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JBMTCT

VOLUME TWO

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Dear transplant colleagues

In 2019 we celebrated the 40th anniversary of the first bone marrow transplant (Tmo) 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 Tmo-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 the first volume of JBMCT, Journal of Bone Marrow Transplantation and Cellular, which will certainly be a periodical to publicize the work of all those who believe that science , research and caring for patients, is the best way to improve our walking.

Fernando Barroso Duarte *Nelson Hamerschlak*

Summary

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CANCER, POVERTY AND LACK OF ACCESS TO THE BEST THERAPIES IN BRAZIL

EDITORIAL

Running head: ACCESS TO THE BEST THERAPIES IN BRAZIL

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This year, I followed a young patient who is being investigated for a probable leukemia,[1] He said he was a gardener. I tried to explain what his diagnostic hypothesis was, but I had a distinct feeling that he hadn't quite understood the situation. I always feel this feeling of anguish, a certain impotence, because the exact understanding involves a minimum amount of knowledge that this gentleman must have about health, citizenship or even general education, which a good part of the population that we treat in public hospitals does not have.

This patient who does not understand his illness very well and what effectively needs to be done for a correct diagnosis and treatment. Added to this is the difficulty of having access to new expensive drugs and, as if that were not enough, some essential drugs for the treatment of cancer, such as carmustine[2], used to conditioning regimen of Bone Marrow transplant, which simply disappeared from the Brazilian market and left with restrict options to treat these patients.

In any case, it is not the first time that we have dealt with this reality, and many will say that there is nothing new in my report or that it used to be much worse. I agree with these two statements, but this process remains very difficult, painful and very worrying. When a patient has a cancer diagnosis and needs a treatment that doesn't have another option, we see clearly that it's necessary discuss this reality and try to find a solution. I participated in february of a congress in the United States; there I could see the main updates in the treatments of onco-hematology and bone marrow transplantation. I presented an article[3] and, throughout the debate, I tried to show my professional colleagues the profound differences, not to say abysmal, between our realities in Latin America and first world countries. This distance becomes increasingly larger as treatment progresses based on targeted and cellular therapies, with drugs such as immunotherapy associated with chemotherapy or the use of "smart" cells that destroy cancer, which are difficult to access.

Thus, we come to the difficult trinomial that consists of cancer, poverty and lack of access. This leads us to a deep reflection on the real paths we are taking and where this modern, technological and fast society will take us all, if we do not pay attention to the need to place the individual as the priority center of all our actions.

CONFLICT OF INTEREST

The authors have no competing interests.

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COVID-19 AND HEMATOPOIETIC STEM CELL TRANSPLANTATION IN BRAZIL: ARE WE COPING?

EDITORIAL

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Ever since the first coronavirus disease 2019 (COVID-19) case was reported in Brazil in late February, 2020, the pandemic has reached virtually every corner of the country. Spanning continental dimensions, it is by far the most affected country in Latin America, with the second highest death toll in the world (almost 150,000), and almost 5 million confirmed cases as of October 4, second only to the Unites States (https://coronavirus.jhu.edu/map.html). The actual death toll might actually be higher, due to both limited testing and inconsistency in nationwide cause-of-death reports. Apart from the available evidence on the benefit of dexamethasone (and other steroids) in patients under respiratory support, no effective treatment has thus far been shown to reduce mortality in this disease.[1] Likewise, despite global efforts and billion dollar investments, none of the dozens of vaccines currently being tested in humans are expected to be available at scalable and nationwide levels within the next few months.

To date, the vast majority of the data gathered about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of non-transplant and non-immunocompromised patients. Little is known about the disease in the hematopoietic stem cell transplantation (HSCT) setting, though one might presume HSCT patients to be at an increased risk of serious complications and death due to COVID-19. As a result of a myriad of collaborative efforts, expert panels have been issuing several recommendations in this regard (https://www.sbtmo.org.br/saibamais/covid-19-e-tmo). As a rule, in general terms, clinicians should follow the available guidelines for managing COVID-19 in non-transplant patients, with stricter attention, though, to the selection of transplant candidates and donors, as well as to the molecular and serologic monitoring of severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) infection among patients, donors, caregivers, and healthcare professionals. Treating COVID-19 in the HSCT scenario may be particularly challenging, given the common coexistence of comorbidities, transplant-related cytopenias, potential drug-to-drug interactions, overlapping toxicities, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease in the allogeneic setting. This complex interaction between both the baseline disease and the various aspects of the procedure itself makes any assessment of the actual attributable impact of HSCT on the severity of COVID-19 even more demanding (https://www.covid19treatmentguidelines.nih.gov/whats-new/). Specific guidelines, including those of Machado C., 2020, on behalf of the Brazilian Society of Bone Marrow Transplantation (SBTMO), coupled with several freely-available HSCT and COVID-19-related webinars, online resources, and continuing education programs, have provided practical, evidence-based guidance to caregivers and healthcare professionals[2] . One has to bear in mind, though, the rapid and ever-changing landscape of the pandemic. This has posed an increasing demand on the transplant community, in its effort to keep itself updated with the latest COVID-19 releases.

While grappling with the best response toward the spread of SARS-Cov2 across HSCT centers in the past six months, many have found themselves adapting their transplant routines and procedures. In a recent nationwide survey (unpublished data) led by Duarte, FB., 2020, on behalf of the SBTMO, from May to June, with the aim of evaluating the overall impact of the SARS-CoV-2 pandemic on Brazilian HSCT center routines and protocols until then, a 60% response rate to the questionnaires (out of a total of 86 certified centers) was obtained, comprising approximately 85% of the adult and pediatric transplant activity in the country. In this study, the authors noted a decrease between 50% and 75% in the general HSCT activity in 59.2% of all participating centers. All such centers fol-

lowed some kind of evidence-based guidance, mainly that from the SBTMO (>90% of cases). A minority of them (5-12%) completely discontinued their transplant programs, 30-43% cut by half their transplant rates, whereas 6-12% did not perceive any substantial changes in this respect. The authors highlighted the initial lack of universal SARS-Cov2 testing of donors and of asymptomatic patients prior to transplant, the main reasons for which seemed to be the lack of access to or delay in obtaining the results of real-time polymerase chain reaction (RT-PCR) tests, and/or of an adequate facility for the collection of samples. This also hampered testing among the healthcare professionals in charge of such patients. Even so, infection rates among these were reported by up to 73% of centers in June. COVID-19 diagnosis raised from one month to the other, with up to 23% and 48% of the analyzed centers reporting cases during hospital stay and post-discharge periods, respectively. Death reports due to COVID-19 raised from 13% to 18% of centers from May to June. As in other non-transplant scenarios, fever and cough were among the most prominent symptoms found, with no distinctive features noted. Azithromycin was the most commonly used treatment (75% of centers), and immunosuppressants, when used, were kept unaltered in most cases. This survey helped depict some of the major barriers to the optimal management and preventive measures noted in the first few months of the pandemic in the country. One might expect that, given the global learning curve acquired since the beginning of the pandemic, with more widespread testing, use of personal protective equipment, and refinement of institutional policies directed toward SARS-Cov2 infection, some of such barriers may have been (or are bound to be) overcome from July onwards, with better results in the months to come.

Further data from the Brazilian Transplant Registry (RBT) of the Brazilian Association of Organ Transplantation (ABTO) from the first semester (http://abto.org.br/) indicate a 20% reduction in the HSCT rate, year on year, which corresponds to an absolute reduction from 1621 to 1302 in the number of transplants, with an even greater drop in the autologous setting (26% compared to a 10% decrease in the allogeneic subgroup). A possible explanation for this might be the chronic and somewhat less urgent nature of the main indication for autologous transplant in our country, multiple myeloma. One might, perhaps, have expected a greater drop in transplant numbers due to the pandemic. Caution is needed, though, in the interpretation of these findings, given the underreporting (of over 10% compared to last year) by the participating sites (HSCT rates might actually have been higher in the first half of 2020). Data on the third quarter of the year are expected for the middle of October.

In a year in which Brazil's Unified Health System (Sistema Único de Saúde- SUS), recognized by the World Health Organization (WHO) as the world's largest publicly funded universal healthcare system to date, upon which depend virtually 75% of the country's population, is supposed to be celebrating its 30th Birthday (http://www.planalto.gov.br/ccivil_03/leis/l8080.htm), both the public and private healthcare sectors (including individual health plans) are faced with the utmost challenge of providing the necessary support to the country's more than 210 million citizens. To make matters worse, health policy has somewhat turned into health politics, which surely undermines much of the concerted efforts needed to counteract the COVID-19 pandemic. Another challenge is that of the need for circumventing the poor housing conditions of many HSCT patients and of their family members within the context of the public healthcare system. This greatly reflects the worrisome socioeconomic and educational status of the most underserved racial and ethnic minorities in the country. Social support systems that are able to provide a solid safety net for a close post-HSCT follow-up are, therefore, a must.

Nonetheless, there seems to be light at the end of the tunnel. Ironically, the COVID-19 pandemic has torn down borders and brought the transplant community even closer together. While social distancing and virtual encounters have become "the rule", in order to keep pace with the ever-changing COVID-19 landscape, we have often found ourselves sharing the intimacy of our homes, turning remote interaction and collaboration into seemingly face-to-face ones. Stronger ties have developed, fostering a myriad of nationwide collaborative efforts, from basic to clinical research, the results of which are eagerly awaited.

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IMPRESSIONS ABOUT THE COVID-19 PANDEMIC AND BONE MARROW TRANSPLANTATION

OPINION LETTER

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Since the start of Covid-19 epidemic first cases in Belo Horizonte, Minas Gerais state capital (sixth largest city, second state with more inhabitants and third richest state in Brazil) we adopted several contingency measures at our Cell Therapy Unit in our Cancer Center. Our center has two infirmaries, both with HEPA filters, positive pressure rooms and isolation structures: the first one, with nine beds, for patients that need agressive chemotherapy treatments, like AML, ALL and relapsed lymphomas patients, and a second unit, with thirteen beds, for patients submited to hematopoietic cell transplants. We decided to keep the HCT unit as a "Covid-19 free zone", performing nasal and throat RT-PCR for SARS-Cov-2 two days before patients and familial care givers hospitalization at the unit,, abolish visitation and familial care givers circulation during the hospitalization and performed weekly RT-PCR from the whole unit assistance team. The other unit was classified as a "yellow zone" with its own team and HEPA filter and positive pressure turned off to allow hospitalization of non tested patients or even Covid-19 positive patients in need of agressive treatment in order to decrease other patients and assistance team contamination risk.

Since april we had 35 medical assistance health workers put in two weeks quarantine due to respiratory symptoms with only four diagnosed with Covid-19, all of them dispensed until negativation of RT-PCR, none of them needed hospitalization due to the infection. No patients had documented infection by any of these workers. We had one 31 years old high risk ALL female patient who was diagnosed with Covid-19 the day before hospitalization for a HLA identical sibling HCT transplant which was postponed. She had a benign outcome of the viral infection but presented a hematologic and CNS relapse during her quarentine time, which was treated with high dose Methotrexate based regimen and reached complete CNS and bone marrow remission with a negative MRD. She is now on day + 7 post an allogeneic MAC TBI based transplant, evolving with a mild hepatic VOD in regression with no other complications. No other programed transplants or chemotherapies were postponed due to the pandemic. No other patient developed Covid-19 since the start of contigency measures.

We believe that the contigency measures adopted sooner in the pandemic outcome was pivotal to keep our units open and allowed us to treat properly and in right time all the patients in need.

1.Recommendations of Sociedade Brasileira de Transplante de Medula Óssea (SBTMO)

2.Recommendations of American Society for Transplantation and Cellular Therapy (ASTCT)

3.Recommendations of European Bone Marrow Transplantion (EBMT)

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COPING WITH THE COVID19 PANDEMIC IN A HEMATOLOGY, TRANSPLANTATION AND CELL THERAPY UNIT IN SOUTHERN BRAZIL

OPINION LETTER

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We started 2020 with perspectives that quickly changed in March when the SARS-Cov-2 pandemic started in Brazil. Our center has a unit, called the Protected Environment with 30 beds with HEPA filters where malignant disease, autologous and allogeneic transplants are performed. In March 2020, the contingency plan designed since January to deal with COVID 19 pandemic of Porto Alegre Clinicas Hospital (HCPA) began highly restricting visits, consultations and elective procedures.

Our challenge was to maintain the best care for our patients and healthcare professional's safety. We suspend all visits and reduce relative patients' companies to only essential. Our team was already one with the highest percentage of hand washing in the hospital, intensified infection control measures and implemented new individual protection equipment surgical masks and face shields. We started a new way to inform family members using digital platforms and improved the Wi-Fi network inside the unit to maintain patient external contact and reduce their loneliness. All Professional meetings and rounds became virtual.[1,2,3]

When the first cases started in Porto Alegre, we had already implemented and validated the performance of the PCR for SARS-COV-2, with result until 24 hours. So, we could organize the flow of patients for hospitalizations avoiding admissions of Covid asymptomatic patients. HealthCare's with any symptoms were kept away from work and quickly tested.

We followed the guidance of the Brazilian society of BMT and started to perform only urgent transplants, greatly reducing the number of autologous transplants performed. All patients candidates stem cell transplant were instructed to maintain isolation for 14 days before admission and collected PCR 24 hours before admission. Related and unrelated bone marrow donors underwent clinical screening and PCR testing 24 hours before collection and the marrow was cryopreserved until results what changed our routine marrow infusion and sometime modified the collection from marrow to peripheral Hematopoietic stem cell in order to obtain adequate cellularity. [1,2,3]

Despite all the difficulties and challenges the Covid pandemic imposed upon us, we managed to perform 16 Transplants from March to September, between autologous and allogeneic and we had no cases of covid transmission inside deaths related to COVID until now. All patients who had COVID19 or tested positive to SarsCov2 were outpatients, either from the Day Hospital or the outpatient clinic and had complete resolution of the condition.

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OUR CHALLENGE IN THE HEART OF BRAZIL

OPINION LETTER

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Faced with the major health crisis of the century – Coronavirus Disease (COVID19) Pandemic, we could see two waves installing in society: incredulity and fear. This issue was politicized several times and the vast amount of scientific publications made the discussion very controversial and consequently society became more and more confused and insecure.

Brasilia - the Capital of Brazil, is the heart of the country, it is centrally located and therefore politically strategic. It was one of the first places in Brazil to spread, under public decree, radical measures of social isolation (such as closing schools, colleges, commerce, and other public places) in mid March / 2020. Only the so-called "essential activities" continued working. When such measures were adopted, the city had just over 50 confirmed cases of COVID19.

Concerns about the pandemic moved the entire local health care assistance, with homeric financial investments by hospitals with massive testing for Coronavirus and a reduction in the number of elective surgeries (important profit providers).

The Bone Marrow Transplant (BMT) Unit, traditionally considered to be a very vulnerable space, gained special focus and numerous efforts were designed to make it virtually a COVID19 free area. The view of doctors during this period was also very heterogeneous, and it varied between fearlessness and major worry. Finding a balance and offering a safe environment for carrying out the procedures proved to be a great challenge, whose building still occurs daily until today.

Despite being a hard social, political and economic moment, it would not be appropriate to shoot all over the place like a war. The elaboration of new protocols, periodically reviewed and modified, was carried out based on intense involvement and collaborative works by the Hospital Coordination, the Infectious Diseases Specialists, doctors and multidisciplinary team. The Good Practices policies published periodically by the Medical Societies of Infectious Diseases and Bone Marrow Transplant guided our local protocols.

Among the main measures adopted are the testing of patients and caregivers with PCR lab test to check the coronavirus infection before hospitalization, the prohibition of visitors and the use of reverse vestments (use of cloaks, gloves, caps and masks), which although controversial, was used to potentially reduce the risk of coronavirus transmission by asymptomatic health professionals. In addition, daily screening of respiratory symptoms was applied to all caregivers and employees of the unit, in order to identify suspected cases and keep them away before contact with patients. Such measures were crucial to the excellent results achieved and to strengthen the medical teams trust in the hospital logistic and support.

According to data published by the Brazilian Organ Transplant Association - ABTO, in the first half of 2020, 31 transplants were performed in two institutions that predominantly receive public institutions patients (3 allogeneic and 28 autologous) and 23 transplants in the private services (18 autologous and 5 allogeneic) - represented by two private hospitals in Brasília[1]. The peak of the pandemic occurred in July and August 2020, with periods of significant overload in the hospital structure in the public and private sectors. The depletion of resources caused by the pandemic associated with previous institutional issues have compromised the care of adult patients who are candidates for BMT from public services. This fact generated an important patient demand for centers in other regions of the country associated with an increase in the obstacles of moving and welcoming these patients in the pandemic scenario.

In private practice, there was a strong and well-structured work-ethic, which allowed the program to continue without impairing the quality of care or the expected outcomes. To date, we have had no cases

of death by COVID19 in the scenario of bone marrow transplantation in Brasília, reflecting the efforts and protocols previously mentioned.

At this moment, we are experiencing a significant reduction in the number of COVID19 cases in Brasilia, making it possible to observe an increase in the number of patients undergoing transplant procedures. This fact reflects the postponement of treatment of non-urgent cases in the previous three months.

After six months of Pandemic, it is essential to recognize the strong presence of the spirit of cooperation, tolerance and patience that has been installed in all the scenarios that permeate the BMT, associated with the relevant growth of all involved. The "new normal" is uncomfortable because it is characterized by restrictions imposed by the pandemic and not by our choices and preferences, but above all it symbolizes our ability to adapt and to have resilience. We are important characters in this memorable historical period, and we carry the desire to continue pulsating in the heart of Brazil.

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THE PANDEMIC SCENARIO AND BONE MARROW TRANSPLANTATION

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The COVID19 pandemic scenario has had a significant impact on the world economy and health. Restrictive measures of social distancing to contain the advance of contamination caused health services the need to review their care protocols and their transplant procedures. The pandemic has brought to light the precariousness of health services and the increased barriers to access health care causing some other problems.

Maintaining bone marrow transplantation activities was a major challenge, as hematological diseases require prompt treatment. Efforts were needed to redefine indications, workflows, hospitalization and isolation. It was essential to have the ability to test our patients, donors and professionals for COVID19. It was also important to ensure that health professionals did not transmit the virus to their patients even without fully understanding the virus's kinetic behavior. Above all, it was extremely important to have a support of an infectologist, and their increasing expertise, acquired almost daily, that could help patients with prevention strategies and care, besides understanding the aggressiveness and diversity of clinical expressions of this disease.

Our patients had to face the fear and uncertainties of their hematological disorders and now also the risks of COVID19. Many of their doubts still has no answer. Social distancing has put another point of stress in this scenario causing more suffering. The effects of the pandemic on the mental health to all of us was an important point to address and treat.

Over the months, which seemed years, we realized that the knowledge gained was unprecedented and made possible to minimize the devastating impact of the virus on our patients. Telemedicine has helped us, as never before, in interacting with other fellow hematologists and their medical and personal experiences around the world. We have never felt so vulnerable as professionals in the face of such a devastating disease and never needed so much interaction and trust in each other before. We learned a lot about hematology, bone marrow transplantation, immunology and inflammatory response but in times of pandemic and health crisis we learned even more about empathy, hope and gratitude.

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ARE WE READY TO INDICATE MYELODYSPLASTIC SYNDROME PATIENTS TO HEMATOPOIETIC STEM CELL TRANSPLANTATION BASED ON THEIR GENETIC STATUS?

SHORT COMMUNICATION

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Myelodysplastic Syndrome (MDS) is a heterogeneous set of malignant disorders related to the impairment of the bone marrow (BM) and its functions. The occurrence of signs of ineffective hematopoiesis, with progressive BM failure; molecular and cytogenetic damages, and the risk of progression into Acute Myeloid Leukemia are meaningful hallmarks of the disease. MDS might occur with a wide spectrum of clinical presentations which may require different proposals as therapeutic approaches.

Nowadays, there are several systems of clinical stratification and prognostic prediction for MDS being the International Prognostic Scoring System (IPSS)[1], Revised-IPSS (IPSS-R), WHO-Classification-based Prognostic Scoring Systems, and the Global MD Anderson System (MDAPPS) widely used worldwide[2,3,4]. The evaluation by such systems frequently demands cytomorphological data, cytogenetic status, severity of cytopenias, age, transfusion requirement, and others. Although IPSS and IPSS-R are systems often used to stratify MDS patients, they have significant limitations given that those are only applied to newly diagnosed cases and overlook secondary MDS and patients under or after previous treatment.[5]

The use of current laboratory tools and efforts to implement and enrich information records of MDS patients improves the way how those data might be used to support clinically patients and allows us to understand better their relationship. A limited repertoire of genetic mutations is often associated specifically with MDS subsets, outcome, drug response, and clonal hematopoiesis age-related, which seems to be a pre-leukemic stage leading to MDS or other myeloid malignancies. In another hand, previous studies point out the possibility of using genetic information as well as novel algorithms to conduct therapeutic strategies. [6 7]

New generation sequencing (NGS) techniques have been widely used to genomic assessment of MDS patients and are being gradually incorporated in the Brazilian center. Its use impacts on diagnosis and also helps to discriminate between MDS and other myelopathies, such as aplastic anemia, idiopathic cytopenias, and myeloproliferative neoplasms. The knowledge of the genomic profile underlying MDS patients might improve the disease classification and identify target genes to drive specific therapies (IDH1/2 inhibitors, for example), as well as to assist the prognostic and track minimum residual disease, even though this is being still explored pre-clinically. [8 9]

Based on the discussion of the following case, a 69-year-old white man with no comorbid presented in May of 2018 mild neutropenia and drop-in hemoglobin levels, although no anemia observed. Complete Blood Count of the diagnosis sample showed Hemoglobin = 13.6 g / dl; Leukocytes = 3,200 / mm3; Neutrophils = 945 / mm3; Monocytes = 750 / mm3; Platelets = 168,000 / mm3. Subsequent exams showed the maintenance of isolated neutropenia and monocytosis (745 to 2437 / mm3, respectively). Peripheral Blood Immunophenotyping, Myelogram and Bone Marrow Biopsy led to the diagnosis of MDS/MPN, Refractory Cytopenia / Chronic Myelomonocytic Leukemia(CMML 0-OMS 2016). karyotype Normal; In situ hybridization panel for (5q31.2 (EGR1), 7q22 (RELN), 11q23.3 (MLL), 16p13.1 (MYH11), 16q22 (CBFB), 17p13.1 (TP53), 20q12 (PT-

PRT) e20q13.1 (MYBL2) and RUNX1T1 / RUNX1 and PML / RARA rearrangements by fluorescence were negative. NGS evaluation showed the presence of a somatic variant in ZRSR2 gene (c.312+1G>T) with allele frequency (VAF) of 90.81%. Also, another variant was observed in the gene RUNX1. Initially, the variant RUNX1 p.Leu56Ser was described as a somatic alteration identified in patients with AML and MDS (REf .: doi: 10.1038 / leu.2011.19; doi: 10.18632 / oncotarget.9026). Later, Drazer *et. al*. demonstrated for the first time the germline origin of this change (Ref .: 10.1182 / blood advances.2017013037), endorsed by a VAF of 40-60% , commonly observed. However, according to the genomic databases, the population frequency of the p.Leu56Ser confirms this is a common polymorphism in southern Asia, Europe, and Latin America [Ref .: gnomAD; https://gnomad.broadinstitute.org]. In general, these data demonstrate the importance of curating properly the data obtained from NGS following rigorous criteria, especially when it pursues somatic variants.

The gene ZRSR2 plays an important role in spliceosome machinery, being then a critical partner over the RNA editing. 16171810 and shows frequently mutated in MDS affecting from 3 to 11% of cases. [19, 6] The variant c.312+1G>T observed in the patient herein discussed occurs in exon/intron boundary and has already been described in a patient with monoclonal gammopathy of undetermined significance (MGUS), an entity underlying to B cell malignancies (Ref .: doi: 10.1016 / j.stem.2017.07.010). Its high VAF might be explained once the ZRSR2 gene is within the chromosome X (homozygous variant) and, possibly, it led to the clonal expansion of the malignant cell.

