that geographic, financial, socioeconomic, cultural, organizational and information factors form an even more diverse network of variables when we think about multiple care models and systems of health in the world. The greatest negative impacts occur on the health of the most socially vulnerable populations. It is challenging to study and characterize these determining factors, as many of the articles found in this review bring local perspectives that cannot be applied in all countries. Despite this, gathering knowledge of these barriers can guide new studies to formulate public policies that can guarantee better access to the procedure, especially in underdeveloped countries, with efficient use of resources to improve equity in access to healthcare.

DISCLOSURES

The authors have states that they have no conflict of interest.

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