Herein, we had a 69-year-old patient, fully asymptomatic, ECOG 0, with no transfusion requirement, with history of neutropenia and monocytosis, cytomorphology and bone marrow immunophenotyping confirming MDS, normal karyotype, and without chromosome aberrations detected by FISH. The NGS identified the somatic mutation in ZRSR2.

When the therapeutic discussion involves the indication of HSCT, proposed with curative intentions, the decision-making process necessarily passes through another complex chain of information. We must consider aspects related to the disease,[2,21,23] patient,16 and also to the availability of an appropriate donor (related, young, male)

If we use the criteria of the IPSS-R, adjusted for age, this is a low-risk patient. However, the gene alteration detected by NGS may indicate higher chance of leukemic transformation and poor overall survival. Disease Risk Index (DRI) indicators 2425 shows an intermediate risk condition for transplantation. If we evaluate the patient's condition and possible risk indicators using the “hematopoietic-cell-transplantation-specific-comorbidity-index” (HCT-I)[26,16] the patient is classified as low risk.

With a curative potential, HSCT is usually indicated for patients under 75 years of age, most often recommended as first-line therapy (with or without previous treatments) in high-risk patients. In lower-risk patients, the usual practice is the indication of monitoring, with transplantation when there are signs of progression.27 Transplants, at the time of diagnosis, using reduced-intensity conditioning in patients over 60 years of age do not result in benefits for low or intermediate-risk groups.[28] A similar study showed that delaying transplantation was beneficial for low- and very low-risk patients, but not for intermediate-risk patients [29]

In the case under discussion, the finding of the mutation in ZRSR2 triggered the discussion about the possibility of transplant indication, due to concerns about the prospect of leukemic transformation. Adding the fact that the patient was in good performance for the procedure.

The lack of a suitable donor, and the real situation of a single haploidentical donor, must be included in the difficulties in decision making. A panel of experts in 2017 recommends that alternative donors be recommended only for high-risk patients.[30] The results with haploidentical transplants, in general, have shown improvements. They must be understood as an alternative, in the absence of a compatible donor.[31, 32]

The case leads us to reflect on the meaning of laboratory findings and their relevance when making therapeutic recommendations. Understanding the exact role of each finding in molecular genetics and its incorporation into the current risk stratification systems is an ongoing action that may result in an adequate therapeutic recommendation and in survival gain of MDS patients.[33] Great possibilities of using electronic tools and artificial intelligence algorithms are being proposed in the context of precision medicine.[34,35,36,37,] Seeking more consistent results involves recommending transplantation to well-selected patients, at the appropriate time, and promoting approaches in the pre- and post-transplant periods that can decrease recurrence rates. For

example, identifying patients and situations which there may be benefits from isolated or combined strategies, involving infusion of donor lymphocytes and hypomethylating drugs.[30]

Consider the perspective that the molecular "target" drugs under development, new hypomethylating agents and formulations can bring benefits and promote changes in strategies.[38] Contextualizing HSCT in the complex information network, despite any exquisite assistance, should still be a medical decision wary to each patient.

The decision, shared with the patient, was not to perform the transplant and monitor him. After 24 months of follow-up after the diagnostic definition, he remains well, asymptomatic and without cytopenias.

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THE EVOLVING LANDSCAPE OF ACUTE MYELOID LEUKEMIA TREATMENT

SHORT COMMUNICATION

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Acute Myeloid Leukemia (AML) is a fatal disease. At least two thirds of the patients die of AML in the first few years of diagnosis, and most of them in the first year. [1]

There are several mutations involved in the pathogenesis of this heterogeneous disease and some impact survival; [2] all result in the abnormal functioning of a component of a molecular pathway involved in cell cycle activity or apoptosis. Some of these latter mutations are targetable, and new target drugs are been tested or already used in clinical practice, with objective impact on disease severity and overall survival. [3, 4]

Additionally, there are several new drugs either targeting leukemia microenvironment molecules, or its biophysical aspects, intent to changing the molecular milieu of the malignant cell surroundings; some targeting the malignant cell metabolism or oncoprotein metabolites, and yet some epigenetic drugs aiming to chromatin stabilization and control of malignant genes transcription activity. [5] These drugs might, in selected cases, be utilized in association with one another or to a less toxic and very effective low dose chemotherapy, or yet as monotherapy for the very old and ill population. Complete and partial remission (CR or PR) or stable disease is seen in this scenario and ways to maintain it are been tested and used.

Technics to measure disease burden evolved in the last decades leading to the understanding of measurable residual disease and its impact in AML prognosis. Measurable tumor burden before stem cell transplant (SCT) is alone a risk factor for relapse and disease progression after transplant, usually leading to death in the first few months. [6-7] By regularly measuring residual disease, relapse can be detected in an asymptomatic patient and preemptive therapy can be putted in place. Usually, in the majority of SCT centers, the first clinical intervention is lowering immunosuppression or withdrawing it completely, sometimes followed by donor lymphocyte infusion (DLI), hoping to harness the graft versus leukemia effect (GVL), frequently and unfortunately, accompanied by graft versus host disease (GVHD). However, GVHD is not particularly prevalent or severe after DLI when utilized in the prophylactic setting according to a recent metanalysis. [8]

Emerging data on the above-mentioned target drugs, are increasingly robust, and better quality of live seems to be one outstanding aspect. Side effects of molecular target drugs are mild and manageable.

For many decades, intensive chemotherapy followed by SCT in intermediate and adverse risks disease is the backbone of AML treatment; [9] however, most patients are elderly and dye during or following intensive treatment, [10, 11] since they frequently have comorbidities and develop several complications during the myeloid and lymphoid ablated periods. Most of them are not eligible for stem cell transplantation (SCT), and once AML relapses, as pointed above, survival is very poor.

The understanding of the graft versus leukemia (GVL) effect and its importance for SCT success, [12] as well as the good results obtained with DLI in obtaining CR or disease control (8) have brought into attention the role that immune cells have in leukemia's control and cure.

SCT for AML should be preferentially myeloablative in order to decrease tumor burden in those with high-risk leukemia and good performance status. Myeloablative strategies by killing abnormal and normal leucocytes, modify bone marrow microenvironment. Steven Rosenberg *et al.* [13] have suggested that myeloablative strategies can affect the

general microenvironment that becomes rich in myeloid and lymphoid colony-factors and stimulating molecules.

Pre-clinical and clinical studies with adoptive transfer of lymphocytes have proven beneficial effects in cancer. [14, 15] However, the ***Vito*** effect have to be taken into consideration in immunotherapy. The patients' resident lymphocytes or leukocytes can kill the incoming cells preventing the infused cells *in vivo* activation, either in blood circulation or at the tissue level. According to Rosenberg, myeloablation and/or lympho-ablation is the optimum scenario for adoptive immunotherapy efficacy. [13]

Systemically infused *in vitro* expanded lymphocytes, once into the circulation, can sense the increased concentration of activating molecules, migrate toward the origin of its production and home to that environment, unleashing its anti-tumor and immunomodulatory activity.

The benefic role of CAR-T cells on B cell malignancies is indisputable and much have been learned from it; one key aspect is that the *in vivo* CAR-T cells expansion/activation appears to be related with a better anti-tumor effect. CAR-T cell therapy has also brought into attention cytokine release syndrome (CRS) as well as its unexpected CNS effects, opening a new path to better understanding *in vivo* immune system function, its pros and cons, and how to clinically manage it. [15] The utilization of anti-PD1 receptor or its ligand monoclonal antibodies have proved that exhausted lymphocytes can be reactivated in the tumor microenvironment – making the case for autologous adoptive immunotherapy, with significant results been seen in the solid tumor scenario particularly in lung cancer. [16] Taken together, these mounting data support immunotherapy trials for the treatment of cancer.

Natural killer cells have repeatedly been shown to have antitumor, [17] and antileukemia effect [18-20], and it appears related to GVL effect as its early emergency after SCT myeloablation is correlated with PDS and OS. [21] Since pioneering studies of Velardi's group, [22] in Italy, in a population of AML patients predominantly in second CR and submitted to a T cell depleted haploidentical SCT, GVL's mediated NK cells anti-leukemia effect have been recognized.

NK cells are innate lymphocytes bearing natural cytotoxic receptors that recognize molecular patterns (common to all effector's cells) and several other receptors to ligands on altered cells' surfaces. Killer Immunoglobulin like Receptors [23] were first described in and are predominantly express by NK cells. Their main role is to inhibit NK cell activation, although some are actually able to promote it. These latter are expressed by individuals belonging to NK cell B Haplotype-type, since NK cells from these individuals are characterized by expressing an excess of KIR activating receptors.

Been able to recognize one's self HLA class I or a normally expressed HLA class I antigen, renders NK cells disabled to kill a normal cell. In summary, NK cell activation, either to develop cytotoxicity or secrete immune molecules, is the result of balancing the amount and activation of activator and inhibitory receptors.

NK cells are CD3 negative and CD56 positive cells. Most of our peripheral blood circulating NK cells also express CD16, a FC receptor to immunoglobulin that promotes ADCC. For many years $CD56^{+}CD16^{+++}$ NK cells were considered the NK cell mature, functional phenotype. [24] However, tissue resident or occasional tissue transiting NK cells express a variable, apparently tissue dependent phenotype, in the lung, as an example 75% of tissue resident NK cells are $CD56^{bright}$ with variable low or no expression of CD16. [25, 26]

Innate lymphocytes are meant to bridging innate and adaptive immunity. [27] As for NK cells, it has been shown they modulate T cell response either by IFN-gamma or through GM-CSF secretion since it has an important role in promoting T cells and Dendritic Cells (DC) maturation and activation, and in the case of DC, also migration and antigen presentation untimely promoting adaptive immune reaction. [28]

It is possible that NK cells are capable of bouncing between its cytotoxic ($CD56^{dim}/CD16^{bright}$) and secretive ($CD56^{bright}/CD16^{dim}$) phenotype as well as in between its shades. *In vitro* exposition of NK cells to certain ligands can render them $CD56^{bright}/CD16^{bright}$ [29], suggesting that there is potential for *in vivo* phenotype shifting according to the molecular milieu. The fact that tissue's NK cells are predominantly of the secretive phenotype calls the attention for its immunomodulation importance and role. Hence, the desirable NK cell effect is also secretion of several cytokines and chemokines: active molecules that modulate immune adaptive system effectors, with higher specificity and less harmful for the organism.

In a recent Phase 1 trial of double bright ($CD56^{brigth}/CD16^{bright}$) NK cell (DB-NK) for refractory or relapsed AML (R/R-AML), we were able to document the persistence of the infused DB-NK cells, however, in

most responding patients T cell recovery predominated; we also showed that NK cell predominant in vivo expansion didn't necessary correlated with leukemia response (submitted manuscript); these results could suggest that antileukemic NK cell cytotoxic and immunomodulation activity results in an adaptive immunity response. In this phase 1 trial including a rather ill population of patients, cryopreserved, DB-NK cells infusions up to 10^7 cells/kg per infusion, in a total of 6 infusions, was well tolerated and its emergent anti leukemia or anti-microbial effects were clinically manageable. No CSR, fever, or serious adverse events were related with infusion, and in spite of some very ill patients been included, none of them died or clinically deteriorated because of NK cell adoptive immunotherapy. We treated 13 patients of whom 5 had primary refractory disease and 9 had relapsed or were refractory to SCT. The median line of previous treatments was 5, and they all received DB-NK cells with active disease. Seventy eight percent of the patients got either into CR (50%) or CRi (only one patient) or had partial response. OS for responders and non-responders were 344 and 254 days, respectively. PFS was 132 days for all and 199 days for responders. We were able to show that DB-NK cell adoptive immunotherapy is not only feasible and safe, but also effective in such an advance AML group of patients, increasing OS in spite of disease burden or localization as we also documented CNS responses. [30]

According to the MRD studies, SCT associated GVL anti-AML effect alone, cannot overcome high tumor burden, suggesting that adoptive immunotherapy ("graft") versus leukemia effect, so to speak, is probable more effective in a situation of minimal measurable disease, or preferentially, minimal residual disease (MRD).

The combination of target drugs, with or without low dose chemotherapy and immunotherapy should be pursued for augmenting good quality survival and possibly, cure in AML.

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AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ITS MAIN INDICATIONS: A SINGLE-CENTER, RETROSPECTIVE STUDY OF 30 YEARS

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ABSTRACT

Objective: Autologous hematopoietic stem cell transplantation is widely used in patients with hematological cancers and in some solid tumors. We aimed to describe the transplant procedures performed in a single institution along 30 years.

Methods: We describe retrospectively the autologous transplants performed from 1987 to 2016 for: acute myeloid leukemia (AML), Hodgkin (HL) and non-Hodgkin lymphoma (NHL), and multiple myeloma (MM).

Results: We analyzed 378 consecutive patients, all with neutrophil engraftment, which was faster with higher CD34 counts (p=0.0001) and slower in patients with AML (p=0.003). Five-year overall survival (OS) was 61%. Receiving transplant in the most recent period (2008-2017) was a protective factor (p<0.0001). For MM, the incidence of relapse was significantly higher in patients not achieving a partial response (hazard ratio, HR = 4.02, p = 0.03). For lymphomas, both patients with partial response (p=0.003) and refractory (p=0.007) had higher relapse rates. The 5-year incidence of disease relapse was 42% for AML, 49% for MM, 41% for HL and 41% for NHL (p=0.88). Non-relapse mortality was 13% in 1 year.
Conclusion: There was an improvement in the outcomes of patients undergoing autologous transplants for oncological and onco-hematological diseases across the last 30 years in our institution.

Keywords: Hematopoietic stem cell transplantation. Bone marrow transplantation. HSCT.

INRODUCTION

Autologous hematopoietic stem cell transplantation (auto-HSCT) is a technique widely used in patients with hematological cancers and some solid tumors. It is also called high-dose chemotherapy with hematopoietic stem-cell support or, simply, autologous bone marrow transplantation. The technique consists of the collection of hematopoietic stem cells from the patient, administration of high-dose chemotherapy, followed by the infusion of previously collected hematopoietic stem-cells. Unlike allogeneic transplantation, in autologous transplantation, there is no need for a donor because the patient himself/herself is the donor.

The number of hematopoietic stem cell (HSCT) transplants has gradually increased over the years. In 1985, it was limited to 10,000 transplants worldwide, ten years later it accounted for around 100,000 transplants, increasing to 500,000 in 2005, and doubled to around one million HSCT by the end of 2012.1 The availability of resources and evidence and the positive regulatory environment was associated with the high number of transplants.

In Brazil, autologous HSCT has been practiced in large hospital centers for at least 30 years, when autologous HSCT was established as part of the rescue

treatment, with curative intent, for patients with relapsed lymphomas. It has also been incorporated into the first-line treatment of multiple myeloma, with the aim of increasing survival.[2,3] Of the total of 2,794 stem cell transplants (HSCT) performed in Brazil in 2017, 59.7% were autologous, which shows the current importance of this type of transplant in the treatment of onco-hematological diseases.[4]

The objectives of this study are to describe the characteristics of autologous transplants performed for 30 years in a single institution and to analyze the results of autologous transplantation in the most frequent diseases.

METHODS

This is an observational retrospective cohort study, which included all patients who underwent autologous HSCT between June 1987 and December 2016 at the HSCT unit of a philanthropic hospital. Only patients with multiple myeloma (MM), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and acute myeloid leukemia (AML) were included in the analysis of results. The study was approved by the local Ethics Committee. The Ethics Committee waived the need to sign a specific consent form for this study.

The data for this study were collected from the patients' medical records and data reported by the hospital to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Demographic data, such as age and gender, were collected. The following clinical data were also computed: underlying disease, disease status, source of stem cells for transplantation, number of cells infused and performance status. The primary outcome was death. Secondary outcomes were the time for neutrophil and platelet grafting and relapse. The disease condition (status) before transplantation was classified as complete remission, partial remission or with refractory disease.

The characteristics of the patients were described as absolute and relative frequencies. The overall survival (OS) and disease-free survival (DFS) curves were estimated using the Kaplan-Meier method and compared using the log rank test.

For each disease, hazard ratios (HR) were estimated with the respective 95% confidence intervals, using a single and multiple Cox proportional hazard model. A two-tailed p-value less than 5% was considered statistically significant. All analyses were made in R, version [3.6.1].

RESULTS

Since the first autologous HSCT in the institution, in 1987, until December 2016, 583 autologous transplants were performed in 526 patients. Of these, 378 were transplanted for multiple myeloma (MM), acute myeloid leukemia (AML), Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL). The characteristics of the patients and the first transplants are shown in Table 1. Briefly, the median age was 43 years, 56% were men, and the most common diagnosis was MM.

All patients had neutrophil engraftment, at a median of 10 days. Factors related to faster recovery were the number of infused CD34 (hazard ratio, HR = 1.05 for each increase in 1x10E6/kg, p = 0.0001) and, for slower recovery, diagnosis of AML (HR = 0.33, p = 0.003, compared with MM).

With a median follow-up of 6.4 years, the 5-year overall survival (OS)was 61%. Survival was significantly worse in patients with non-Hodgkin's lymphoma (Figure 1). In the multivariate analysis, both Hodgkin's lymphoma (HR = 3.02, p = 0.0006) and non-Hodgkin's lymphoma (HR = 2.00, p = 0.0003) were associated with worse survival. Age was also a poor-prognosis factor (HR = 1.04, for each year older, p <0.0001). Transplantation in the most recent period (2008 - 2017) was a protective factor (HR = 0.42, p <0.0001).

The 5-year incidence of disease relapse was 42% for AML, 49% for MM, 41% for HL and 41% for NHL (p = 0.88). For MM, the incidence of relapse was significantly higher in patients who did not achieve a partial response (HR = 4.02, p = 0.03). For lymphomas, both patients who achieved partial response (HR = 5.16, p = 0.003) and those who were refractory (HR = 5.06, p = 0.007) had higher relapse rate.

Progression-free survival (PFS) was 41% at 5 years, with no difference between diagnoses (44% for AML, 39% for MM, 51% for LH, and 41% for NHL; p = 0.50). In the multivariate analysis, the factors of poor prognosis were age (HR = 1.03 for each additional year, p = 0.003), partial remission (HR = 3.22, p = 0.0003) and refractory disease (HR = 4.73, p = 0.003) for lymphomas. For MM, only pre-transplant disease status (HR = 2.11, p = 0.01 for partial remission, and HR = 19.5, p <0.0001 for patients who did not achieve partial response) were identified as risk factors.

Non-relapse mortality was 13% in 1 year. We did not find any factors associated with non-relapse mortality.

DISCUSSION

This analysis of the results of a single autologous transplant center in multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma and acute myeloid leukemia is one of the largest in the world.[5,6,7,8,9] It shows that the modality rendered an overall survival of 61%. There were no grafting failures and the times for neutrophil and platelet engrafting were compatible with literature data.[10]

The indication of autologous transplantation for patients with multiple myeloma should be maintained even with the advent of novel treatments. Several studies show that, even with the new proteasome inhibitors and pre-transplant immunomodulators, autologous HSCT increased progression-free survival, especially in patients younger than 70 years old. At the American Association of Hematology last meeting, the importance of the procedure for this group of patients was also demonstrated.[9,11] Current studies comparing transplanted versus non-transplanted patients corroborate our findings. They show an advantage for autologous transplantation as a complement to treatment instead of following with observation or even maintenance.[9,12,13]

Possibly, one of the reasons for the success is the adequate selection of patients in conditions to be transplanted, with good functional status. All patients selected for transplantation in this sample were generally in good clinical condition, usually less than 75 years old and without major comorbidities. In our institution, for patients older than 65 years old (which represented 11% of patients), we use the Comprehensive Geriatric Assessment.[14,15] Still, mortality was higher in older patients. However, when considering only mortality up to 100 days, age was not a prognostic factor. Also, we have seen an improvement in overall survival in the most recent period.

Our results showed that patients with multiple myeloma with a median age of 58 years had 39% disease-free survival at 5 years. The overall survival was 69%. This data is compatible with other findings in the literature.[16] As with most diseases, we also demonstrated that patients' pre-transplant disease status is fundamental in the outcome. That is, patients with stable disease have worse disease-free survival.[16]

Patients with non-Hodgkin's lymphoma are usually transplanted as part of the treatment of relapsed chemosensitive patients. The cure rate of patients with aggressive B lymphoma in first remission varies from 50% to 90% depending on the prognostic indexes.[17] Our results show that, following relapse, 41% of the patients remained in complete remission after 5 years. The prognosis of patients who were not at complete remission was poor and even worse for refractory patients. CD19+ Non-Hodgkin lymphomas are discussed for their future replacement by other methods of cell therapy, such as the chimeric antigen receptor T-cells (CAR-T cells) against CD19, but this is not yet established.

This situation is similar to that with Hodgkin's lymphomas. These have high cure rates with the initial treatments, ranging from 75 to 90%. In relapses, autologous transplantation is a treatment option, and our data show that 51% remained in complete remission in five years. Literature data point to 40 to 70%, depending on the prognostic index.18,19 In our sample, we did not classify patients because it is a retrospective study in which data were not always available. The only data we had was pre-transplant status. As with multiple myeloma, autologous transplantation in Hodgkin's and non-Hodgkin's lymphoma continues to be used even with the advent of new therapies and transplant modalities.

In the case of acute myeloid leukemia, the situation is different, as this modality, more defended by the Europeans and less by the Americans, had only one reference at the ASH 2018 meeting, presented on a poster precisely by Europeans. In that study, they suggest that patients who achieve complete remission after induction, depending on their cytogenetics and molecular factors, should undergo allogeneic transplantation or four to five consolidations or one to two consolidations and autologous transplantation.[20,21] These patients are those with good prognosis or intermediate prognosis who do not have a compatible donor. In our population, the disease-free survival in 5 years was 44%, and the global was 65%. The choice between several consolidations versus autologous transplantation in this group of patients is still controversial and is the subject of several comparative studies.[22,23] In patients at intermediate risk, data showing that haploidentical transplants are similar to allogeneic transplants from unrelated donors end up endorsing its use in this category in detriment of autologous ones.[24,25]

The results showing a 50% long-term survival rate agree with data from the literature, which reveals the recurrence rate as a major concern in this type of transplant compared to allogeneic transplants. In these, the leading cause of death is procedure toxicity, with a higher rate of infections and the presence

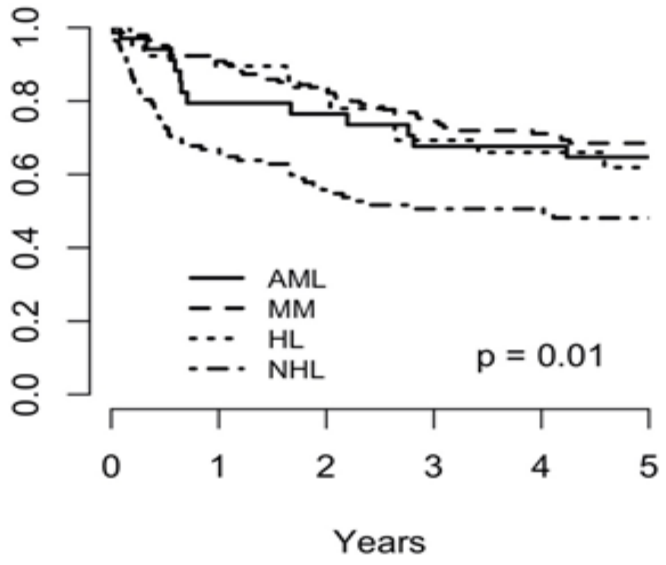
of graft versus host disease.[26] Patients with poor prognoses, such as those with complex cytogenetics or presence of FLT3 mutated gene (tyrosine kinase 3 Fms-related), if they are not submitted to allogeneic transplantation, have a high chance of recurrence of the disease in a short period.[27] On the other hand, patients with good prognostic cytogenetics, such as t[8:21] or inv16, and those with normal karyotype, with negative FLT3 and positive NPM1, would have a higher risk with allogeneic transplantation28, which presents greater toxicity compared to intensive chemotherapy such as consolidation or autologous transplantation. Only randomized studies will demonstrate the superiority or otherwise of autologous transplantation over chemotherapy in these low-risk or intermediate-risk patients.[8]

In summary, the profile and historical path of autologous transplants for oncological and onco-hematological diseases performed in the last 30 years in a Brazilian institution demonstrated evolution according to the medical literature, giving the possibility of recovering a significant number of patients with Hodgkin's lymphoma, non-Hodgkin lymphoma, multiple myeloma and acute myeloid leukemia. The continuous study of the performance of autologous transplants in the light of new therapies allows reframing their indications when compared to new therapies. Thus, even with the advent of new therapies, the indications for autologous first-line transplantation for young and fit patients with multiple myeloma remain, and their use in relapsed or refractory patients with Hodgkin's and non-Hodgkin's lymphoma as second-line consolidation of treatment. However, in acute myeloid leukemia, autologous transplants would only have some indication in patients with a favorable prognosis. Only prospective studies will show whether its use exceeds the performance of several cycles of consolidation with cytarabine.

TABLE 1 - Patients' characteristics

	TOTAL
Total	526
Age – mean (SD)	44.6 (17.9)
Gender	
Male	292 (55.5%)
Female	234 (44.5%)
Diagnosis	
AML	44 (8.4%)
MM	159 (30.3%)
HL	45 (8.6%)
NHL	129 (24.6%)
Others	148 (28.2%)
Status prior to transplant	
Complete remission	97 (36.3%)
Partial remission	137 (51.3%)
REF	33 (12.4%)
Stem cell source	
PBSC	451 (85.7%)
BM	25 (4.8%)
BM+PBSC	50 (9.5%)
CD34 – mean (SD)	5.9 (4.5%)
Period	
1987-1997	144 (28.6%)
1998-2007	201 (40%)
2008-2017	158 (31.4%)

SD = standard deviation; AML = acute myeloid leukemia; MM = multiple myeloma; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; PBSC = peripheral blood stem cell; BM = bone marrow



GRAPHIC 1 - Overall survival

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SARS-COV2 POSITIVE IN BONE MARROW TRANSPLANTATION ASYMPTOMATIC PATIENTS: THE EXPERIENCE IN A SINGLE CENTER OF CEARA, BRAZIL

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ABSTRACT

The bone marrow transplantation (BMT) recipient are susceptible to virus respiratory disease and their complications. The emergence of pandemic COVID-19, adapted their routine. We are a public school hospital bone marrow transplantation center, localized in Fortaleza/Ceará, Northeast of Brazil. Objective: In the article we are described the asymptomatic SARS-CoV2 PCR positive in recipient pre and post bone marrow transplantation.

Methods: In total of 13 recipients collected of SARS-CoV2 PCR. The donors and recipients with high risk disease and selected to bone marrow transplantation in april to july of 2020 are submitted a nasopharyngeal and throat swab to collected PCR multiplex SARS-CoV2. Results: In total of 13 recipients we have 5 patients asymptomatic with positive results of the SARS-CoV2, 3 allogeneic recipient and 2 autologous. The 2 in patients follow the program because we have the result after the end of condition, we use GCSF in both and none had febrile neutropenia.

Conclusion: The results show us the importance of PCR multiplex SARS-CoV2 before hospital admission to avoid bone marrow transplantation at the moment of viral load and to organized the prevention precautions. This cases are important because described patients with SARS-CoV 2 PCR positive in the early transplant with asymptomatic course.

Keyword: asymptomatic, SARS CoV2, bone marrow transplantation.

INTRODUCTION

The bone marrow transplantation (BMT) recipient are susceptible to virus respiratory disease and their complications1. Until the emergence of pandemic COVID-19, the bone marrow of transplant centers around the World, based on Guidelines of the international societies, adapted their routine. We are a bone marrow transplantation center in a public university hospital, localized in Fortaleza/ Ceara, Northeast of Brazil. This city had the first case of COVID-19 diagnosed in March, 15 and the peak of epidemic in May2. During pandemic, in our center, only transplant for high risk disease are performed (aplastic anaemia, leukemias and lymphoma diseases)3,4, family visits to the unit were prohibited, we moved away the symptomatic health professional, acquired and freeze stem cell product before conditioning, turn off the positive pressure in the unit and performe the screening with SARS-CoV 2 RT- PCR to donors and recipient before hospitalization until April. The health professional screening with SARS-CoV 2 PCR were - performed every two weeks. In this article we are describing the asymptomatic SARS CoV2 RT-PCR positive in recipient pre and post bone marrow transplantation.

METHODS

This is a prospective study with donors and recipients with high risk disease and selected to bone marrow transplantation in april to july the 2020 submitted a nasopharyngeal and throat swab to collected PCR multiplex SARS-CoV2. The analyses were realized in Central Laboratory of Ceara (LACEN). All of them were informed about the social isolation until 28 days of the test and asked about symptoms and contact of suspected cases of COVID-19. SARS-CoV 2 RT-PCR positive collected of asymptomatic recipient were selected. The analyzed variables were: age (years) , sex, disease, type of transplantation, time of transplantation of SARS-CoV2 positive previous symptoms, date of previous symptoms, previous SARS-CoV2 RT-PCR negative, date of positive test, date of negative test after positive, inpatient at the moment of RT-PCR positive, without corticoid and D+ graft neutrophils. The symptoms analyzed were fever, myalgia, fatigue, headache, cough, rhinorrhea, dyspnea, hypoxemia, throat ache, anosmia5.

RESULTS

In total of 13 recipients collected of SARS-CoV2 RT-PCR, we have 5 patients asymptomatic with positive results. Three patients to allogeneic transplant and two autologous. Two of them are inpatient, both collected when we had a mild symptomatic positive PCR multiplex SARS-CoV2 patient in the unit, one in the second day of hospitalization and the other in the seventh day. Two of then collected previous the hospitalization. And the last one, after two days of hospital discharger after mobilization failure, she was contact inpatient of positive RT-PCR multiplex SARS-CoV2. No one had progression to symptomatic disease two weeks after the positive results. The oldest patient has 68 years old. One patient has high blood pressure. The two inpatients follow the program because we have the result after the end of conditioning chemotherapy, we use GCSF in both and none had febrile neutropenia. The patients had good clinical course, without symptoms, bone marrow failure or Graft versus Host Disease. In the same time, there was another inpatient, he was asymptomatic too and had three negatives tests RT-PCR SARS-CoV2. The inflammatory exams (C reactive protein) are normal.

TABLE 1 - Characteristic patient asymptomatic positive RT-PCR multiplex SARS-CoV2

ANALYZED VARIABLES	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age (years)	31	24	39	54	68
Sex	Male	Female	Male	Female	Female
Disease	Acute lymphoblastic leukemia Ph+	Aplastic anaemia	Acute myeloid Leukemia	Acute promyelocitic leukemia	B cell non Hodgkin Lymphoma
Type of transplantation	Match related allogeneic	Match related allogeneic	Match related allogeneic	Autologous	Autologous
Time of transplantation of SARS-CoV2 positive	Before BMT	Before BMT	D-6 conditioning	Infusion Day	Mobilization
Previous symptoms	No	Yes	No	No	No
Date of previous symptoms	No previous symptoms	May, 17 (mild)	No previous symptoms	No previous symptoms	No previous symptoms
Previous SARS-CoV2 PCR negative	Yes	Not collected	Yes	Yes	Yes
Date of positive test	06/16/2020	06/30/2020	06/12/2020	06/12/2020	06/16/2020

Date of negative test after positive	07/07/2020 15/07/2020	7/07/2020	07/14/2020	Not collected	07/08/2020
Inpatient at the moment of PCR positive	No	No	Yes (1 day)	Yes (7 days)	No (2 days after hospital discharge)
Without corticoid	Yes	Yes	Yes	Yes	Yes
D+ graft neutrophils	Not reported	Not reported	D+11	D+9	Not reported

DISCUSSION

The immunocompromised state, comorbidity and high risk of morbimortality infection related with bone marrow transplantation become the COVID-19 a disease with high impact in our routine. The endemic Coronavirus is the forth cause of respiratory viral infection (17%), and 34 of 112 (30%) progressed to lower respiratory tract. The graft-versus-host disease (GVHD), corticosteroids, hypoalbuminemia, and older age are associated with infectious disease progression[1,4].

The time to had symptoms, after the contamination, varies between 2-14 days, and we have mild symptoms to severe acute respiratory distress syndrome4,5. And the asymptomatic patients occur in immunocompromised patient too.

The results show us the importance of RT-PCR multiplex SARS-CoV2 before hospital admission to avoid bone marrow transplantation at the moment of viral load and to organized the prevention precautions.

The strategies of prevention were implemented in our unit: hand washing, avoid visits, sick employees stay home, SARS-CoV2 RT-PCR screening for asypmtomatic employees and patients before hospitalization and adequate individual protective equipment.

Unfortunately, the nosocomial transmission occurs, the precautions, with PCR screening, avoid the admission to hospital to three patients asymptomatic and control the outbreak in the unit.

After the lifting of restrictions, several cities documented small outbreak, the careful and vigilance are important in the context of BMT. Follow with transplants in that conditions were a challenge. In that time, we need to return the frequency of service before outbreak with the same precautions.

This cases are important because described patients with SARS-CoV2 RT-PCR positive in the early transplant with asymptomatic course.

CONCLUSION

The results show us the importance of PCR multiplex SARS-CoV2 before hospital admission to avoid bone marrow transplantation at the moment of viral load and to organized the prevention precautions. This cases are important because described patients with SARS-CoV 2 PCR positive in the early transplant with asymptomatic course.

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COVID-19 INFECTION IN A CANDIDATE FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION: A CASE REPORT

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ABSTRACT

The pandemic for the new coronavirus SARS-CoV-2 has been the causeof enormous challenges for the entire health system, especially in programs who dealwith Hematopoietic Stem Cell Transplantation (TCTH), since sequelae related to COVID-19 can be a hindrance to a possible HSCT. In case report, VBF, 61 years old, diagnosis of classic lymphocyte-rich Hodgkin'slymphoma in 2018 with initial treatment with ABVD, due to the return of the disease, an ICE regimen was started, but with disease progression after 5 cycles. Then, an IGEV scheme was started with a schedule of autologous hematopoietic cell transplantation, which took place in the third cycle in May / 2020. However, at the end of May / 2020, he was admitted to the emergency department with confirmation of SARS-Cov-2 infection by means of PCR of the nasal and oropharyngeal swab. He evolved during hospitalization with hypoxemic respiratory failure, mechanical ventilation and signs of secondary pulmonary infection, using multiple antimicrobial regimens, showing improvement and finally being extubated. However, he presented important pulmonary sequelae, with chest CT showing extensive cavitation in the left upper lobe and reticular opacities, with distortion of the pulmonary architecture. He was reassessed as to the possibility of autologous hematopoietic cell transplantation, but this was contraindicated due to pulmonary sequelae. In the case reported, the patient complied with the formal indication for HSCT, which would be refractoriness or relapse in a second remission in patients up to 70 years old with sensitivity to rescue schemes. However, due to pulmonary sequelae acquired after COVID-19, HSCT was contraindicated. This case leads us to the conclusion that the pandemic by the SARS-CoV-2 coronavirus can directly affect HSCT services and that in addition to preventing infection in this group of patients, they should be reevaluated after the recovery of COVID-19 for evaluation of structural and functional respiratory sequelae.

Keywords: Hematopoietic Stem Cell Transplantation, SARS-CoV-2

INTRODUCTION

The pandemic for the new coronavirus SARS-CoV-2 has been the cause of enormous challenges for the entire health system, especially in programs who deal with Hematopoietic Stem Cell Transplantation (HSCT).

Due to the lack of specific treatments and the high mortality of this infection in hematological patients[1], centers that deal with bone marrow transplantation have been paying special attention to the entire process, from a more rigorous assessment of donors, monitoring of recipients to testing the health team who watches them[2] .

However, care must also be directed to patients who are still in the process of indicating a transplant, since sequelae related to COVID-19 can be a hindrance to a possible HSCT.

HSCT has been shown to be one of the most effective treatments in patients with Hodgkin's or non-Hodgkin's Lymphoma who have relapses[3], with the contraindication to the procedure being a poor prognostic factor for hematological disease.

In this work we report a case in which a patient with Hodgkin's lymphoma who had his Hematopoietic Stem cell transplant contraindicated due to sequelae related to COVID-19.

CASE REPORT

VBF, 61 years old, diagnosis of classic lymphocyte-rich Hodgkin's lymphoma in 2018 with initial treatment with ABVD (Adriamycin + Bleomycin + Vinblastine + Dacarbazine) from december to july showing partial remission.

Subsequently, due to the return of the disease, an ICE regimen (Ifosfamide, Etoposide, Carboplastine) was started, but with disease progression after 5 cycles. Then, an IGEV scheme (ifosfamide, gemcitabine, vinorelbine) was started with a schedule of autologous hematopoietic cell transplantation, which took place in the third cycle in May / 2020.

At the end of May / 2020, he was admitted to the emergency department with productive cough, fever and dyspnea 4 days prior to admission, with confirmation of SARS-Cov-2 infection by means of PCR of the nasal and oropharyngeal swab. He evolved during hospitalization with hypoxemic respiratory failure and the need for intubation and mechanical ventilation, being admitted to the covid ICU of the Hospital Universitário Walter Cantídio on May 2020.

He showed signs of secondary pulmonary infection in the ICU, using multiple antimicrobial regimens, showing improvement and finally being extubated. However, he presented important pulmonary sequelae, with chest CT showing extensive cavitation in the left upper lobe and reticular opacities, with distortion of the pulmonary architecture (Image 1).

After returning to the ward, no longer using antibiotics, he was reassessed as to the possibility of autologous hematopoietic cell transplantation, but this was contraindicated due to pulmonary sequelae.

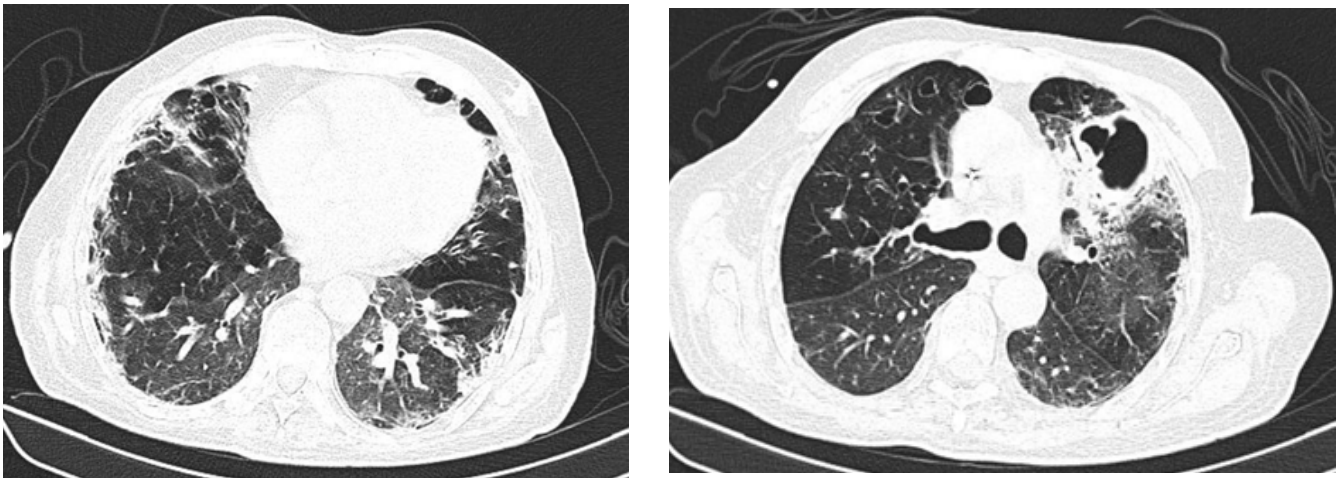
Considering the contraindication to HSCT, the patient was discharged with the schedule of trying a new rescue chemotherapy scheme.

DISCUSSION

In the scientific society is known about the role of coronaviruses in serious infections that affect humans and animals. In December 2019, a new coronavirus was identified and confirmed as causing pneumonia in citizens of the city of Wuhan, China, which spread rapidly around the world. In February 2020, the World Health Organization confirmed that COVID-19, a disease that causes coronavirus, was then called SARS-CoV-2, coronavirus 2 for severe acute respiratory syndrome.

After contact with the virus, the disease developed in up to 14 days, with manifestations starting between four and five days more common. The most common symptoms are a common flu syndrome, with involvement of the upper respiratory tract, myalgia, low fever, diarrhea, asthenia, taste and smell disorders, the latter two being more common in COVID-19 in other viral infections. Pneumonia appears as the most common serious manifestation of the disease, manifested by dry cough, high fever,

Image 1 - Computed Tomogphy.



dyspnea associated with hypoxia and bilateral infiltrate seen on chest tomography, and also of variable spectrum, reaching severe respiratory failure, shock and organ dysfunction (injury acute kidney disease, myocarditis, liver damage).

Regarding the profile of patients with more severe disease, what was most observed was with regard to comorbidities. It was seen that in older individuals, over 60 years, with, mainly, cardiovascular disease, diabetes mellitus, obesity, hypertension, neoplasia (hematological, pulmonary and metastatic), chronic lung disease, smoking were associated with a more severe incidence of the disease and higher mortality.

Among the serious complications of the disease, the main one was respiratory failure due to Acute Respiratory Discomfort Syndrome (ARDS) associated with severe disease, with a good part of these patients being candidates for invasive ventilatory support. Cardiovascular complications were also observed, such as arrhythmias, acute cardiac injury (myocarditis) and shock. Thromboembolism in the form of a stroke in younger patients and without exuberant risk factors for this, in addition to pulmonary embolism. Intense inflammatory responses, characterized as an "inflammatory storm", have been said to be the main cause of all complications resulting from prolonged infection by coronavirus 2, both as already described and in other neurological manifestations in the form of neuropathies. Such exuberant inflammatory condition was evaluated by laboratory alterations such as elevation of d-dimer, C-Reactive Protein, ferritin, being also used as markers of prognosis and evolution of the disease. Finally, in the case of a severe patient with significant inflammatory changes, secondary infections were also part of complications, mainly pulmonary, whether or not they were related to mechanical ventilation.

The recovery time can vary in about two weeks in milder conditions and from three to six weeks in more severe conditions, in addition to being related to age and previous comorbidities. Among the most common persistent symptoms were dyspnea, asthenia, joint pain and non-anginal chest pain. There is still no relevant data regarding long-term sequelae related to COVID-19, but the little that has been seen and compared with other coronaviruses has the potential for lasting respiratory impairment. This idea is due to the long-term exacerbated inflammatory state, associated with the necessary therapy, such as the use of glucocorticoids, prolonged intubation and greater use of neuromuscular and sedative blockers. It is also unknown about post-intensive care syndrome or sequelae of ARDS, being seen as pulmonary changes in patients after COVID-19 persistent abnormalities of lung function in mild and severe pneumonias, the most common of which are reduced diffusion and restriction capacity, especially in the severe ones, with patients undergoing intensive care being left out and there was no basic data to know the risk of developing loss of lung function and it is not known for how long this change persisted.

Although there are limited data on the impact of COVID-19 on transplant candidates and bone marrow transplant therapy donors and recipients, there is sufficient concern that COVID-19 may have a significant impact on post-transplant or post-therapy outcomes

Based on this concern, the American Society for Transplantation and Cellular Therapy (ASTCT) advises that if SARS-CoV-2 is detected in a respiratory sample, cell therapy and hematopoietic cell transplantation procedures should be postponed, including in patients with high-risk malignancies. The postponement should occur until the patient is asymptomatic and undergoes at least two consecutive negative CRP tests, with approximately one week between exams, if available [4].

Approximately 3% of patients undergoing autologous bone marrow transplantation have severe pulmonary complications requiring mechanical ventilation [5]. Therefore, assessment protocols for BMT candidates usually include lung function assessments in the expectation of decreasing the number of serious complications with therapy.

In the case reported, the patient complied with the formal indication for HSCT, which would be refractoriness or relapse in a second remission in patients up to 70 years old with sensitivity to rescue schemes. However, due to pulmonary sequelae acquired after COVID-19, HSCT was contraindicated and another therapeutic option was chosen.

This case leads us to the conclusion that the pandemic by the SARS-CoV-2 coronavirus can directly affect HSCT services and that in addition to preventing infection in this group of patients, they should be re-evaluated after the recovery of COVID-19 for evaluation. structural and functional respiratory sequelae.

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INFLAMMATORY RESPONSE IN SOLID ORGAN AND TISSUE RECIPIENT WITH COVID-19

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ABSTRACT

Introduction: The COVID-19 infection is caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infection, which was first reported in Hubei, Wuhan province, China, in December 2019. There is a concern that immunocompromised patients are at greater risk of morbidity and mortality due to COVID-19 infection, although there is limited data on these patients. Here, we present an evolution of a series of cases of patients with COVID-19 in our service.

Patients and methods: This is a retrospective cohort study conducted at the Hospital Universitário Walter Cantídio in Fortaleza-CE, Brazil. All patients hospitalized due to COVID-19 were screened for a history of organ or tissue transplantation, with a total number of 77 patients. Only patients confirmed for COVID-19 were included in the study. The inflammatory response and initial laboratory results, as well as the CALL score, were compared to a cohort of patients with COVID-19 not transplanted at the same time in our clinical ward or intensive care unit (ICU). The clinical course and clinical findings recorded during treatment were extracted from the electronic medical record. A bilateral P <0.05 (5%) was considered significant. Results: The total number of hospitalizations until July 24, 2020 for confirmed cases of COVID-19 was 77 patients. Of the total, 33 (42%) patients needed ICU. Most patients were male (61%). The median age was 62 [95% CI: 54-63] years, 31 (37%) had a previous diagnosis of hypertension, 24 (28%) of type 2 diabetes mellitus (DM-2). The total lethality of our service was 22%. The CALL score of patients admitted to the clinical ward and in the ICU was analyzed, with a higher average observed in the patients admitted in ICU, the average was 9.34 in the patients admitted in the clinical ward and 10.9 in the patients who required ICU. (p = 0.003) . The effect of neutrophil/lymphocyte ratio(NLR) at admission on the need of ICU care was analyzed by ROC curve and AUC and was found to be significant (AUC: 0.708, p = 0.002, 95% CI = 0.593 to 0.823). The number of transplant recipients in our service was 17 patients. The mean age was 56 years and the median was 55 years [95% CI: 45-65 years]. Of this subgroup, 6 patients (35%) required ICU, with no statistical difference when compared to non- transplanted patients (p = 0.443), and only 3 evolved to death (17%), also without statistical difference when compared to the subgroup of non-transplanted patients (p = 0.484). When compared to the sample of non-transplanted patients, lower values were found of the White Blood cells count, neutrophils and ferritin. However, despite lower values of fibrinogen, D-dimer, C-reactive protein (CRP) and lactate dehydrogenase (LDH), there was no statistical difference.

Conclusion: It is a new disease, with few data, mainly in the studied population. Our sample was a reduced sample, however it was surprising to see a lower inflammatory tendency, although without statistical significance and with mortality similar to the general population. In addition, it is worth emphasizing the importance shown on the neutrophil / lymphocyte ratio of admission demonstrated by the ROC curve in patients who evolve in need of an ICU care.

Keywords: Inflamatory response, Transplant, Kidney, Liver, Covid-19

INTRODUCTION

The COVID-19 infection is caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infection, which was first reported in Hubei, Wuhan province, China, in December 20191. With rapid spread, on March,11 2020, the World Health Organization declared pandemic situation. In Brazil, the overall disease mortality rate is 3.6%2. Mortality appears to be age-dependent, with higher rates among older adults (age 50-59: 1.3%, 60-69: 3.6%, 70-79: 8%, 80+: 14.8%)3. Mortality among the transplanted population appears to be higher in lung transplant recipients and lower in liver and heart transplant populations4. There is a concern that immunocompromised patients are at greater risk of morbidity and mortality due to COVID-19 infection, although there is limited data on these patients. Here, we present an evolution of a series of cases of patients with COVID-19 in our service.

PATIENTS AND METHODS

This is a retrospective cohort study conducted at the Hospital Universitário Walter Cantídio in Fortaleza-CE, Brazil. All patients hospitalized due to COVID-19 were screened for a history of organ or tissue transplantation, with a total number of 77 patients. Only patients confirmed for COVID-19 were included in the study.

Between the 77 patients, 17 were solid organ or tissue recipient patients, with 14 solid organ transplanted patients (8 patients with kidney transplant, 6 patients with liver transplant) and 3 patients were bone marrow recipients. The inflammatory response and initial laboratory results, as well as the CALL score (score that evaluates prognosis based on the variables comorbidity, age, lymphocyte levels and lactate dehydrogenase) 5, were compared to a cohort of patients with COVID-19 not transplanted at the same time in our clinical ward or intensive care unit (ICU). The clinical course and clinical findings recorded during treatment were extracted from the electronic medical record. Categorical variables were frequency and percentage rates and continuous variables by median and interquartile range (IQR). Significance was tested using the Kruskal - Wallis test or Fisher's exact test. The performance of neutrophil/lymphocyte ratio(NLR). was assessed using receiver operating characteristic (ROC) curve analysis and by calculating the area under the curve (AUC) of the ROC curves. A bilateral P <0.05 (5%) was considered significant.

RESULTS

General

The total number of hospitalizations until July 24, 2020 for confirmed cases of COVID-19 was 77 patients. Of the total, 33 (42%) patients needed ICU. Most patients were male (61%). The median age was 62 [95% CI: 54-63] years, 31 (37%) had a previous diagnosis of hypertension, 24 (28%) of type 2 diabetes mellitus (DM-2). The blood count and inflammatory markers of admission are assigned to table 1. The total lethality of our service was 22%. The CALL score of patients admitted to the clinical ward and in the ICU was analyzed, with a higher average observed in the patients admitted in ICU, the average was 9.34 in the patients admitted in the clinical ward and 10.9 in the patients who required ICU. (p = 0.003) (figure 1). The effect of neutrophil/lymphocyte ratio (NLR) at admission on the need of ICU care was analyzed by ROC curve and AUC and was found to be significant (AUC: 0.708, p = 0.002, 95% CI = 0.593 to 0.823) (figure 2).

Transplanted Patients

The number of transplant recipients in our service was 17 patients. The mean age was 56 years and the median was 55 years [18-80]. Of this subgroup, 6 patients (35%) required ICU, with no statistical difference when compared to non-transplanted patients (p = 0.443), and only 3 evolved to death (17%), also without statistical difference when compared to the subgroup of non-transplanted patients (p = 0.484). A descriptive analysis of the CALL score of the group of non-transplanted and transplanted patients is shown in figure 3. The blood count and inflammatory markers of admission are available in table 2. When compared to the sample of non-transplanted patients, lower values were found of the White Blood cells count, neutrophils and ferritin, however, despite lower values of fibrinogen, D-dimer, C-reactive protein (CRP) and lactate dehydrogenase (LDH), there was no statistical difference.

Kidney Transplant

The number of kidney transplant recipients admitted to our service by COVID-19 confirmed was 8 patients. The mean age was 56 years (28-80 years) and median 54 years. Of these, 3 required an ICU care and 2 died. Lethality in this subgroup was 25%. Six patients were using Sirolimus and Tacrolimus at the time of admission, 1 patient was using cyclosporine associated with prednisone and 1 patient was using mycophenolate mofetil and tacrolimus. Only in pa-

tients who evolved with severe acute respiratory failure, immunosuppressants were removed.

Liver Transplant

The number of liver transplant recipients admitted to our service by COVID-19 confirmed was 6 patients. The mean age was 59 years (46-69 years) and the median was 60 years. Of these, 2 needed an ICU bed and 1 died. Lethality in our service for this subgroup was 14.1%. Patients remained on previous immunosuppressants, however, in two patients it was necessary to remove them after severe hemodynamic instability (severe acute respiratory failure requiring orotracheal intubation).

Bone Marrow Transplant

Only 3 allogeneic bone marrow recipients were admitted, only one of them required ICU. The mean age was 39 years (18-70 years) and the median was 31 years. In this subgroup, there was no death. Two patients were male. There was no statistical difference between the subgroup of transplant patients.

DISCUSSION

In the present study, a cohort of 77 laboratory-confirmed positive COVID-19 cases is reported. The median was 60 years with a greater preponderance of males (61%) in consensus with other published cohorts. 6,7,8 The most common comorbidities were hypertension and diabetes, with a prevalence of 37% and 28%, respectively. In the laboratory exams on admission, it was observed that higher values in patients who died of the WBC, number of neutrophils, of the NLR, fibrinogen and LDH with statistical significance. The values of hemoglobin, lymphocytes and monocytes, although reduced values were observed, had no statistical significance when comparing the groups of survivors and deaths, as well as in the inflammatory markers, C-reactive protein, D-dimer and ferritin in which increased values were observed in both the groups but without statistical difference when compared.

The CALL score, created to predict progression risk in patients with COVID-19, analyzes 4 easily accessible variables: comorbidity, age, lymphocytes and LDH. The minimum score is 4 points and the maximum 13 points. In the original study, it was seen that a score greater than 6 points had a 50.7% chance of developing severe COVID-19 and below 6 points only a 1.5% chance of reaching the same outcome.5 In our service, the mean of patients admitted to the clinical ward was 9.34 points and 10.9 points in patients who were admitted to the ICU, with statistical significance. However, when comparing the CALL score between living patients and deaths, there was no statistical significance between groups. Showing its benefit to assess prognosis and not outcome.

The overall hospital mortality of COVID-19 is approximately 15% to 20%, but up to 40% among patients requiring admission to the ICU. However, mortality rates vary between cohorts, reflecting differences in test completeness and case identification, variable limits for hospitalization and differences in results. Hospital mortality ranges from less than 5% among patients under 40 years of age to 35% for patients aged 70 to 79 years and greater than 60% for patients aged between 80 and 89 years. 9 The total lethality of our service was 22%, 42% in patients admitted to the ICU. Regarding the age group at our service, there was no death below 40 years, 45% mortality between 70 and 79 years and 50% between 80 and 89 years.

Like other respiratory viral diseases, such as influenza, it is believed that deep lymphopenia can occur in individuals with COVID-19 when SARS-CoV-2 infects and destroys T lymphocyte cells. In addition, the viral inflammatory response, which it consists of the innate and adaptive immune response (comprising humoral and cell-mediated immunity), impairs lymphopoiesis and increases lymphocyte apoptosis.10 Therefore, Nalbatant et al showed the relationship between NLR as an independent predictor for the diagnose of COVID-19. 11 We analyzed NLR in patients admitted to the ICU, showing an independent variable, with an area under the curve of 0.708 ($p = 0.002$, 95% CI = 0.593 to 0.823). When comparing the group of living patients and deaths, RNL was higher in the group of deaths, with an average of 8.2 in living patients and 12.9 in patients who died, $p = 0.03$. This shows that this relationship can be a valuable low-cost tool to assess outcome in patients with COVID-19. However, more robust studies are needed to reach an adequate conclusion.

The immune response of organ receptors, particularly the immune response of T cells, is suppressed due to the long-term use of immunosuppressive agents. In recipients with COVID - 19 who develop extensive pneumonia, which may require intubation, our current therapeutic approach includes stopping immunosuppressive therapy (using steroids as the only anti-rejection drugs) to help promote the specific antiviral immune response. In our group of transplant patients, the median age was 55 years. In our population, 35% of this group needed ICU care, versus

42% of the group of non-transplant patients, however, with no statistical difference between them (p = 0.581). Higher rates of inflammatory markers were noted in the non-transplanted population, but there was no statistical difference, except for ferritin, which had a statistical difference between groups with higher values in the transplanted population. The lethality rate was 17% in the group of transplant patients admitted to our service versus 22% of the non-transplant population, with no statistical difference between the groups. There is a limited number of studies that analyze this population and with small samples size, as in our study.

CONCLUSION

It is a new disease, with few data, mainly in the studied population. Our sample was a reduced sample, however, it was surprising to see a lower inflammatory tendency, although without statistical significance and with mortality like the general population. In addition, it is worth emphasizing the importance shown of the neutrophil / lymphocyte ratio of admission demonstrated by the ROC curve in patients who evolve in need of an ICU care. Further studies with a larger population are needed to reach an appropriate conclusion.

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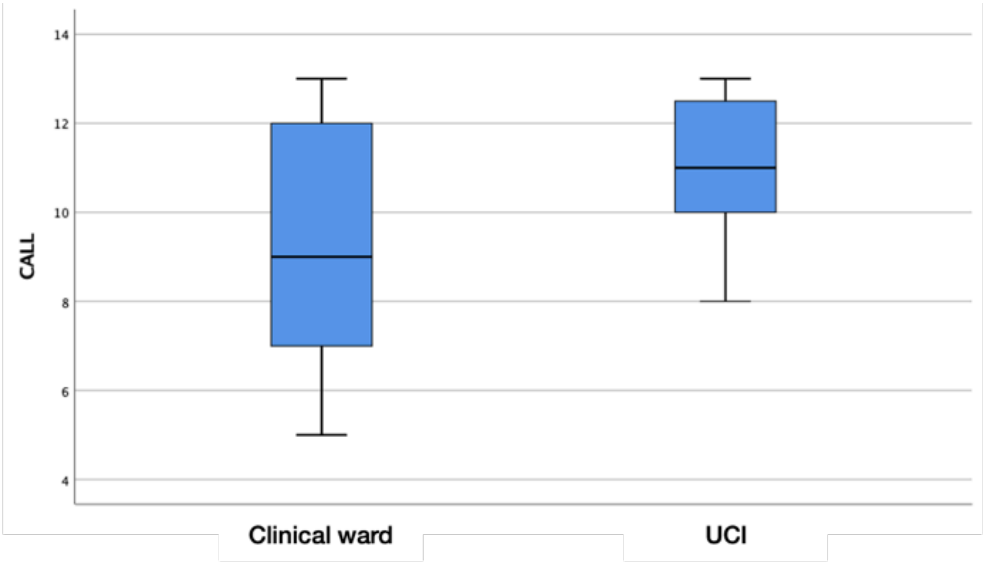
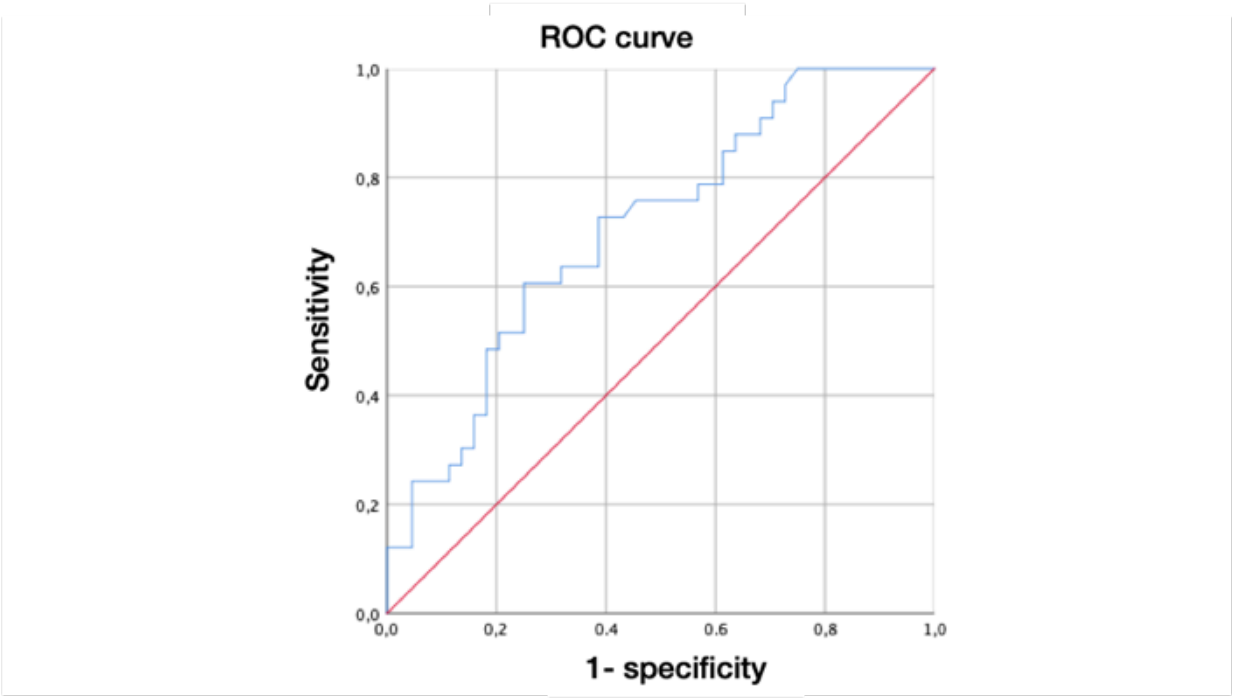
TABLE 1 - General (N=77)

	ALIVES	DIED	P VALUE
Hemoglobin*	10.99	10.97	0.934
White blood cell (4000-11000/mm3)	8155	11873	0.045
Neutrophil (1600-7500/mm3)	6376	9918	0.033
Lymphocyte (800-45500/mm3)	1128	925	0.386
NLR	8.2	12.99	0.034
Monocyte (800-1000/mm3)	485	623	0.324
Platelet (150000-500000/mm3)	199860	227030	0.485
Fibrinogen (180-350 mg/dL)	468	667	0.012
D-dimer (<0.5)	3.45	1.93	0.52
CRP (≤0.5 mg/dL)	8.8	9.77	0.870
Ferritin (28-365 ng/mL)	882	1347	0.103
LDH (230-460 U/L)	592	807	0.011

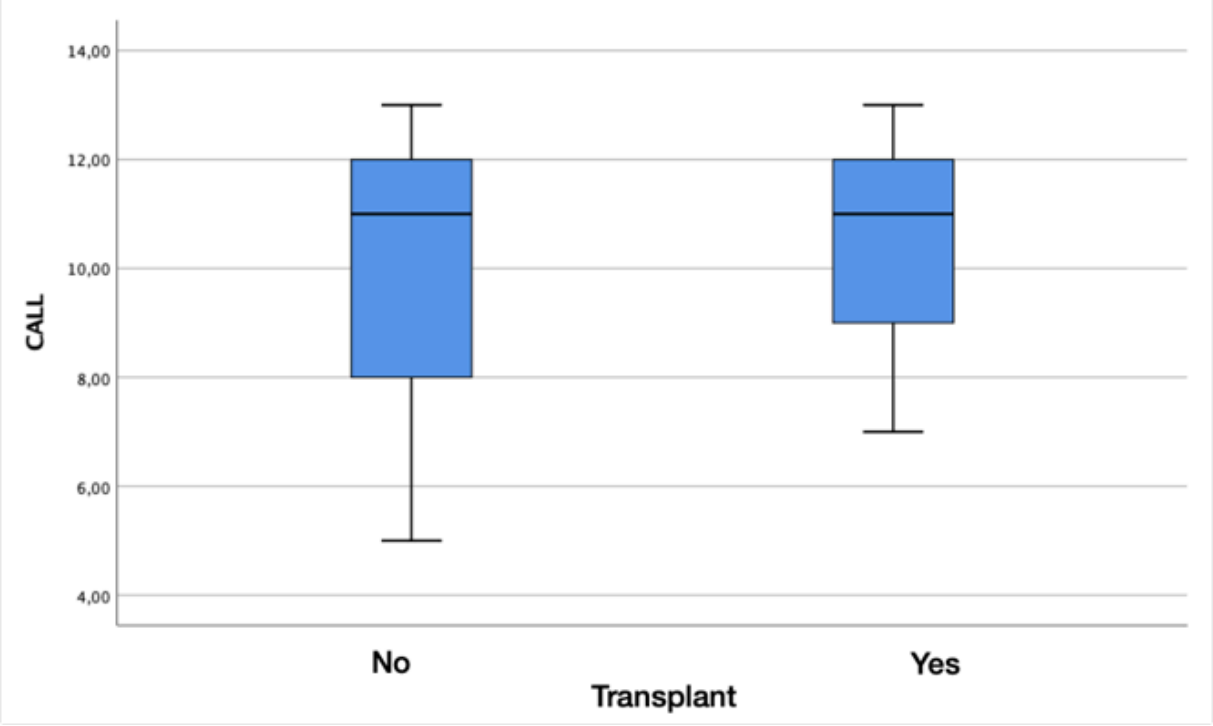
NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein (CRP) and LDH: lactate dehydrogenase
* To male: 13.5-18g/dL and to female 12.0-16.0 g/dL.



GRAPHIC 1- CALL score analyses in clinical ward and ICU patients.



GRAPHIC 2 - ROC curve to neutrophil/lymphocyte ratio at admission on the need of ICU care



GRAPHIC 3 - Score CALL analyses in transplanted and non-transplanted patients

TABLE 2 - Admission blood count and inflammatory markers of transplanted and non-transplanted patients

	TRANSPLANTED	NON-TRANSPLANTED	P VALUE
Hemoglobin*	9.76	10.82	0.107
White blood cell (4000-11000/mm3)	5280	10100	**0.004**
Neutrophil (1600-7500/mm3)	5280	8213	**0.033**
Lymphocyte (800-45500/mm3)	1076	1011	0.766
Monocyte (800-1000/mm3)	368	562	0.118
Platelet (150000-500000/mm3)	158284	213842	0.485
Fibrinogen (180-350 mg/dL)	468	667	**0.012**
D-dimer (<0.5)	3.45	1.93	0.52
CRP (≤0.5 mg/dL)	8.8	9.77	0.870
Ferritin (28-365 ng/mL)	882	1347	0.103
LDH (230-460 U/L)	592	807	**0.011**

NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein (CRP) and LDH: lactate dehydrogenase
* To male: 13.5-18g/dL and to female 12.0-16.0 g/dL.

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INCIDENCE AND RISK FACTORS FOR ORAL MUCOSITIS AFTER BONE MARROW TRANSPLANTATION PATIENTS UNDER LOW INTENSITY LASER THERAPY: A LONGITUDINAL STUDY

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ABSTRACT

Bone marrow transplantation (BMT) has been used to treat numerous malignant and non-malignant hematological diseases, genetic and immunological diseases with a high risk of oral mucositis (OM) due to the action of antineoplastic drugs. As photobiomodulation therapy (FBMT) with low-level laser is a proven non-invasive treatment for OM, the objective of this study was to evaluate the incidence of OM in patients on BMT undergoing FBM. 53 patients undergoing treatment received FBMT (red laser, 2J, 20s, 100mW) as a preventive protocol. If OMwas observed, an infrared laser (4J, 40s, 100W) was administered. The following data were collected from patients' medical records: sex, age, chemotherapy protocol (QT) and type of BMT. An incidence of 34% was observed in the population studied (20% grade I, 11.3% grade II and 1.9% grade III). Prevention protocols using FBMT significantly reduced the incidence of oral mucositis ($p = 0.004$). Now, young patients with myeloid leukemia, the time between QT and BMT ($p = 0.010$) and time of QT ($p = 0.018$) were directly associated with the increased incidence of oral mucositis. It was concluded that low-intensity preventive laser therapy was associated with a reduction in the incidence of oral mucositis, showing the importance of this therapy in the management of patients undergoing BMT.

Keywords: Hematopoietic Stem Cell Transplantation; Mucositis; Low Intensity Light Therapy

INTRODUCTION

Bone marrow transplantation (BMT), also called stem-hematopoietic cell transplantation (HSCT), is a highly complex procedure that has been used for many cases of malignant and non-malignant hematological diseases, solid neoplasms, in addition to genetic and immunological syndromes [1,2,3]. The HSCT modalities can be divided in three ways, when the hematopoietic stem cells come from the patient himself, called autologous; when hematopoietic stem cells can be obtained from a family donor (related HSCT) or not (unrelated HSCT) it is then called an allogeneic transplant; and the syngeneic transplant, when the donor is an identical twin [3].

The most used chemotherapeutic agents in the HSCT conditioning regimens are: busulfan, cyclophosphamide, melphalan, cytarabine, carmustine, etoposide, fludarabine and carboplatin, which are grouped in different protocols depending on both the specificity and the response of neoplastic cells. [4,5,6,7,8,9].

Unlike other measure treatments, antineoplastic agents act systemically, at the cellular level, more specifically, in cells that are in the process of active cell division, interfering in the growth and division process, and they do not have a specific action, that is, they do not selectively and exclusively destroy cancer cells. In general, they are toxic to tissues of intense proliferation, characterized by high mitotic activity and short cell cycles [10,11,12]. Since they present a systemic mechanism, antineoplastic agents can have several side effects such as dysgeusia, dysphagia, dry mouth, vomiting, nausea, stomatitis and mucosal necrosis [9,13].

The toxic effects caused by treatment with antineoplastic agents can have an indirect action, when toxicity occurs in bone marrow cells, leading to myelosuppression. Direct damage occurs in the mucous membranes due to the exposure of connective tissue, which may implicate the entire alimentary tract [8,12]. The oral cavity is a frequent target of toxic effects of chemotherapeutic agents because it presents rapid cell division tissues [13].

The rate of cell division is higher on non-keratinized oral surfaces when compared to keratinized surfaces and these differences have important implications in the tissue repair process, especially when considering the effects of antineoplastic therapy on the oral cavity. Treatments with antineoplastic agents represent a challenge to the integrity of the oral mucosa, as they limit the proliferation of epithelial cells and thus, the epithelium becomes thin and ulcerated [14,15].

The most common oral alterations are: mucositis, xerostomia, bacterial infections, periodontal diseases, odontogenic infections and cavities [16]. The non-keratinized mucosa is the most affected, being the most common sites, the labial and cheek mucosa, the floor of the mouth, lateral and ventral fauces of the tongue, and the soft palate [1,6,9,16,17].

Oral mucositis (OM) is an adverse effect related to the toxicity of the antineoplastic treatment commonly observed in patients undergoing HSCT. It consists of inflammation of the oral mucosa and gastrointestinal tract, which can progress to painful ulcers, causing difficulty in chewing and swallowing, leaving the patient predisposed to secondary infection, with a significant impact on the nutritional status of the patients [1,3,9,16,18,19].

As a way of avoiding treatment interruption and improving the quality of life of these patients, there are some forms of preventive treatments and therapies for OM [19]. Therefore, the goal of treating oral mucositis is to control pain, heal ulcers, recover the mucosa and the prevention of secondary infection. Therapy mainly involves oral antiseptics, corticosteroids for local use and chamomile tea washes. Additional drugs can be used for the local treatment of mucositis, such as antibacterials, antifungals and antivirals, or other drugs that stimulate the regeneration of the injured mucosa [9,18,19].

In addition to these therapies, the use of low power laser or light, a photobiomodulation technique, which acts on wound repair and tissue regeneration, has been positively influencing the inflammatory and proliferative process, with an analgesic effect [20,21,22]. Photobiomodulation is a non-invasive treatment that involves the local application of a monochromatic, visible light source, of low intensity, density with several wavelengths, with the length of 660 - 730 nm, the Red spectrum and the 880 nm, the Infrared spectrum. When applied locally, it has potential effects on free radicals (ROSs) and / or pro-inflammatory cytokines (TNF-α, IL-6 and IL-8); which contribute to the pathogenesis of OM. Therefore, laser therapy is a method capable of preventing chemotherapy-induced OM [16,18,19,20,23].

Considering that OM is a debilitating oral disorder and that among the therapeutic and / or preventive modalities, low-level laser is the one that presents local effect without causing systemic changes, the objective of the present study is to evaluate the incidence of OM in post-HSCT patients submitted to photobiomodulation as well as to associate this condition with risk factors.

MATERIALS AND METHODS

Study Design and Analyzed Population

This is an observational, longitudinal, prospective, quantitative study with post-bone marrow transplant patients at the Walter Cantidio Hospital (HUWC) of Federal University of Ceará, a national reference center for stem-cell transplants located in Fortaleza, capital of the State of Ceará. These patients were referred for laser therapy treatment during chemotherapy conditioning or after HSCT, since it starts 3 to 7 days before the day of the hematopoietic stem cell infusion, depending on the chemotherapy conditioning protocol. The laser therapy treatment was carried out by the team of Graduate Students in Dental Clinic (concentration in the area of Stomapatomatology) of the Dentistry Course at the Federal University of Ceará (UFC), linked to the Oral Laser extension project.

Inclusion, Exclusion and Withdrawal Criteria

Individuals of both sexes and aged 13 years or over were included. Participants were mandatorily admitted to the HUWC to perform HSCT and received a preventive and / or therapeutic protocol for oral mucositis with laser therapy in the period from November 2018 to September 2019.

Patients that for some reason interrupted prophylactic or therapeutic treatment with laser therapy during HSCT were excluded from the study. Patients who died before beginning laser therapy sessions or who evolved with complications and needed orotracheal intubation were removed from the study.

Sample Calculation

Based on the study by Valeh *et al.,* (2018) [24] who observed that the time of oral mucositis in patients who undergo bone marrow transplantation differs significantly between different types of treatment (multiple myeloma: 8.6 ± 3.3 days; leukemia: 10.9 ± 3.2 days), it is estimated to be necessary to evaluate 42 patients in order to obtain a sample that represents the incidence of oral mucositis in patients after bone marrow transplantation, adopting a 90% power and a 95% confidence spectrum. In view of the possibility of sample loss during the study, 25% was added to this study, totalizing 53 Patients Evaluated Longitudinally.

Pre, Trans and Post Hsct Oral Care

During the hospitalization period, when starting the conditioning process with high doses of chemotherapy, which varied according to the service protocol based on the disease to be treated, the patients were followed up by the HUWC nursing team and, if they evolved with oral mucositis, the therapeutic protocol with laser therapy was initiated. Upon reaching D-2 (three days for HSCT to be performed), the prevention protocol with laser therapy was instituted and lasted until D + 12 (twelve days after the transplant). However, if it evolved to OM, the therapeutic protocol of laser therapy was implemented and extended until the complete involution of OM.

As part of the pre-HSCT protocol, every patient is referred for dental evaluation prior to admission and is accompanied by the HUWC Dental Surgeon, in which the condition of mucous membranes, teeth (presence of cavities, periodontal disease) and jaw are evaluated. All necessary dental intervention is performed prior to transplantation, aiming to reduce risks during treatment.

Patients are advised on oral hygiene care during their hospital stay.

Chemotherapy Protocol

Conditioning for HSCT starts 3 to 7 days before the day of hematopoietic stem cell infusion, depending on the chemotherapy protocol. Negative days are considered before the day of the stem cell infusion (D-7; D-1). The day of the infusion is considered the zero day (D-0). From the day of the infusion, the time count in post-transplant days is positive (D+1, D+3, D+7) [7,8].

Patients were admitted to receive the conditioning regimen with high doses of chemotherapy varying with the disease and its service protocol. The allogeneic related myeloablative conditioning is done with BuFlu (Busulfan 0.8 mg / kg and Fludarabine 30 mg / m^2), starting at D-7 until D-3 and at D+1, the patient receives the infusion of four doses of Metrotexate 10mg / m^2. The haploidentical conditioning occurs with BuFluCy (Busulfan 110mg / m^2 and Fludarabine 25mg / m^2), from D-7 to D-4, followed by Fludarabine 25mg / m^2, Cyclophosphamide 14.5 mg / kg and Mesna 0.4 and with a concentration of 8 on D-3 and D-2. After infusion of hematopoietic stem cells (HSC), a new dose of Cyclophosphamide 50 mg / kg and Mesna 0.4 and 8 are administered, on D+3 and D+4. The related allogeneic conditioning of myeloablative is done with FluMel 180, started on D-6 through D-4 with Fludarabine 30 mg / m^2, followed with Fludarabine 30 mg / m^2 and Melfalan 90 mg / m^2 until D-2. After HSC infusion, a new conditioning is performed with Metrotexate 10 mg / m^2. Regarding the allogeneic conditioning of Aplastic Anemia, FluCyATG is used, which is initiated on D-6 with Fludarabine 30 mg / m^2, Cyclophosphamide 30 mg / m^2, Mesna 30 mg / kg and on D-4, antithymocytic globulin is added (ATG) of rabbit with 2.5 mg / kg until D-2. After HSCT, the patient receives new chemotherapy doses with Metrotexate 15 mg / m^2 on D+1, D+3, D+6 and D+11. The Myeloblative conditioning for Promyelocytic is the CyBu, composed of Cyclophosphamide 60 mg / kg, Mesna 30 mg / kg at hour 0, followed by Mesna 15 mg / kg at hour 4 and 8, on days D-7 and D-6. On days D-5 to D-2 is done the conditioning with Busulfan 0.8 mg / kg.

The chemotherapy protocol called LACE, used for lymphoma cases, consists of Lomustine 200 mg / m^2, Etoposide 1000 mg / m^2 and Cytarabine 2000 mg / m^2 and it is implemented from D-7 to D-5, however from D-4 up to D-2 it is done the conditioning with Cyclophosphamide 1800 mg / m^2 with Mesna 1800 mg / m^2.

The protocols with Melfalano of 200 mg / m^2 or Melfalano of 100 mg / m^2 are performed for the conditioning of Multiple Myeloma.

Application of Low Intensity Laser Therapy

The prophylactic application of the laser was initiated depending on the referral of the nursing team to the Oral Laser extension project team. Usually, patients were referred during chemotherapy conditioning between D-3 to D0 (HSCT day) or up to three days after transplantation (D+3). In addition, patients with OM in the oral cavity received the therapeutic laser therapy protocol.

For the application of laser therapy, the low-power laser THERAPY XT (DMC, São Carlos, SP, Brazil) with a wavelength of λ660nm (Red laser) and 808nm (Infrared laser) was used, with a fixed power of 100mW. The protocol used for red light (V) (λ660nm) was the point and contact application, perpendicular to the oral mucosa, with energy of 2J, 20 seconds per point, energy density 71.42 J / cm2, calculated for the device used with a spot size of 0.028 cm^2. On the other hand, for the infrared (IV) laser (λ808nm), at the same power (100mW), 4J, 40 seconds per point, with an energy density of 142.85 J / cm2, calculated for the device with size spot of 0.028 cm2, at the site of the lesions, one point for each 0.25 cm2 of area.

The point applications of the preventive protocol started with 2J, V, being performed in buccal mucosa (bilateral) with three points, lateral border of tongue (bilateral) with five points, floor region with three points and palate region with three points (Figure 1). For the therapeutic protocol, the punctual technique was performed with 4J, IV covering the entire length of the lesion.

The application in oropharynx was performed in patients with painful symptoms when swallowing, with the therapeutic protocol with 4J, IV in the punctual technique, with 4 points running through the oropharynx (bilateral).

Statistical Analysis

The data were tabulated in Microsoft Excel and exported to the Statistical Packcage for the Social Sciences (SPSS) version 20.0 for Windows software, in which the analysis was performed adopting a 95% confidence.

The absolute and percentage frequencies of clinical and therapeutic variables were calculated and for the age and the periods between QT, the mean and standard deviation were calculated. To assess risk factors, oral mucositis in HSCT patients undergoing PBMT, categorical data were subjected to Fisher's exact test or Pearson's chi-square test and quantitative data to the Kolmogorov-Smirnov normality test and the t test of Student (parametric data).

Ethical Aspects

The study was approved by the Ethics and Research Committee with Human Beings of the Federal University of Ceará (UFC) and of HUWC with protocol number CAAE 36765514.1.0000.5045 and it was started after the approval and signature of the informed consent form by each patient that was included in the study.

RESULTS

Characterization of the sample of HSCT patients undergoing PBMT

The sample consisted of 53 patients, of whom the majority (n = 31, 58.5%) were female and the average age was 43.9 ± 15.3, ranging between 13 and 72 years. The most prevalent base disease was Multiple Myeloma with 17 (32.1%) cases. The most used chemotherapy protocol was LACE (n = 12, 22.6%), followed by BUFLU (n = 11, 20.8%) and melphalan (n = 10, 18.9%). Among the different types of bone marrow transplantation (HSCT), the most prevalent was autologous, represented by 31 (58.5%) patients, the mean time between QT and HSCT was 5.7 ± 2.6 days. Patients spent an average of 4.5 ± 2.2 days on QT and all underwent PBMT.

The average number of days of application of PBMT was 10.6 ± 5.9 days ranging from three to 28 days of application of PBMT. The incidence of oral mucositis was 34% (n = 18), with most patients presenting grade 1 (n = 11, 20.8%), followed by grade 2 (n = 6, 11.3%) and only one patient (1.9 %) presented grade 3 mucositis (Table 1; Figure 2).

Risk factors associated with oral mucositis in HSCT patients undergoing PBMT

There was no significant difference in the incidence of oral mucositis by sex (p = 0.876), but the patients who presented mucositis had a significantly lower average age than the patients who did not present it (p = 0.013). The base diseases most strongly associated with oral mucositis were chronic myeloid leukemia and acute myeloid leukemia (p = 0.010) and the chemotherapy regimens was BUFLU (p = 0.005). The type of HSCT did not significantly influence the incidence of oral mucositis (Table 2).

The most used type of PBMT was the protocol with Laser V, 2J, 20sec and the use of Laser IV, 4J, 40sec was directly associated with mucositis (p = 0.048). Prevention protocols significantly reduced the incidence of oral mucositis (p = 0.004) and the time between QT and HSCT (p = 0.010) and QT time (p =

0.018) were directly associated with an increased incidence of oral mucositis. As a result, patients who developed mucositis had a longer PBMT time than patients who did not develop it (p = 0.039) (Table 3). The patient who presented grade 3 mucositis required 28 sessions of PBMT (Figure 3).

The need for post-prevention treatment was significantly less in patients who did not develop oral mucositis (p <0.001) as well as treatment in the oropharynx (p <0.001). Oral mucositis was not associated with the incidence of deaths (p = 1,000) or with the number of HSCT (p = 0.598) (Table 3).

DISCUSSION

In the present study, most patients (66%) did not develop mucositis. A similar result was observed in another study, with patients undergoing HSCT and who received preventive laser therapy, where 66.7% of the patients did not present mucositis [21]. It is added that, in another study, Silva *et al.*, (2014) [25], observed that 72.8% of patients on preventive laser therapy protocol also did not developed the condition. It is emphasized that, among the patients evaluated in the present study who presented mucositis, most were classified in grade 1, where there is no ulcer, as observed in the works by Silva *et al.*, (2015) [26] and Bezinelli *et al.*, (2015) [3], who evaluated patients under a preventive protocol.

The appearance of mucositis was associated with younger patients, with data corroborated by other studies [27,28]. On the other hand, Vagliano *et al.*, (2011) [27] stated that the incidence and severity of oral mucositis is more associated with the type of transplant and conditioning regime, than the patient's age, since the conditioning can be more or less toxic to the oral mucosa. However, in the present study, the type of HSCT was not related to the incidence of mucositis in patients.

Leukemia was the disease most associated with the appearance of oral mucositis, as described by other authors, where this disease was associated with a higher incidence of the lesion, in addition to greater severity [28]. However, the same authors believe that this finding is much more directly related to the conditioning regime used for patients than any other factor. In the present study, the chemotherapy protocol used to treat leukemia was BUFLU, in which the association of these protocols with extreme toxicity has been described in the literature, especially in tissues with rapid cell division, such as the oral cavity [9,19].

The most used preventive protocol was Laser V, 2J, 20sec, although the protocols are quite variable in the literature, which is a major limitation for the establishment of an effective standard protocol for the prevention of oral mucositis. Even so, there is a certain standardization for the use of red spectrum laser for prevention [23,26,29,30].

In the present study, the preventive protocol was effective in reducing the incidence of mucositis, and this result is well described in the literature [21,29,30], evidencing the preventive potential of laser therapy for oral mucositis in patients undergoing HSCT. The mechanisms by which laser therapy helps prevent oral mucositis are not yet fully elucidated but are better understood today. These are mainly associated, among others, with the stimulation of greater ATP production by the cell, increased production of growth factors, increased proliferation and differentiation rates, in addition to important factors for healing [32].

The time between QT and HSCT and QT time were associated with an increased incidence of mucositis. These data are in agreement with the literature where it has already been described that due to longer exposure time of the oral cavity to conditioning drugs, associated with their toxicity, time is a triggering factor for oral mucositis [27].

Among the patients who developed mucositis, there was a need for post-prevention treatment. Associated with this result, patients who did not develop the lesion required less time for post-prevention treatment, as well as treatment in the oropharynx. These findings are related to the fact that once the lesion arises, the use of the laser is maintained daily until it is fully healed [29,33], this time can be extended for several days, as in the case of one of the patients of the current research that required 28 daily sessions for the healing of the mucosa. In patients who do not develop the lesion, the preventive protocol has a more limited number of days [9,19,29,31,33,34].

CONCLUSION

Low-level preventive laser therapy was associated with a reduction in the incidence of oral mucositis, showing the importance of this therapy in the management of patients undergoing HSCT. The main risk factors for the development of oral mucositis in the population studied were age (young patients), the conditioning regime (BLUFLU) and base disease (myeloid leukemia).

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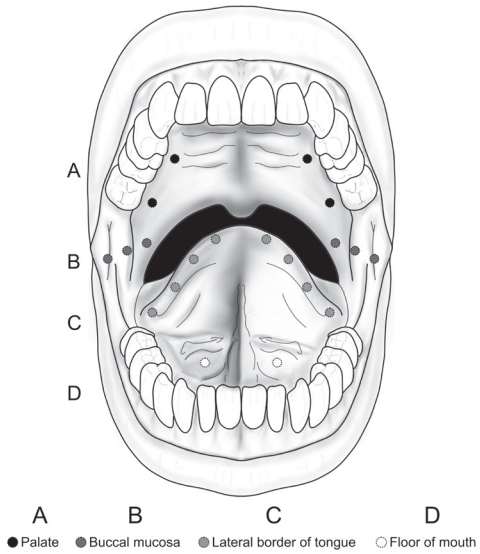
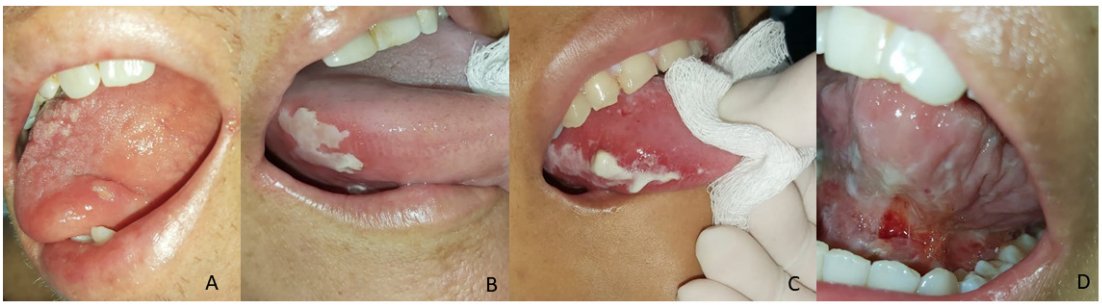


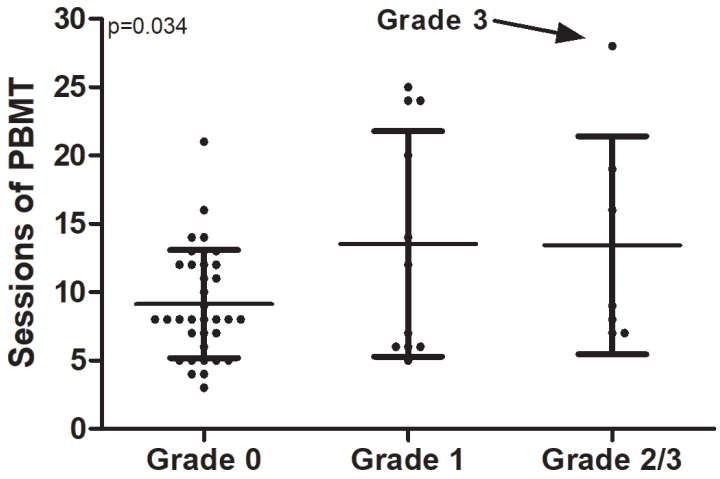
FIGURE 1 - Schematic drawing of the application of preventive protocols of PBMT in the oral cavity of patients undergoing HSCT.



Classification of Oral Mucositis according to WHO: 1 (A), 2 (B), 3 (C), 4 (D) - personal archive photos

DEGREES OF MUCOSITE					
ESCALA	0	1	2	3	4
Oral Mucositis Toxicity (WHO)	No changes	Sensitivity and erythema	Erythema, Ulcer, possible to swallow	Ulcer, extensive erythema, difficulty swallowing	Ulcer, bleeding, extensive lesion and unable to swallow

FIGURE 2 - Representation of degrees of oral mucositis (1, 2, 3 and 4) in post-HSCT patients undergoing PBMT in the oral cavity.



GRAPHIC 3 - Mean and standard deviation of the number of PBMT sessions of patients who did not develop and patients who developed grade 1, 2 and 3 oral mucositis undergoing PBMT.

TABLE 1- Clinical and therapeutic profile of patients undergoing bone marrow transplantation and PBMT for prevention and treatment of oral mucositis

TOTAL	53 (100.0%)
Gender	
Masculine	22 (41.5%)
Feminine	31 (58.5%)
Age	43.9±15.3 (13-72)
Base disease	
Dendritic Leukemia cell l	1 (1.9%)
Chronic myeloid leukemia	6 (11.3%)
Multiple Myeloma	17 (32.1%)
Acute Myeloid Leukemia	8 (15.1%)
Follicular T Lymphoma	1 (1.9%)
LCM - Mantle Cell Lymphoma	5 (9.4%)
Hodgkin's lymphoma	6 (11.3%)
Aplastic Anemia	3 (5.7%)
Acute Lymphocytic Leukemia	5 (9.4%)
Germ Cell Tumor	1 (1.9%)
QT Protocol	
BUFLU	11 (20.8%)
MELPHALAN 100	7 (13.2%)
BUFLUCY	3 (5.7%)
LACE	12 (22.6%)
BUFLUATG	3 (5.7%)
FLU MEL	2 (3.8%)
MELPHALAN 200	10 (18.9%)
FLUCYATG	4 (7.5%)
CYBU	1 (1.9%)
TCTH type	
Allogeneic	14 (26.4%)
Autologous	31 (58.5%)
Haplo	3 (5.7%)
NAP	5 (9.4%)
Time between QT and TCTH	5.7±2.6 (2-16)
QT Time	4.5±2.2 (1-19)
Days in LLLT	10.6±5.9 (3-28)
Mucositis Grade	
0	35 (66.0%)
1	11 (20.8%)
2	6 (11.3%)
3	1 (1.9%)

Data expressed as absolute frequency and percentage or average ± SD (minimum - maximum).
QT – Chemotherapy; BuFlu – Bulsufan and Fludarabine; BuFluCy – Bulsufan, Fludarabine and Cyclophosphamide; FluMel – Fludarabine and Melphalan; FluCyATG – Fludarabine, cyclophosphamide and rabbit ATG; CyBu – Cyclophosphamide and Mesna; LACE – Lomustine, Etoposide and Cytarabine; TCTH – Stem-Hematopoietic Cell Transplantation ; LLLT – Low Level Laser Therapy.
Patients submitted to HSCT at Walter Cantidio Hospital of Federal University of Ceará- Fortaleza-CE.

TABLE 2 - Influence of the clinical and therapeutic profile of patients undergoing bone marrow transplantation and PBMT on the incidence of oral mucositis

	MUCOSITIS GRADE		
	NO	YES	P-VALUE
Gender			
Masculine	14 (40.0%)	8 (44.4%)	0,756[a]
Feminine	21 (60.0%)	10 (55.6%)	
Age	47.6±15.0	36.7±13.8	***0,013***[b]
Base disease			
Dendritic leukemia cells	0 (0.0%)	1 (5.6%)	***0,010***[a]
Chronic myeloid leukemia	2 (5.7%)	4 (22.2%)*	
Multiple Myeloma	15 (42.9%)*	2 (11.1%)	
Acute Myeloid Leukemia	3 (8.6%)	5 (27.8%)*	
Follicular T Lymphoma	0 (0.0%)	1 (5.6%)	
LCM - Mantle Cell Lymphoma	5 (14.3%)*	0 (0.0%)	
Hodgkin's lymphoma	5 (14.3%)*	1 (5.6%)	
Aplastic Anemia	3 (8.6%)*	0 (0.0%)	
Acute Lymphocytic Leukemia	2 (5.7%)	3 (16.7%)	
Germ Cell Tumor	0 (0.0%)	1 (5.6%)	
QT Protocol			
BUFLU	4 (11.4%)	7 (38.9%)*	***0,005***[b]
MELPHALAN 100	5 (14.3%)	2 (11.1%)	
BUFLUCY	1 (2.9%)	2 (11.1%)	
LACE	10 (28.6%)*	2 (11.1%)	
BUFLUATG	1 (2.9%)	2 (11.1%)	
FLU MEL	0 (0.0%)	2 (11.1%)	
MELPHALAN 200	10 (28.6%)*	0 (0.0%)	
FLUCYATG	4 (11.4%)*	0 (0.0%)	
CYBU	0 (0.0%)	1 (5.6%)	
TCTH type			
Allogeneic	7 (20.0%)	7 (38.9%)	0,058[a]
Autologous	25 (71.4%)	6 (33.3%)	
Haplo	1 (2.9%)	2 (11.1%)	
NAP	2 (5.7%)	3 (16.7%)	

*p<0,05, aFisher's exact test or Pearson's chi-square test (n, %); b Student's t test (mean ± SD).
QT – Chemotherapy; BuFlu – Bulsufan and Fludarabine; BuFluCy – Bulsufan, Fludarabine and Cyclophosphamide; FluMel – Fludarabine and Melphalan; FluCyATG – Fludarabine, cyclophosphamide and rabbit ATG; CyBu – Cyclophosphamide and Mesna; LACE – Lomustine, Etoposide and Cytarabine; TCTH –Hematopoietic Stem Cell Transplantation
Patients submitted to HSCT at Walter Cantidio Hospital of Federal University of Ceará- Fortaleza-CE.

TABLE 3 - Influence of the PBMT protocol on the incidence of oral mucositis in patients with HSCT

	MUCOSITIS GRADE		
	NO	YES	P-VALUE
Laser type			
Laser V, 2J, 20seg	32 (91.4%)*	12 (66.7%)	***0,048[a]***
Laser IV, 4J, 40seg	3 (8.6%)	6 (33.3%)*	
LLLT Intent			
Treatment	1 (2.9%)	6 (33.3%)*	***0,004[a]***
Prevention	34 (97.1%)*	12 (66.7%)	
Time between QT and TCTH (Days)	5.1±2.2	7.0±2.8	***0,010[a]***
QT Time (Days)	4.03±2.3	5.6±1.8	***0,018[b]***
LLLT Time (Days)	9.1±3.9	13.5±7.9	***0,039[b]***
Post-prevention treatment			
No	34 (97.1%)*	5 (27.8%)	***<0,001[a]***
Yes	1 (2.9%)	13 (72.2%)*	
Oropharynx treatment			
No	34 (97.1%)*	8 (44.4%)	***<0,001[a]***
Yes	1 (2.9%)	10 (55.6%)*	
Death			
No	32 (91.4%)	16 (88.9%)	1,000
Yes	3 (8.6%)	2 (11.1%)	
TCTH Quantity			
1	33 (94.3%)	16 (88.9%)	0,598
2	2 (5.7%)	2 (11.1%)	

*p<0,05, aFisher's exact test or Pearson's chi-square test (n, %); b Student's t test (mean ± SD).
QT – Chemotherapy; V- Red light; IV – Infrared Light; TCTH – Stem-Hematopoietic Cell Transplantation; LLLT – Low Level Laser Therapy.
Patients submitted to HSCT at Walter Cantidio Hospital of Federal University of Ceará- Fortaleza-CE.

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OVERVIEW OF THE BRAZILIAN OUTCOMES FROM FIRST MULTICENTRIC STUDY WITH USE FROM DATABASE CIBMTR. A PILOT STUDY

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ABSTRACT

To better understand the outcomes of HSCT in Brazil, we conducted a multicenter study using the CIBMTR database. Seven participating centers extracted their own data through the Data Back to Center tool. Main indications for HSCT-auto were MM(51%), NHL(18%) and HL(17%); Allogeneic, AML(24%), ALL(23%) and SAA(15%). For acute leukemias, risk of death was higher in the 18-40 years group (HR=1.18,p=0.022), 40-60(HR=1.19,p<0.001) and 60+(HR=1.39,p=0.007), compared with 0-18 years, in ALL (HR=1.05,p <0.001, compared with AML) and with partially-matched related donor (HR=1.59,p= 0.003, compared with matched sibling), while URD was not. HSCT in CR2+(HR=1.28,p=0.01) and relapse (HR=2.44,p< 0.001) were risk factors for death. 2y-OS for MM was 83%(95CI:80-86), similar to the 2y-OS in the CIBMTR (85%) during the period of 2011-2017, according to their public summary slides. For AML, it was 49%(95CI:44-52) for adults and 52%(95CI:43-62) for children, while in the CIBMTR were 50 and 59%. For ALL, 2y-OS for adults and children were 45%(95CI:39-51) and 55%(95CI:49-63), somewhat poorer than the CIBMTR: 62 and 70%, respectively. Limited access to novel drugs for most centers and lack of molecular risk information are possible explanations for these differences. Further studies are necessary to better evaluate our findings and the DBtC tool enables multicenter studies.

Keywords: Hematopoietic Cell Transplant, CIBMTR, Outcomes, Cox model, Kaplan Meier, Outcomes and Brazil.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a therapy that can cure or extend survival of many malignant and non-malignant hematological diseases, congenital and acquired immune system disorders, solid tumors and even some hereditary disorders of metabolism [1].

According to the Center for International Blood and Marrow Transplant Research (CIBMTR), more than 227,906 autologous transplants, 196,209 related and unrelated allogeneic transplants and 11,225 cord blood transplantation procedures (2) were reported in the CIBMTR. According to the Brazilian Association of Organ Transplantation (Associação Brasileira de Transplantes de Órgãos, ABTO), in 2019 3,805 transplants were registered in Brazil, 1,428 allogeneic and 2,377 autologous [3].

Understand the HSCT scenario in Brazil is challenging because of the lack of a national registry that would

enable the analysis of outcomes and provides greater scientific production and national benchmarking. Therefore, over the years, through a working group composed of physicians and data managers (DM) and with the collaboration of CIBMTR and the Brazilian Society of Bone Marrow Transplantation (SBTMO), strategies such as continuing education to DM, communications channels, Data Managers Working Group (DMWG) and regularization of the sending of data to CIBMTR were developed (4), in order to promote the process of affiliation to the CIBMTR of Brazilian transplant centers,

since part of the data inserted in the registry can return to the affiliated centers in a standardized and codified way favoring the analysis of outcomes.

OBJECTIVE

Primary Objective

Describe the results of the first Brazilian multicenter study that uses the CIBMTR database to collect, store and extract data.

Secondary objective

To evaluate the possibility of using the CIBMTR Data Back to Center (DBtC) tool in the context of a Brazilian multicenter study, as well as the difficulties encountered.

Methodology

Seven bone marrow transplant centers affiliated to CIBMTR accessed the CIBMTR portal and extracted their own data, referring to the period from 2008 to 2018. The study was approved by the ethics committee. The spreadsheets were sent to the data analyst, where there was the process of merging the files in Excel. This is not an official study of CIBMTR.

In the study analysis, only patients who underwent the 1st autologous or allogeneic HSCT (3,655 patients) were analyzed. The independent variables studied were gender and age of the recipient and donor, underlying disease, disease status, HSCT type and stem-cell source. The outcome studied was overall survival. Overall survival curves were built using the Kaplan-Meier method (and compared with the long rank test), and multivariable analysis for risk of death were performed with the Cox model.

Results

Of the 7 centers participating in the study, 5 were from public institutions and 2 were private. 3,655 patients were included, with a median follow-up of 2.2 years. The baseline profile of the patients can be found in Table 1. In brief, the median age was 34 years and 59% of the patients were male. The most common indication for autologous transplantation (1256 patients) was multiple myeloma (MM, 51%, 638 patients), non-Hodgkin lymphoma (NHL, 18%, 222 patients) and Hodgkin lymphoma (HL, 17%, 207 patients). For allogeneic HSCT (2399), most frequent diagnosis were acute myeloid leukemia (AML, 24%, 575 patients), acute lymphoblastic leukemia (ALL, 23%, 597 patients) and severe aplastic anemia (SAA, 15%, 366 patients).

The 2-year OS of patients who underwent autologous HSCT was 77% (95CI: 75-80) and for allogeneic, 57% (95CI: 55-59), p<0.00001. Syngeneic HSCT had 84% 2y-OS (95CI: 69-100), HLA-identical sibling, 59% (95IC: 56-62), other HLA-matched related, 56% (95CI: 42-74), unrelated donor (URD), 55% (95CI: 52-59) and partially-matched related HSCT, 50% (95CI: 43-48), p=0.0002.

2-year OS for adult patients (≥18) was 63% (95CI: 62-65) and 66% (95CI: 63-69) for pediatric patients (<18), p = 0.001. At 5 years, the survival of children was 61%, and of adults, 48%. 73% (95CI: 70-77) of patients with non-malignant diseases were alive after 2 years of HSCT and 62% (95CI: 60 -64) for patients with malignant diseases (p<0.00001).

The 2-year OS for the main indications of autologous HSCT (MM, HL and NHL, figure 1), in this study, in adult patients, were respectively 83% (95CI: 80 - 86), 80% (95CI: 74-80) and 73% (95CI: 67-80), p=0.20. For pediatric patients, referring to HL and NHL, 2y-OS were 91% (95CI: 82-100) and 69% (95CI: 48-96), p = 0.10, (figure 2). 2y-OS for AML for adult patients was 49% (95CI: 44-52) and 52% (95IC: 43-62) for pediatric, p = 0.70, (figure 3). In ALL, it was 45% (95CI: 39-51) for adults and 55% (95CI: 49-63) for children, p = 0.01, (figure 4).

We performed multivariable analysis including only patients with acute leukemia (table 3). Age was a risk factor for death: 18 to 40 years, 40 to 60 and equal to or greater than 60 relative risks, were respectively, HR=1.28 (95CI 1.04,1.59, p = 0.02), HR=1.66 (95CI 1.3,2.11, p< 0.001) and ≥ 60 years, HR=1.95 (95CI 1.2.3.17, p=0.007), compared with 0 to 18 years. ALL was also a risk factor (HR=1.22, 95IC 1.02,1.46, p=0.03, compared with AML. Partially-matched related donor yielded inferior results (HR=1.59, 95CI: 1.16,2.17, p= 0.003) compared with matched-sibling donor, while URD, not (HR=1.17 95CI: 0.97,1.41, p=0.111). Patients transplanted in CR2+ or relapse had inferior survival (HR= 1.28, 95CI 1.06,1.55, p=0.01, and HR= 2.44, 95CI 1.86,3.19, p< 0.001) compared with CR1.

DISCUSSION

Our results show that the survival of allogeneic transplantation in two years was 57%, which is in accordance with the published literature. Allogeneic transplantation presents greater complexity and complications, such as GVHD, VOD and infections, and this may shorten patient survival. The most common indication was AML, for adult patients, 24% (575), with a 49% 2y-OS. For autologous HSCT, 2-year OS was 77%, and the most prevalent indication for adult patients was MM, with 51% (638), and a 2-y OS of 83%. In addition, survival in children was higher, 66%, as well as survival in patients with non-malignant diseases, 73%.

For pediatric patients, overall survival at 2 years was higher when compared to adults, 66% versus 63%, p=0.001. The team HSCT of this study inserted 1240 pediatric transplants in CIBMTR, from 2008 to 2018. In this group, more than 20% of diseases were transplanted with a curative intent for non-malignant diseases, such as SCID, other disorders of the immune and metabolic or hematopoietic system disorders.

We compared the results of partially-matched related and unrelated HSCT, which are the most popular types of transplantation among those lacking a matched-sibling donor. The partially matched related donor group included haploidentical donors and related donors with 1 HLA-mismatch. The URD was no different when compared to the partially compatible family option, 55% versus 50% respectively. Prospective studies are needed to validate and better understand the role of the haploidentical HSCT compared with URD HSCT.

The 2y-OS for non-malignant diseases was higher, 73%, compared with 62% (p<0.00001) for malignant disease. The most frequent malignant diseases were AML, NHL, HL, MM and ALL. For AML, the results of the present study (2y-OS 49% for adults and 52% for pediatrics) are similar to those reported by the CIBMTR (5) during the period of 2011-2017, where the 2y-OS for adult AML was 50% (±1%) and for pediatric AML was 59% (±1%). For MM, the 2-year OS in the CIBMTR was 85%, and 83% in the current study. For HL, the OS in 2 years in the CIBMTR was 91%, while our result was slightly poorer for adults (80%) and equal to the pediatric, 91%. For ALL (CIBMTR), the 2-year OS in CIBMTR was 70% for pediatrics and 62% for adults, which was higher compared with our results (45% for adults and 55% for children). Besides, there is limited information of molecular risk of those patients and further analysis is necessary to explain

Multivariable analysis for patients with acute leukemias showed a higher risk of death with increasing age. The absolute difference between 0-18 y/o and 18-40 y/o, however, was small. There was also a significant higher risk of death with mismatched-related donors (HR=1.59), compared with matched-sibling donors. URD was not a risk factor. Prognosis of ALL (HR=1.22) was slightly worse than AML. For patients who underwent HSCT in CR2+ (HR=1.28, p=0.01) or relapse (HR=2.44, p<0.001), survival was inferior compared with CR1.

The use of the CIBMTR tool to collect, store and extract data from the study centers went uneventfully, both in the standardization and categorization of data and in the download of the Excel spreadsheets, by a Business Intelligence (BI) tool, called QlikView, which extracts a large volume of data in a short period of time. The process of merging the databases of the 7 centers and analyzing them took approximately 15 days, which is an indicative of the effectiveness of using a single registry to collect and store Brazilian data. The CIBMTR tool presented some weaknesses, such as the non-return of all data, like disease recurrence, prophylaxis for GVHD, leading some centers to have parallel databases to meet the internal and external demand, the non-differentiation of the haploidentical of HLA 9x10 or any other incompatibility, the non-return of the dates of chronic GVHD, which prevents the analysis of this variable as time-dependent as time-dependent, in addition to the time of updating the CIBMTR database of new cases inserted in the registry, where the time is 3 to 4 months. However, the CIBMTR is receptive to the improvement of the tool, as a way to encourage the increase of affiliation to the CIBMTR. Another point to be taken into account is the lack of update of the follow-up of patients in the CIBMTR by the active centers in the registry, making it difficult to analyze survival for a long-term result. One evidence of this was the median follow-up of the patients analyzed, 2.2 years, for the period from 2008 to 2018. An important point is that this transplant centers had a representativeness of 18% (702) of the transplants registered in the Brazilian Registry of Transplants (Registro Brasileiro de Transplantes, RBT) in 2019, being 28% (405) allogeneic and 12% (297) autologous. Another positive point is the number of patients analyzed, in the thousands.

CONCLUSION

We conclude that the use of the CIBMTR database and the data return tool (QlikView) to develop mul-

ticenter studies is feasible, since the variables are standardized and codified, allowing the analysis of data more quickly and speeding up the writing of abstracts and original articles. The database generated by the data recorded in the CIBMTR allows each center to know some of its outcomes, in addition to the possibility of using information for Brazilian public management based on decision making. The outcomes in this study were similar to those presented by CIBMTR. Besides, there is limited information of molecular risk of those patients and further analysis is necessary to explain these mortality rates, socioeconomic issues and Brazilian public health system should be taken into account for this type of comparison.

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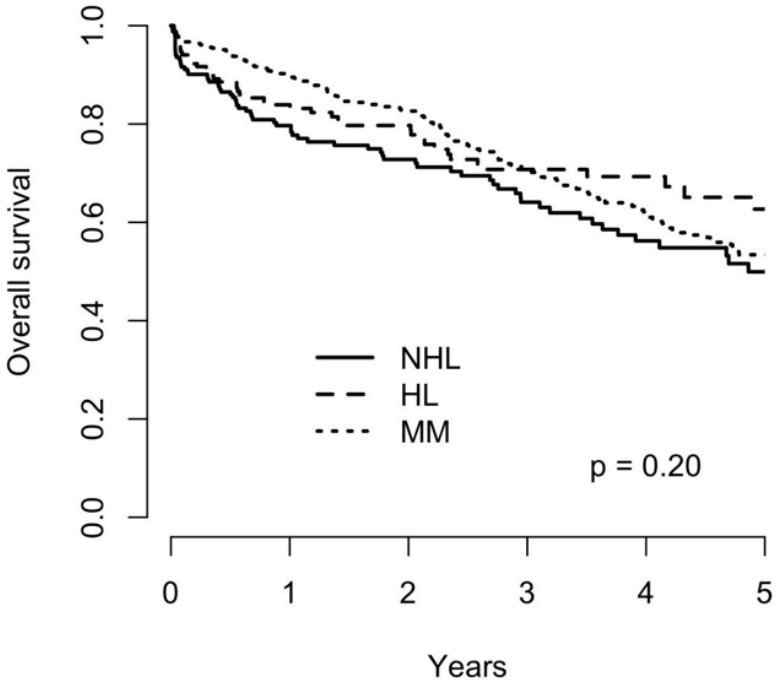
TABLE 1 - Patients baseline profile

	ALLO	AUTO	TOTAL	P VALUE
Total	2659	1574	4233	
idade				< 0.001
median(IQR)	25 (11,42)	49 (29,58)	34 (15,51)	
Gender				0.627
Male	1571 (59.1)	918 (58.3)	2489 (58.8)	
Female	1088 (40.9)	656 (41.7)	1744 (41.2)	
Primary.Disease				< 0.001
Acute myelogenous leukemia	648 (24.4)	26 (1.7)	674 (15.9)	
Non-Hodgkin lymphoma	72 (2.7)	293 (18.6)	365 (8.6)	
Hodgkin lymphoma	51 (1.9)	263 (16.7)	314 (7.4)	
Plasma cell disorder/Multiple Myeloma	18 (0.7)	775 (49.2)	793 (18.7)	
Acute lymphoblastic leukemia	597 (22.5)	2 (0.1)	599 (14.2)	
Other Malignancies	3 (0.1)	181 (11.5)	184 (4.3)	
Other leukemia	29 (1.1)	1 (0.1)	30 (0.7)	
Severe aplastic anemia	391 (14.7)	0 (0)	391 (9.2)	
Inherited abnormalities erythrocyte differention or functuntion	201 (7.6)	0 (0)	201 (4.7)	
Chronic myelogenous leukemia	188 (7.1)	0 (0)	188 (4.4)	
SCID and other immune system disorders	99 (3.7)	0 (0)	99 (2.3)	
Myelodysplastic/myeloprolifterative disorders (please classify all preleukemias)	275 (10.3)	0 (0)	275 (6.5)	
Inherited abnormalities of platelets	2 (0.1)	0 (0)	2 (0)	
Inherited disorders of metabolism	29 (1.1)	0 (0)	29 (0.7)	
Histiocytic disorders	7 (0.3)	0 (0)	7 (0.2)	
Autoimmune Diseases	4 (0.2)	32 (2)	36 (0.9)	
Acute leukemias of ambiguous lineage and other myeloid neoplasms	36 (1.4)	0 (0)	36 (0.9)	
Other, specify	9 (0.3)	1 (0.1)	10 (0.2)	
Donor.Recipient.Sex				
Unknown	175 (6.6)			
M-M	833 (31.3)			
M-F	574 (21.6)			
F-M	613 (23.1)			

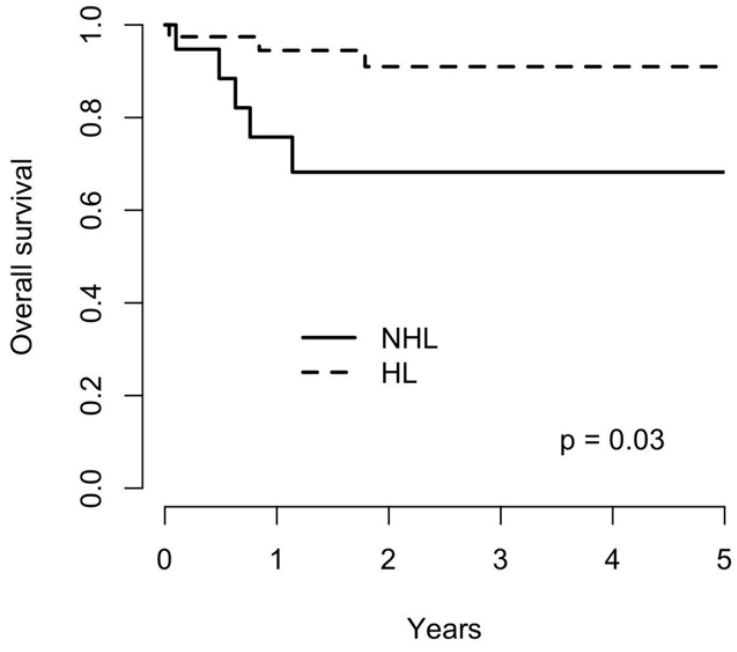
F-F	464 (17.5)			
Graft Type				< 0.001
Bone marrow	1699 (63.9)	46 (2.9)	1745 (41.2)	
Peripheral blood	796 (29.9)	1505 (95.6)	2301 (54.4)	
Umbilical cord blood	154 (5.8)	2 (0.1)	156 (3.7)	
BM + PB	3 (0.1)	21 (1.3)	24 (0.6)	
BM + UCB	6 (0.2)	0 (0)	6 (0.1)	
Unknown	1 (0)	0 (0)	1 (0)	
TED.Donor.Type				
HLA-identical sibling (may include non-monozygotic twin)	1402 (52.7)			
sysgeneic (monozygotic twin)	22 (0.8)			
HLA-matched other relative	56 (2.1)			
HLA-mismatched relative	262 (9.9)			
Unrelated donor	915 (34.4)			
Unknown	1 (0)			

TABLE 2 - Main outcomes

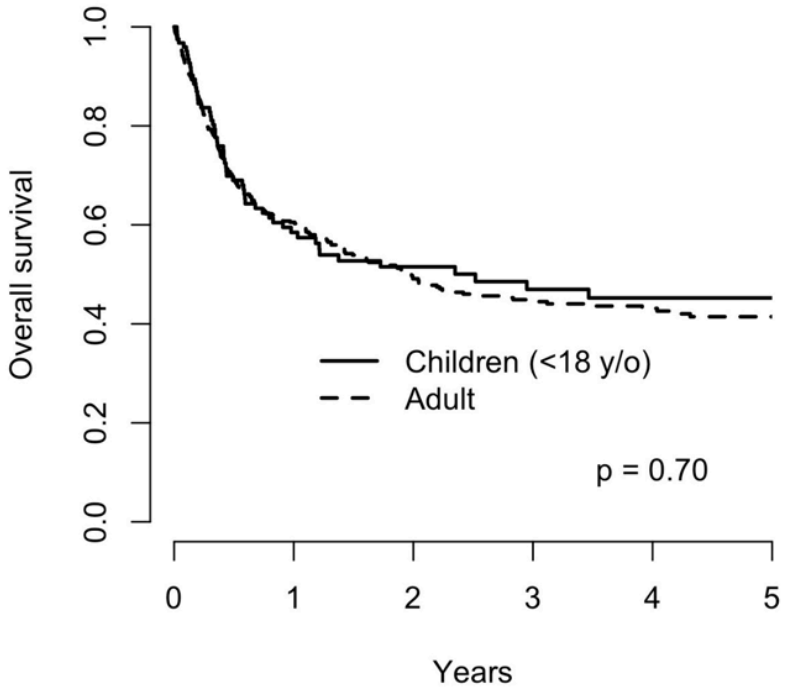
	2-YEAR OS	95% CI	P
Allogeneic	57%	(55-60)	
Autologous	72%	(75-80)	<0.00001
≥18	63%	(61-65)	
<18	66%	(63-69)	0.001
HLA-identical sibling	59%	(57-62)	
Syngeneic	84%	(69-100)	
other HLA-matched related	56%	(42-74)	
Partially-matched related	50%	(43-58)	
Unrelated donor	55%	(52-59)	0.0002
Malignant diseases	62%	(60-64)	
Non-malignant diseases	73%	(70-77)	<0.00001
NHL, Adult	73%	(67-80)	
HL, Adult	80%	(73-87)	
MM, Adult	83%	(80-86)	0.20
NHL, Pediatric	69%	(48-96)	
HL, Pediatric	91%	(82-100)	0.10
AML, Pediatric	52%	(43-62)	
AML, Adult	49%	(44-54)	0.70
ALL, Pediatric	55%	(49-63)	
ALL, Adult	45%	(39-51)	0.01



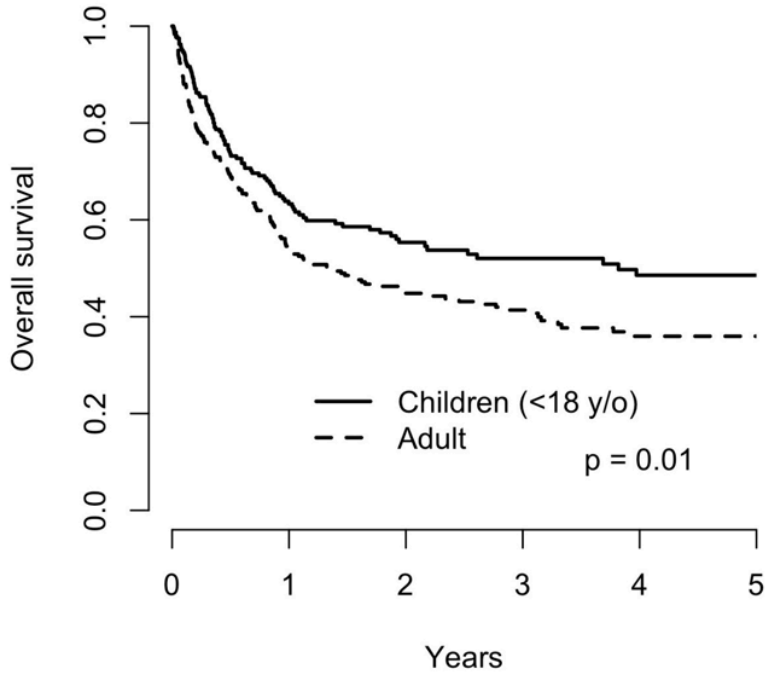
GRAPHIC 1 - Overall survival of adult patients to MM, HL and NHL



GRAPHIC 2 - Overall survival of pediatric patients to NHL to HL



GRAPHIC 3 - Overall survival of pediatric and adult patients to AML



GRAPHIC 4 - Overall survival of pediatric and adult patients to ALL

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COMPARATIVE ANALYSIS OF THE DATA ON THE INFLUENCE OF THE SARS-COV-2 PANDEMIC ON BONE MARROW TRANSPLANTATION AND THE PROTOCOLS ADOPTED IN BRAZIL BETWEEN MAY AND JUNE 2020

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ABSTRACT

This is an observational and cross-sectional study, carried out in May 2020, targeting adult individuals of both sexes who are members of multiprofessional teams working in Brazilian HSCT units in the current period of the pandemic by completing and analyzing a questionnaire. pre-formulated. HSCT units that cannot access the questionnaire were excluded from the study. The analysis of the operation profile of HSCT units in Brazil, through the application of a pre-structured questionnaire, is not an accurate tool, since it assumes some premises that may prove to be wrong, especially in this current scenario in Brazil. However, the data reveal the vulnerability of patients with onco-hematological diseases to infection by COVID-19, especially during HSCT procedures, in relation to the general population. Despite its limitations, it can be valuable to plan policies.

Keyboard: SARS-CoV-2, bone marrow transplantation, protocols.

INTRODUCTION

In December 2019, in Wuhan, China, a new betacoronavirus (initially denominated 2019-nCoV) was discovered. In January 2020, the World Health Organization (WHO) declared this outbreak as a global health emergency and named the 2019-nCoV-associated disease as 2019 coronavirus disease (COVID-19). On the same date, the Coronavirus Study Group (CSG) of the International Virus Taxonomy Committee designated the 2019-nCoV as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). On March 11, 2020, WHO classified the COVID-19 as pandemic due to the rapid worldwide spread of virus [1,2]. In this scenario, Hematopoietic Stem Cell Transplantation Centers (HSCT) as well as other entities of onco-hematological treatment [3,4] faced the challenge of continuing therapy and, in the case of HSCT, defining criteria for their realization. The Brazilian Society of Bone Marrow Transplantation (SBTMO) follows the recommendations of several international representative entities [5-10] preparing recommendations from SBTMO itself, aware of the need to adapt to our country, which has approximately 209 million inhabitants, continental proportions and profound regional disparities.

To evaluate the impact of the SARS-CoV-2 pandemic on HSCT and protocols adopted in Brazil.

MATERIALS AND METHODS

This is a cross-sectional study carried out from May to June 2020, through the application of a pre-structured questionnaire of 14 questions about the possible interventions carried out in the HSCT units in the face of the COVI-19 pandemic, such as: if the service was working in the pandemic and what percentage; the use of recommendations from medical societies and which ones; the use of RT PCR for patients and donors and what are the difficulties performing the tests; COVID-19 infection in intra-transplantation and post-HSCT, which therapy was used and which were the symptoms; death due to COVID-19 in the intra or post-HSCT; contamination of health professionals; testing of contaminated healthcare workers for COVID-19; screening for COVID-19 by exams in asymptomatic employees and some comments about the HSCT procedures, patient and donor experiences. The project was approved by the Research Committee of the Walter Cantídio University

Hospital (HUWC), in Fortaleza, Brazil, following the recommendations of the national Resolution 466/12 of the National Health Council regarding ethics in research involving human beings. Before completing the questionnaire, those responsible for completing it signed a digital consent form, aiming to ensure the confidentiality, veracity, and security of the information. The questionnaire was published on the website of the Brazilian Society of Bone Marrow Transplantation (SBTMO) to be filled in by the technical health officials of the Brazilian HSCT units. Data were collected using the Google Forms application and analyzed using the Excel program.

RESULTS

Out of a total of 86 qualified centers in Brazil, 51 centers (59.3%) responded to the questionnaire in May, which represents approximately 85% of all adult and pediatric transplants performed in Brazil. In June, 52 centers (60.4%) answered the questionnaire. In May, only 4% of the centers interrupted the HSCT program and 12.2% maintained their operation without reduction. In most of them, there was a decrease in the number of HSCT, varying from 50% to 75% of the typical number in 59.2% of all centers. In June, this variation was 79.2% (Figure 1A) All of them followed some recommendation, and the most cited was of the SBTMO both in May (98%) and in June (90.4%) (Figure 1B). The orientation for testing the donor and the asymptomatic patient in the pre-HSCT assessment was initially a reason for discussion in the country, due to the difficulty in making the exams available, but both in May (88.2%) and in June (88.5%) in most transplants and in those who do not, the collection of the RT-PCR exam is the greatest difficulty, due to the absence of a test or even an adequate place for the collection of samples (Figure 1C). The main symptoms were fever, cough, anosmia and headache (Figure 1D) and the drugs most used for treatment were azithromycin (75%), hydroxychloroquine (55%), corticosteroids and ivermectin (both 15%) (Figure 1E). Those who were using immunosuppressants, these were maintained in 38.1%, decreased in 19% and discontinued in 14.3%. About 58% of health professionals were infected and removed in May. In June, this contamination increased to 73.1% (Figure 1F). In May 88.9% of these professionals underwent a laboratory test to confirm the SARS -CoV-2 infection and in June 95% (Figure 1G). When asked about testing asymptomatic health professionals directly involved with HSCT, only 26% of centers were tested in May and 44.2% in June (Figure 1H), this measure may have decreased the viral transmission of asymptomatic workers and the chain of transmission to the patient and their relatives of these professionals.

CONCLUSION

The analysis of the profile of the operation of HSCT units in Brazil, through the application of a pre-structured questionnaire is not an accurate tool, as it assumes some assumptions that may prove to be wrong, especially in this current scenario in Brazil. However, the data reveal the vulnerability of patients with onco-hematological diseases to infection by COVID-19, especially during the HSCT procedures, in relation to the general population. Despite its limitations, it can be valuable for planning political and health measures at the regional and federal levels.

In conclusion, most of the centers report that they are following the coping recommendations proposed by scientific societies and are reducing the number of procedures during the pandemic. The current profile in Brazilian HSCT centers, related to the recommendations for coping with COVID-19 infection, will assist in making public policy decisions in a country such as Brazil, which suffers from increasing numbers of infection and rationalizing HSCT, so that patients who have urgency in their procedures are not harmed.

ACKNOWLEDGEMENTS

We would like to thank all the centers that contributed to this study, Dr. Clarisse Machado and Dr. Mary Flowers.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

Ethical approval to report this case was obtained from Research Ethics Committee involving human beings (CEP) of the Federal University of Ceará and the Hospital Walter Cantídio (APPROVAL NUMBER: 4.079.804).

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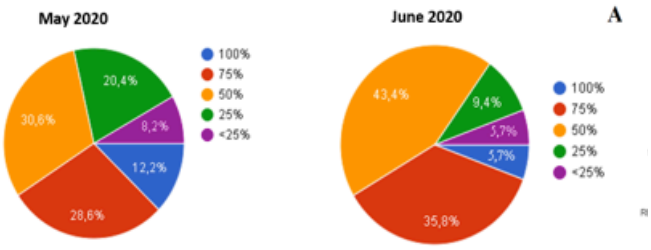


A

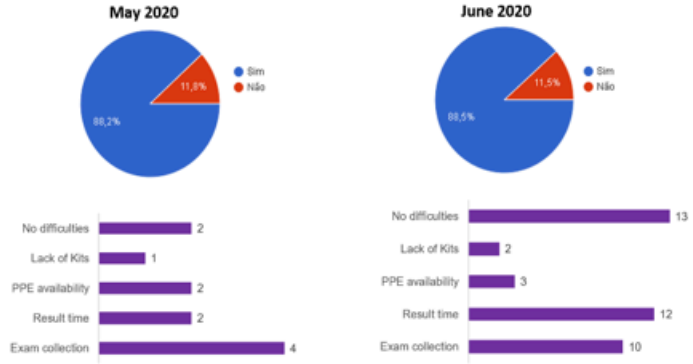
C

100% of the centers are following some recommendation

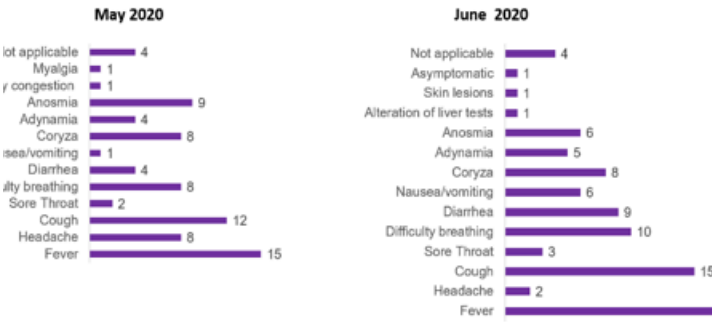
B

D

C



D



F

GRAPHIC 1 A – Operating estimate. B - Recommendation of medical societies followed by health professionals. C - Availability to perform RT-PCR for COVID-19 for patients and donors. D - Main symptoms observed in symptomatic patients for COVID-19. E - Therapy most used in cases with COVID-19 in the intra or post-BMT. F - Contamination by COVID-19 in health professionals. G - Contaminated health workers who have been laboratory tested for COVID-19. H - Death by COVID-19 in the intra or post-HSCT.

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RECENT ADVANCES IN HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR INHERITED BONE MARROW FAILURE SYNDROMES

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ABSTRACT

The inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of genetic disorders characterized by the inadequate production of at least one of the hematopoietic lineages, leading to the development of both isolated cytopenia (anemia, neutropenia, or thrombocytopenia) or pancytopenia. Different biological mechanisms justify the pathophysiological changes found in the IBMFS, emphasizing the repair pathways in Fanconi anemia (FA), maintenance of telomeres in congenital dyskeratosis, and ribosome biogenesis in Shwachman Diamond syndrome (SSD) and Blackfan Diamond anemia. These disorders are generally associated with the presence of congenital malformations and an increased risk of cancer, mainly hematological, gynecological, and head and neck neoplasms. Although the diagnosis occurs typically in childhood, adult patients, mostly below 40 years of age with signs and symptoms suggestive of IBMFS, should be investigated. Currently, hematopoietic stem cell transplantation (HSCT) is the only curative option for hematological complications related to IBMFS. It is essential to highlight that these patients must be monitored throughout their lives to prevent or detect early treatable neoplasia.

Keywords: Anemia, Diamond-Blackfan, Fanconi Anemia, Shwachman, Telomere Diamond Syndrome, Bone Marrow Transplantation and Hematopoietic Stem Cells

INTRODUCTION

The inherited bone marrow failure syndromes (IBMFS) are genetic disorders characterized by inadequate blood cell production, usually associated with physical malformations and a predisposition to cancer [1,2] IBMFS often presents with isolated cytopenia (pure red cell aplasia, neutropenia, or thrombocytopenia) that may progress to pancytopenia over time (3) Although the diagnosis is usually performed in childhood, an increasing number of patients with IBMFS may present to adult hematologists with atypical presentations. [1,4] Significant overlap between these syndromes is usually observed, and a correct diagnosis is critical to allow for adequate treatment, genetic counseling, and long-term surveillance for cancer. The patient and the family's history need to be carefully investigated to detect the presence of bone marrow failure, hematological malignancies, pulmonary or hepatic abnormalities, and cancer in other members of the family. Patients with IBMFS should undergo a comprehensive evaluation, and a review of systems involved in these syndromes was recently published by Alter in 2017 [5]. As many individuals lack a specific phenotype and may appear normal, screening family members is essential to exclude them as potential donors.

Over the last few decades, there has been considerable improvement in elucidating the genetic aspects

related to IBMFS, leading to significant progress in better understanding the normal hematopoiesis and how this affected patients with bone marrow failures. These advances provided valuable information about the different biological mechanisms involved in IBMFS, such as the repair mechanism in FA, the maintenance of telomeres in DC, and the biogenesis of ribosomes in Shwachman Diamond syndrome (SDS) and DBA [3,6]. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for the hematological complications related to the IBMFS [7]. Results are excellent when patients are transplanted from matched donors before complications related to previous infections, transfusions, or clonal evolution are detected. Challenges include the treatment of adult patients, patients with advanced diseases, and the treatment of cancer. An additional concern is the potential of the HSCT procedure, including conditioning regimen, infection, and chronic graft versus host disease (GvHD), to increase the risk of malignancies [2,7]. As a general rule, radiation containing regimens should be avoided for all patients with IBMFS, and bone marrow is considered the preferred stem cell source [7]. While the use of related cord blood from unaffected matched related donors is associated with excellent transplant outcomes, unrelated umbilical cord blood should be avoided whenever possible [7–9]. Increasing awareness of these diseases is of utmost importance, and the decision to proceed with the transplant must be made by a multidisciplinary team. Also, HSCT should be performed in specialized centers, with particular attention to early and long-term toxicity and lifelong medical surveillance for secondary neoplasms. In this paper, we summarize the information and recent advances regarding HSCT for IBMFS.

FANCONI ANEMIA

Fanconi anemia (FA) is a chromosomal instability syndrome resulting from a DNA damage repair defect. [10]. It is considered the most frequent IBMFS and is characterized by progressive BMF, various congenital abnormalities, and a predisposition to developing malignancies, especially myelodysplasias, acute leukemias, tumors of the head and neck, and gynecological cancers [11]. Patients with FA usually present with a clinical manifestation variable like short stature, skin abnormalities, a triangular "Fanconi" face, upper limb abnormalities, renal and heart anomalies, genitourinary abnormalities, and cardiac defects [12,13]. Endocrinological complications are also persistent before and after transplant in FA patients. The majority exhibit at least one difficulty, such as growth hormone deficiency, hypothyroidism, dyslipidemia, hypogonadism, and infertility [14]. The risk of insulin resistance and abnormal glucose metabolism is also higher and may be aggravated by GVHD treatment with steroids [14]. Patients with FA should be evaluated annually and, when necessary, treated according to the recommendation for the general population [15]. HSCT outcomes have improved dramatically over the past decades, and it is indicated when patients develop pancytopenia, MDS, or acute myeloid leukemia (AML). Overall survival after HSCT for young patients transplanted in aplasia from matched related or matched unrelated donors with 80-90% overall survival in experienced centers [16–18].

Currently, RIC regimens are considered standard. In addition, for matched related transplantation, the use of low dose cyclophosphamide with or without fludarabine and r-ATG is sufficient to achieve excellent engraftment and low incidence of GVHD [17]. It is essential to remind that irradiation is not necessary for the conditioning regimen for this group of patients [19]. Curitiba's group has transplanted 91 patients in aplastic phase using CY 60mg/kg with or without ATG with an excellent 95% overall survival and a median follow-up of 7 years [20].

Although HSCT outcomes are excellent for patients in aplastic phase transplanted below the age of 10, transplant strategies for adults and those with advanced diseases need to be improved. A recent publication by Bearings *et al*., including almost 200 adults, demonstrated an overall survival and non-relapse mortality at four years of 38% and 51%, respectively. Factors associated with improved outcomes in multivariate analysis were the use of fludarabine and an HLA-matched donor [16]. FA patients with a clonal evolution have a dismal prognosis, usually related to increased toxicity to the preparatory regimens and higher risk of relapse [15,21]. To improve outcomes for this group of patients, the French and Brazilian groups treated 18 patients with FA in advanced MDS or AML with FLAG chemotherapy followed by sequential HSCT in aplastic phase using a RIC regimen. With this approach, the 3-year cumulative incidence of relapse and progression-free survival was 13% and 53%, respectively [22]. Patients without a matched related or unrelated donor may also benefit from haploidentical transplants performed with or without in vivo T cell depletion [23,24]. Bonfim et al. demonstrated a one-year OS of 73% (95% CI, 64% to 81%) using a modified haplo-PTCY platform [24]. These results were also achieved by Ayas et al. using a similar haplo-PTCY platform with an overall survival of almost 90% in 19 patients [25].

Patients with FA are expected to live longer, and the risk of cancer increases with age. Long-term follow-up is essential in this population with particular attention to detect cancer and other specific complications. Thus, dental and head and neck physician exams should be done every [6-12] months. Early detection of cancer with brushing/biopsy of suspicious lesions and consequent treatment (surgery) is associated with better results considering the patients do not tolerate irradiation or chemotherapy [26,27]. Also, new drugs may have less side effects and may be very useful to treat cancer [28]. Importantly, patients whose FA is due to mutations in FANCD1/ BRCA2 or FANCN/ PALB2 need genotype-specific cancer screening because of increased risks of medulloblastoma, Wilms tumor, and other cancers [26].

DYSKERATOSIS CONGENITA

Dyskeratosis congenital (DC), a severe form of telomere biology disease (TBD), is a rare IBMFS characterized by abnormal skin pigmentation (reticulated skin hyperpigmentation), nail dystrophy, and oral leukoplakia. DC is frequently associated with BMF and organ involvement, mainly pulmonary fibrosis and liver abnormalities. There are two severe forms of DC; Hoyeraal Hreidarsson syndrome (HHS), a classical DC disease associated with BMF, intrauterine growth retardation, microcephaly, and cerebellar hypoplasia, and Revesz syndrome (RS), which is related to progressive bilateral exudative retinopathy (Coats retinopathy), intrauterine growth retardation, fine, sparse hair, fine reticulate skin pigmentation, ataxia secondary to cerebellar hypoplasia and cerebral calcifications [29,30].

Bone marrow failure and hematologic malignancies (MDS or AML) represent the main indication for HSCT. Although transplant is the only curative option for DC, the results are still disappointed with a poor long-term survival rate. Pulmonary and vascular complications, hepatic cirrhosis, graft failure, graft-versus-host disease (GVHD), and sinusoidal obstruction syndrome still represent the most important causes of morbidity and mortality after transplant, which explain the disappointing long term survival [31–33]. Gadalla *et al.* studied 34 cases who underwent HSCT between 1981 and 2009 and demonstrated a probability of overall survival of 70, 57, and 15% in 1, 5, and 12 years respectively. In this study, almost 80% of patients received a myeloablative conditioning regimen, and the authors highlighted the severe transplant-related toxicities observed over the years. [34] Similar results were published by Barbaro *et al*., where the long-term cumulative survival rates were 57% and 23% at 5 and 10 years post HSCT in a series of 109 cases [32]. Considering these poor results, some groups have recommended reduced-intensity conditioning containing fludarabine as a standard regimen [35,36]. Regarding a Brazilian experience, the OS of 28 patients transplanted for TBD in Curitiba between 1993 and 2019 was 53,6% at a median follow-up of 6 years [37].

DIAMOND BLACKFAN ANEMIA

Diamond-Blackfan anemia (DBA) is a rare inherited red cell aplasia caused by an intrinsic defect of erythropoietic progenitors leading to severe anemia in early infancy ninety percent of the patients diagnosed within the first year of life [38,39]. Currently, DBA is classifying as a "ribosomopathy" once haploinsufficiency of either a small or large subunit-associated ribosomal protein is present in the majority of patients [38,40]. Diagnosis should be suspected in all children under one year of age presenting with macrocytic or normocytic anemia and reticulocytopenia, with normal marrow cellularity and a decrease or absence of red cell precursors in the bone marrow [41]. Approximately 50% of patients have congenital anomalies associated [41]. Similar FA and DC, DBA is considered a cancer predisposition syndromes, with a higher risk of hematologic (AML) and solid tumor (colon carcinoma and osteogenic sarcoma) development [42,43]. The therapeutic approach is based on red cell transfusions, corticosteroid therapy, and HSCT. Steroids, considered the first-line treatment with about 80% success response, should be started in the second year of life considering its negative effect on infants' physical and neurocognitive development. Thus, red cell transfusions are used mainly in infants and patients refractory to corticosteroid therapy [41,44,45]. HSCT, potentially curative treatment for DBA, is indicated for patients who are non-response to steroids or remain transfusion-dependent despite the use of steroids (dose requirement ≥0.3 mg/kg/day). Other indications are erythroid alloimmunization, progressive pancytopenia, and progression to SMD / AML [7,46]. HSCT should preferably be performed between 2 and 5 years, as older patients tend to have a worse evolution due to iron overload and alloimmunization [7,47].

In the last decades, HSCT has been employed with success in DBA patients. In 2006, data from North American DBA Registry reported an OS of 73% with MSD and 19% with alternative donors (P= 0.01) (48). Besides, the International Bone Marrow Transplant Registry, published in 2005 a 3-year OS of 64% (76% for MSD and 39% for alternative donor transplants) while the

Italian Group (AIEOP HSCT Registry) reported an OS of 74,4% in patients transplanted between 1990 and 2012 [47,49]. All of these findings are similar to those published by the Pediatric Study Group of the Brazilian Society of Bone Marrow Transplantation (SBTMO), which included 44 patients and had a 5-year OS of 70% (95% CI: 57 – 85%) in pediatric patients transplanted for DBA in Brazil. It was 80% (95% CI: 65-97%) from an MSD (n=25), 73% (95% CI: 52-100%) from a MUD (10/10 HLA Matched, n=12) and 29% (95% CI: 9-92%) from a MMD (n=7) [50]. Recently German DBA group and French HSCT registries published an excellent OS of 91% (95% CI: 84-98%) with a median follow-up of 4.5 years [51]. Myeloablative conditioning with busulfan-based regimens is currently recommended for patients with DBA, although treosulfan-based reduced-toxicity regimens have been demonstrating promising results [7,51,52]. It is important to keep in mind that the use of intravenous busulfan and adjustable pharmacokinetic monitoring correlates with better OS and EFS in children transplanted for non-malignant diseases like DBA [53,54]. Patients with DBA should benefit from a pretransplant and early posttransplant iron chelation therapy once the high iron overload is associated with inferior outcomes after HSCT [55,56]

SHWACHMAN-DIAMOND SYNDROME

Schwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder caused by mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene localized on chromosome 7 and found in 90% of the cases. It is characterized by exocrine pancreatic dysfunction with malabsorption, skeletal abnormalities, BMF, and predisposition to hematologic neoplasia [57,58]. In addition, like DBA, the molecular pathogenesis of SDS is associated with defective processing of rRNA and ribosome assembly. Some patients' clinical manifestations include short stature, with metaphyseal dysostosis, particularly at the hips and femurs in about half the patients, variable immune dysfunction, delayed dentition, and structural and functional abnormalities of the liver. Neutropenia is the most common hematological abnormality, although they may have other cytopenias present in up to 80% of the patients [59].

HSCT is the only potentially curative treatment for SDS and should be recommended for all patients with progressive pancytopenia and clonal evolution, mainly acute leukemia, and MDS. HSCT should also be considered for patients refractory to high doses of G-CSF (10 µg/kg or more per injection at least three months a year) to maintain protective neutrophil values (between 1.0 and 5.0 × 109/L), [5,7,60]. A RIC regimen is considered standard once patients with SDS are more susceptible to transplant-related toxicity, especially cardiac and pulmonary toxicities [61,62]. Recently, Cesaro et al. published the results of 74 patients with SDS treated with HSCT between 1988 and 2016. The 5-year overall survival and non-relapse mortality were 63.3% (95% CI 50.8–73.4) and 19.8% (95% CI 10.8–30.8), respectively [60].

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare IBMFS caused by mutations in the gene coding for the thrombopoietin receptor MPL. It is characterized by isolated thrombocytopenia and a reduction or absence of megakaryocytes in the bone marrow. Most patients develop hypocellular bone marrow and progressive pancytopenia within the first decade of life. Unlike other IBMF, clonal evolution is an infrequent event [63–65]. HSCT is the only curative therapy for CAMT. As with many rare genetic disorders, there are only a few reports about HSCT for CAMT in the literature since the first case in 1990.

Nevertheless, the transplant should be offered to patients with transfusion-dependent thrombocytopenia or alloimmunization, pancytopenia, or clonal evolution (MDS or AML) [64,65]. As for other IBMF syndromes, HSCT from an HLA- matched sibling is the treatment of choice for SAA while Matched [10/10)] unrelated donor is an acceptable choice. MAC conditioning based on fludarabine and either busulfan or treosulfan is considered standard [7,64–66]. Until now, increased regimen toxicity usually present in Fanconi anemia, and DC has not been reported with MAC [67]. Regarding UCB, a report from the Eurocord group suggests that UCB transplantation is a reasonable option for patients with CAMT, mainly if a sibling donor is used [8]. On the other hand, data from unrelated HSCT demonstrated inferior results [65].

SEVERE CONGENITAL NEUTROPENIA

Severe neutropenia is a heterogeneous group of congenital disorders characterized by impaired maturation of neutrophil granulocytes and persistent absolute neutrophil count (ANC) of less than 0.5 × 10 9 /L. Among several associated genetic mutations, ELANE and HAX1 genes are responsible for 60% of cases. Usually, clinical manifestations include bacterial infections, including deep tissue infections, sepsis, and fever. The regular use of granulocyte colony-stimulating factor (G-CSF) is routine [68,69]. An additional concern, clonal evolution (leukemia and MDS) affects about 10% of patients [70]. Despite the excellent re-

sults achieved using G-CSF therapy, HSCT is still considered the only curative treatment. Currently, non-response to G-CSF treatment, and patients who develop AML or MDS are the main indications for transplantation. Bone marrow is considered the standard stem cell source, and myeloablative conditioning, usually with busulfan and Cyclophosphamide, and GVHD prophylaxis regimen consist of CSA and methotrexate are preferred. [7,71]. In 2015, Fioredda *et al*. reported the analysis of 136 patients transplanted from 1990 and 2012 by the European Bone Marrow Transplant group. The 3-year overall survival was 82 % and TRM 17 %. In multivariate analysis, HSCT below ten years of age from a matched related or unrelated donor in recent years was associated with better results [71].

CONCLUSION

The IBMFS is a group of rare genetic diseases associated with inadequate blood cell production, and up until now, allogeneic HSCT is considered the only curative option. Ideally, HSCT is indicated as soon as the patients begin to develop pancytopenia and before severe infections, clonal evolution, or the need for multiple transfusions. As these diseases may present with subtle findings, screening of family members should be performed before transplantation. However, it is essential to keep in mind that transplantation may only correct damaged hematopoiesis without changing the course of other complications related to the disease. Thus, we recommend that the decision to proceed to allogeneic HSCT should be discussed with the experts' team. Patients/families should be advised about the increased risk of cancer and organ damage progression. Finally, we strongly recommend that patients have a continued follow-up after HSCT, focusing on early detection, prevention, and treatment of head and neck squamous cell carcinoma, hematological neoplasia, and solid tumors (colon carcinoma and osteogenic sarcoma).

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ACUTE MYELOID LEUKEMIA IN CHILDREN AND ADOLESCENTS IN BRAZILIAN INSTITUTIONS: REALITY AND CHALLENGES

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ABSTRACT

Objective: To describe the outcome of acute myeloid leukemia (AML) among children treated in Brazilian institutions. Methods: A structured online questionnaire was sent to pediatric oncologists affiliated to the Brazilian Society of Pediatric Oncology. The physicians and institutions were unidentified. Results: One hundred and four pediatric oncologists in all Brazilian regions answered the questionnaire. The treatment-related mortality rate was reported to be higher than 30% by 29.8% of the participants. Difficulty in accessing the intensive care unit (ICU) was reported by 54.8%. About 85% had access to cytogenetics, 78% to molecular testing, 94% to the measurement of residual disease by flow cytometry. About 90% of participants reported access to HSCT, but 86% of them had difficulties in providing HSCT timely. About 95% of the participants indicated the need to create a national treatment protocol, and 89.4% are willing to collaborate with a national study group. Conclusion: Our study demonstrated large gaps in the treatment of pediatric AML. To improve outcome, a national protocol will have to consider the regional differences and adapt the management according to the local resources.

Keywords: Pediatric AML. HSCT. Brazil

INTRODUCTION

Myeloid neoplasms represent a heterogeneous group of hematological disorders that originate from the myeloid, monocytic, erythroid and megakaryocytic precursors. Among them, acute myeloid leukemia (AML) is the most frequent in pediatric and adolescent age group, representing between 15-20% of all acute leukemias 1. When treated with conventional chemotherapy regimens, about 80-90% of these patients attain complete remission (CR). The 5-year event-free survival (DFS) and overall survival (OS) rates approach 60% and 70%, respectively, in high-income countries [2, 3].

Eradication of the leukemia cells and restoration of the bone marrow function are the main treatment goals in AML. The use of intensive chemothera-

py regimens to obtain rapid myelosupression is standard practice. The combination of cytarabine, daunorubicin and etoposide form the basis of most remission induction treatment protocols [4, 6]. With two courses of intensive chemotherapy, the complete remission (CR) rates are above 90%. Refractory or resistant disease rates are approximately 5% [2, 7]. Other strategies aimed to optimize the treatment include reducing the interval between the initial cycles of chemotherapy ("intensive timing") 8 and replacing daunorubicin with idarubicin 4 or mitoxantrone 6. Several international study groups (BFM, CCG, NOPHO, LAME, MRC) have observed that the intensification of induction along with optimal supportive care increases the CR but not the EFS rates [5, 9].

Post-remission strategies also did not improve EFS, because of failure to significantly reduce the relapse. The improvement of OS rates observed over the past 25 years is due to improvements in salvage therapies, including hematopoietic stem cell transplantation (HSCT). The better outcome of pediatric AML after 1999 coincided with the broader utilization of HSCT. Without HSCT, the EFS and likely OS will not surpass 50%, irrespective of the frontline chemotherapy employed [10].

The intensity of the treatment utilized to attain and maintain remission, including HSCT in first or subsequent remission have raised concerns about acute and long-term side effects. It is estimated that over 30-40% of children with AML die from refractory disease/relapse or treatment-related toxicity 11. Recent studies have shown that the use of low-intensity induction schemes can result in long-term remissions with less treatment-related toxicity, but with relapses associated with the selection of treatment-resistant clones [12, 13].

Central nervous system (CNS) therapy is a critical component in many therapeutic protocols because CNS relapse is relatively common in pediatric AML 14. Intrathecal chemotherapy without cranial radiotherapy has been used 5-7. Systemic minimal-myelossuppressive maintenance therapy was routinely used in several protocols but because of the lack of benefits, most modern treatment protocols do not prescribe maintenance regimens [7, 11].

High rates of toxicity and death have been observed in the induction of AML in Brazil with the use of conventional international protocols. Strategies to reduce the intensity of the regimens used in induction to decrease early treatment-related mortality might be an option for countries with limited resources. A study group, within the Brazilian Society of Pediatric Oncology (SOBOPE), denominated Childhood Acute Myeloid Leukemia Study Group (GELMAI), aims to start a dialog among pediatric oncologists of Brazilian institutions treating children and adolescents with AML and elaborate a uniform treatment protocol adapted to the local resources. The strategy is to administer a minimally myelosuppressive regimen for the first induction remission and risk-adapted therapy for the subsequent courses. The main goal is to avoid early treatment-related mortality. To initiate this effort, we developed a questionnaire directed to pediatric oncologists treating children and adolescents in institutions in different Brazilian regions. In this study, we report an analysis of surveyed data provided by treating physicians on pediatric AML in Brazil.

METHODS

Study design

This is a transversal quantitative and descriptive study conducted in Brazil between 1st and 30th of May 2020 with pediatric oncologists associated with SOBOPE (Brazilian Society of Pediatric Oncology), based on the individual perception of the participants, without identifying the respective institutions. A multiple-choice online questionnaire developed by the GELMAI group containing 21 questions was sent by the google forms application to all pediatric oncologists registered with SOBOPE.

Variables included

The variables analysed included information regarding the number of medical doctors and multidisciplinary staff in each team, the number of available beds, the accessibility to exams, the treatment availability including chemotherapy, antibiotics, antifungals, transplantation of hematopoietic stem cells (HSCT), the access to intensive care and other items related to therapy and patient support. Using a dichotomous question, the interest of the medical doctors in participating in the protocol and national study group was consulted.

Statistical analysis

All answers were tabulated in excel format. Descriptive statistical analyzes were used to calculate the absolute and relative values of each variable and graphic analyzes were included. All analysis were performed using Microsoft Excel 2016.

Ethical approval

This study was previously approved by the Ethics Committee (code CAAE: 53705016.7.1001.0097) and the ethical principles were in accordance with Declaration of Helsinki on human subject research.

RESULTS

The Brazilian Society of Pediatric Oncology (SOBOPE) have 272 registered medical doctors who received the questionnaire. From this cohort, 104 (38.2%) agreed to participate in this research. All regions of Brazil were represented, and the majority of participants (37.5%) were from the southeast region (figure 1).

When questioned about AML pediatric treatment in Brazil, 97 (93.3%) believe that there is a need for a Brazilian treatment protocol for pediatric AML, and 93 (89.4%) expressed interest in participating in the construction/elaboration of new protocols with SOBOPE. The quantification of all answers related to opinions regarding the institution is described in table 1. Institutions conditions are concerned especially related to the absence of HEPA filter in 46 (44.2) cases and the impairment of care by the lack of a multi-professional team in 15 (14.4%) and lack of nursing staff in 18 (17.3%) of participating institutions.

Table 2 describes the quantification of answers about treatment access and quality in pediatric AML care. Service quality is concerned in some of the aspects of patient treatment and care, especially regarding lack of access to blood transfusion for 14 (13.5%) of the participants, delay or absence of blood products during critical periods like holidays in 35 (33.6%) of the cases, rare access to prophylactic antifungals in 15 (14.4%) of the cases and absence of HSCT for 7 (6.7%) of the participating institutions.

Figure 2 represents the exams access for AML diagnosis and disease control and management during treatment regardless of whether they are performed in the service or not (considering access of exams and results in a timely manner as not to compromise patient's treatment). Despite being a developing country, almost half of the participants (47.1%) have access to the necessary exams for appropriated disease management.

Figure 3 depicts the drugs available in the surveyed institutions. Among prophylactic antifungals, the most frequent used was micafungin. The chemotherapic agents most frequently used was idarubicin and between other classes such as cardioprotector was the cardioxane.

Regarding the estimatives of number of AML pediatric patients per year, mortality rate and the treatment expectations (Table 3), it's possible to observe that most participants manifested interest in participating in a cooperative protocol. Furthermore, the estimated number of patients was less than five in 42 (40.4%) of participating institutions and between 6-10 n 39 (37.5%). Finally, the estimated mortality rate due to treatment complications was between 11-30% in 43 (41.3%) of the participating institutions.

DISCUSSION

Brazil is a developing country with about 209 million inhabitants; 56,4% of them residing in the southeast and south, the richest regions of the country. The median family income in Brazil is only up to US$ 330 per month, depending on the region of the country 15. Only 30% of the population have private medical insurance 16 while the remaining individuals depend on governmental resources and structure, and cannot pay for medical care. There is substantial inequality in Brazil and due to informal economic networks, it is hard to generalize information and generates precise outcome data in each area.

Low-income countries such as Brazil will present limitations regarding treatment options and laboratory tests for diagnosis and disease follow-up. For instance, Brazil's public health system (SUS, created in 1988), which attends the majority of Brazilian patients, has a considerable difficulty in sponsoring genetic AML characterization of the diagnosis. Due to the high costs, access to diagnostic tests is limited to conventional karyotype. A few centers have access to a basic panel of molecular tests [17, 18].

The high treatment intensity can partially explain the low rates of long-term survival among pediatric AML in Brazil patients. A study group with participants of different regions utilizing a uniform treatment protocol with predetermined adaptations for each institution has the potential to improve the overall outcome. Understanding the real situation of the treatment of pediatric AML in Brazil will make possible to unify treatment approaches creating chemotherapy and supportive care guidelines, and a forum for ongoing discussion would allow for improved outcome. Mortality rates during induction remission remain high in developing countries but can be reduced by improved supportive care and adapted initial chemotherapy. It is expected that by discussing the case in group and adapting uniform treatment in real time, the early mortality will decrease. A Brazilian study, that involved 1472 children and adolescents, treated for acute lymphoid leukemia, showed an increase in survival among those treated on protocols when compared with those not enrolled on protocols [19].

Another important point is linked to treatment-related cardiotoxicity, which significantly influences over-

all survival and event-free survival, as demonstrated by the Children's Oncology Group in AAML0531 trial 20. Events may be acute during treatment, or late. Cardioprotection measures to mitigate and prevent this expected and unwanted adverse effect, in a socially and economically diverse country such as Brazil, requires a broad strategy that includes a detailed initial assessment of cardiac function, combined with cardioprotective use and continuous cardiac monitoring during and after treatment, in a rational and cost-effective manner [21].

The benefit of allogeneic HSCT as post-remission consolidation treatment in pediatric AML is well-documented in specific risk groups [22]. Pediatric AML in first CR and favorable karyotype may not be benefited from allogeneic HSCT. The indications of allogeneic HSCT in first remission must take into consideration the benefit and toxicity for those patients with an indeterminate prognosis; the objective is to decrease the rate of toxic death by avoiding HSCT in this group because the morbidity and mortality related to the procedure. In cases of definitive poor prognosis, the intention is to perform the HSCT in first remission. Because of the lack of laboratory support and other limitations related to the availability of transplantation in our country, we may not have opportunity to increase the number of HSCT in CR1 as recommended. In the meantime, patients who relapse should be considered for HSCT [23].

Improvements in genetic molecular classification, efforts aiming to improve salvage therapy and increasing access to HSCT will provide a better outcome for all these patients.

CONCLUSION

Our study reveals the challenges of managing pediatric AML in a country with limited resources and wide regional economic and cultural disparity. The understanding of the needs of each of the regions can be addressed by the implementation of uniform guidelines adapted to the current resources of each of the regions. A study group networking collaboratively with pediatric oncologists and hematologists from the diverse regions may bring changes that improve to outcome of Brazilian children with AML.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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TABLE 1 – Quantification of pediatric oncologists opinions regarding institution infrastructure for pediatric AML care

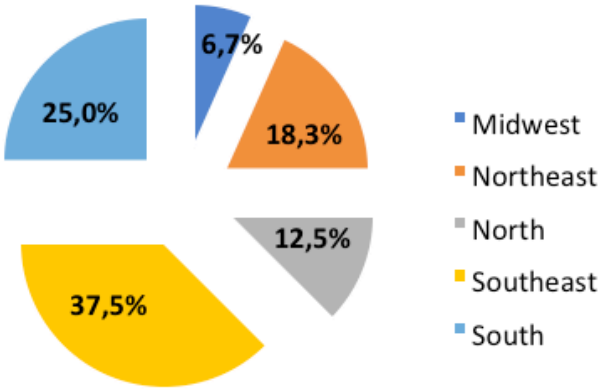
Regarding the number of medical professionals directly involved in leukemia treatments, in your service you consider that:	**N (%)**
The team is adequate for the number of patients	64 (61.5)
The number is reduced, impairing the quality of care (care for children, considering the number of visits)	6 (5.8)
The number is reduced, generating overwork, but without compromising the quality of care	34 (32.7)
Regarding the number of beds for patient care in your ward:	**N (%)**
Care is compromised due to lack of beds in some periods	14 (13.5)
The number of beds is adequate for the demand	49 (38.5)
The number of beds is generally adequate for the demand with periods of higher occupation, without seriously compromising the assistance	41 (39.4)
The AML patient	**N (%)**
Shared bed with HEPA filter	7 (6.7)
Shared bed without HEPA filter	39 (37.5)
It is in an isolated bed with HEPA filter	12 (11.5)
It is in an isolated bed without HEPA filter	46 (44.2)
Regarding access to the ICU	**N (%)**
Eventually there is some difficulty of vacancies, but patients are able to be served more than 90% of the time without clinical damage	46 (44.2)
There is difficulty in access with clinical impairment in up to 25% of the time	7 (6.7)
There is difficulty in access with clinical impairment in more than 50% of the times	2 (1.9)
There is difficulty in access with clinical impairment between 25% and 50% of the time	2 (1.9)
Whenever necessary, we have a place in the ICU	47 (45.2)
Regarding the nursing team	**N (%)**
The nursing team is adequate at the Hospital	40 (38.5)
Eventually there is a lack of professionals, but without serious damage to assistance	44 (42.3)
The nursing staff is deficient in relation to the number of patients frequently, impairing care	18 (17.3)
I prefer not to comment	2 (1.9)
Multiprofessional Team (except nursing)	**N (%)**
The multidisciplinary team is adequate at the Hospital	44 (42.3)
The team at the Hospital is not complete, but the support institution helps us, maintaining adequate care	24 (23.1)
Eventually there is a lack of professionals, but without serious damage to assistance	21 (20.2)
Professionals are often lacking, impairing care	15 (14.4)
Support house (suitable or not)	**N (%)**
The house sometimes lacks beds	19 (18.3)
The house often lacks beds	5 (4.8)
The house has beds available with ease	66 (63.5)
We don't have or have a lot of difficulty with support house beds	9 (8.6)
I prefer not to comment	5 (4.8)

TABLE 2 - Quantification of answers about treatment access and quality in pediatric AML care in Brazil

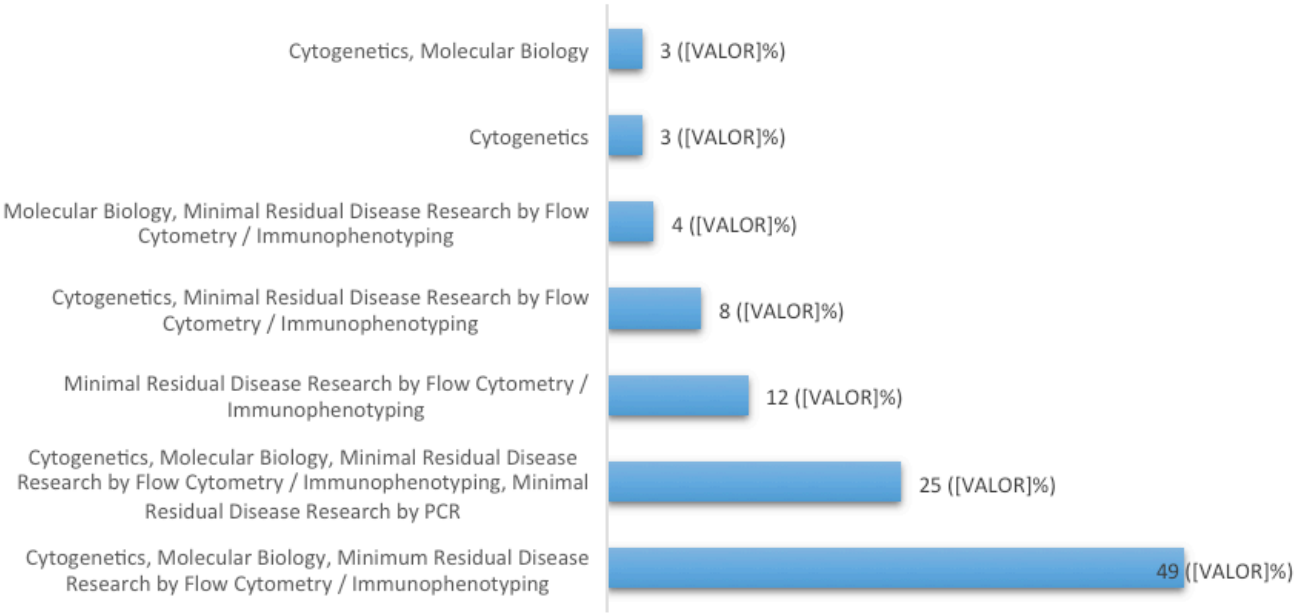
Regarding venous access, you consider that in your service	**N (%)**
Most or almost all patients who need catheter access are able to place it in a timely manner	73 (70.2)
Some patients are able to place the catheter at the correct time, but others cannot	26 (25.0)
My patients have difficulty placing a catheter	5 (4.8)
Regarding the procedures (collection of CSF / Intrathecal / Myelogram)	**N (%)**
Most procedures are performed at the time and under the conditions that I consider appropriate	34 (32.7)
I can do them in the time and under the conditions I consider appropriate	70 (67.3)
Regarding blood transfusion	**N (%)**
I do not have access to irradiated and leukocyte-depleted blood components if necessary	14 (13.5)
I prefer not to comment	1 (1.0)
I have access to irradiated and leukocyte-depleted blood components if necessary	61 (58.6)
I have partial access to irradiated and leukocyte-depleted blood components if necessary	28 (26.9)
Your blood bank or transfusion agency	**N (%)**
Meets needs almost always with rare delays or missing components	64 (61.5)
Delays frequently or we lack blood components frequently up to 50% of the time	5 (4.8)
Has occasional delays or absences, particularly during critical periods such as extended holidays	35 (33.6)
Do you think you have access to the prophylactic antifungals that you would like to use to treat AML	**N (%)**
Eventually, but the administration or Infection Control Service makes it difficult to use	8 (7.7)
I prefer not to comment	5 (4.8)
Rarely	15 (14.4)
Yes	45 (43.3)
Yes, but the Infection Control service or administration makes it difficult to use	31 (29.8)
Regarding Bone Marrow Transplantation	**N (%)**
More than 50% of patients are affected by delays	4 (3.8)
We don't have access	7 (6.7)
I prefer not to comment	4 (3.8)
We have access at the Hospital or partner hospital and the same is done with delays affecting between 25% and 50% of patients in the queue	11 (10.6)
We have access at the Hospital or partner hospital and the same is done with delays affecting at least 25% of patients in the queue	24 (23.1)
We have access at the Hospital or partner hospital and the same is done with small delays	40 (38.5)
We have access at the Hospital or partner hospital and the same is done without delays	14 (13.5)

TABLE 3 – Estimatives and expectations of pediatric AML treatment protocol and outcomes for medical doctors of Brazilian institutions.

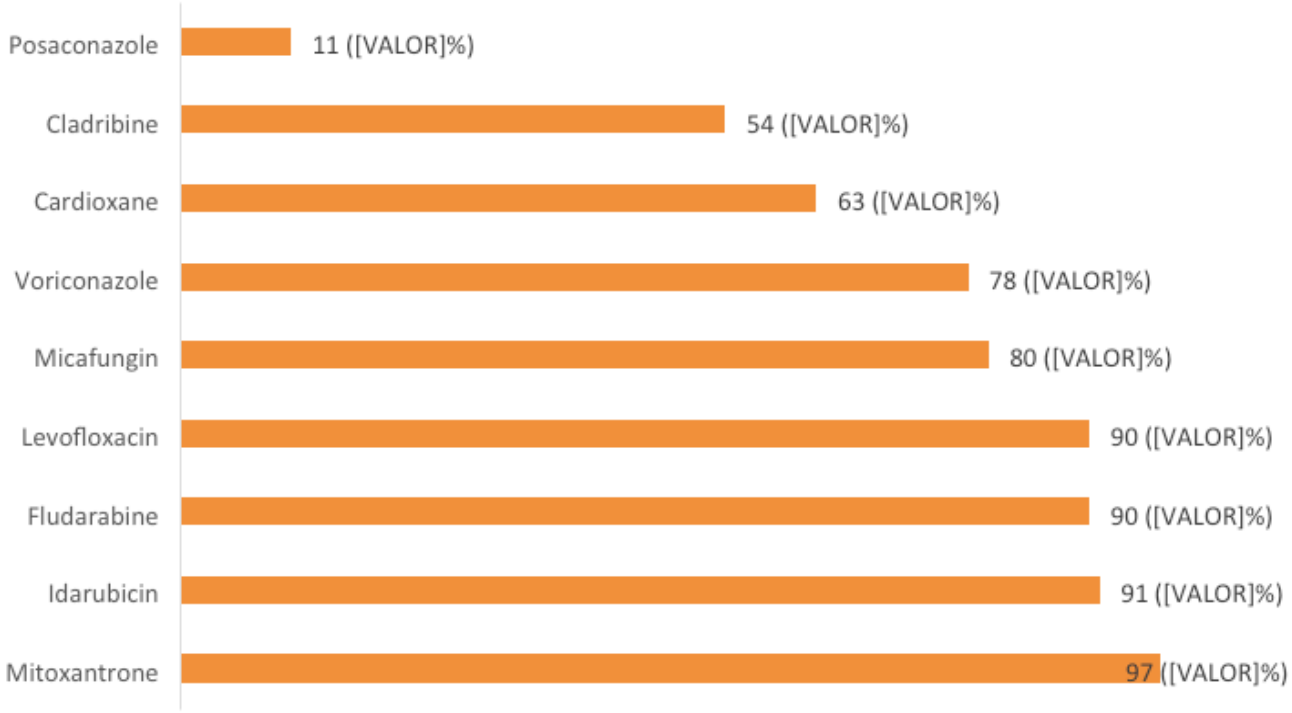
Regarding to the treatment of pediatric AML (except M3 and Down syndrome), you:	**N (%)**
Would you be willing to participate in a cooperative protocol	73 (70.2)
Will continue the local protocol or already participate in another group	1 (1.0)
Participate depending on the type of protocol proposed	29 (27.9)
Prefer to have only a treatment guide made	1 (1.0)
What number of pediatric AML patients does the service serve per year?	**N (%)**
16-20	7 (6.7)
More than 26	1 (1.0)
Less than 5	42 (40.4)
I don't know	3 (2.9)
11-15	12 (11.5)
6-10	39 (37.5)
In your experience, what has been the mortality rate due to treatment complications?	**N (%)**
11-20%	23 (22.1)
21-30%	20 (19.2)
31-40%	11 (10.6)
41-50%	11 (10.6)
5-10%	17 (16.3)
Above 51%	9 (8.6)
I don't know	13 (12.5)



GRAPHIC 1 – Institutions participating in the study according to the region of Brazil



GRAPHIC 2 – Number of Brazilian institutions that have access to the specialty tests regardless of whether they are performed locally.



GRAPHIC 3 - Treatment availability in the Brazilian surveyed institutions.