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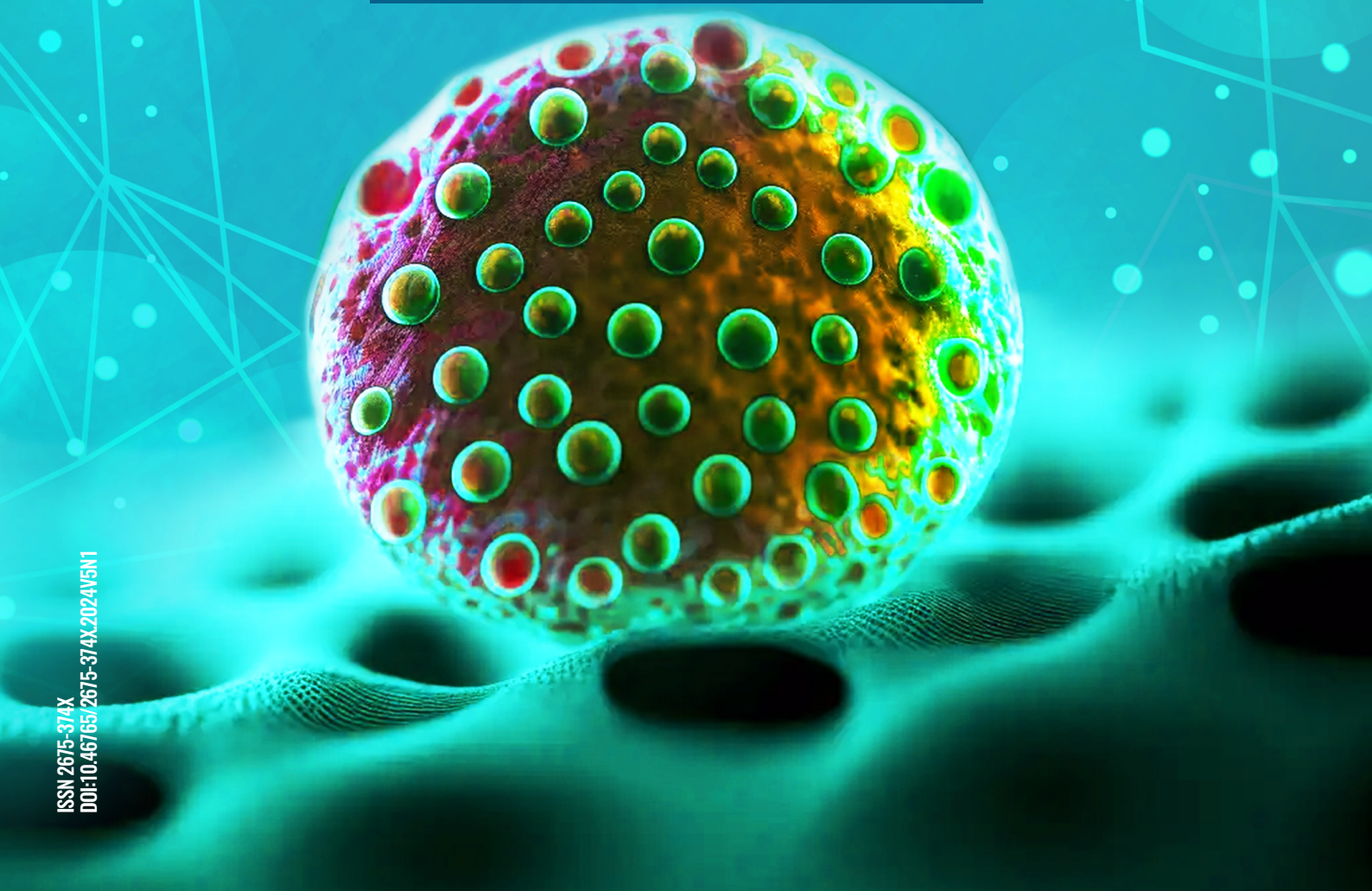

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EDITORS-IN-CHIEF
Fernando Barroso Duarte and Nelson Hamerschlak

MANAGING EDITOR
Romélia Pinheiro Gonçalves Lemes

E-MAIL
journalbmtct@sbtmo.org.br

WEBSITE
www.jbmtct.com.br

ADDRESS
Rua Haddock Lobo 72, sala 407
Estácio – Rio de Janeiro
Zip Code: 20260-132
Phone: +55 21 2273-8390

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The cover of this edition features an illustration of a stem cell, created using generative artificial intelligence.

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Dear transplant colleagues

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

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

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

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

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

Fernando Barroso Duarte *Nelson Hamerschlak*

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EDITORIAL

NATURAL AND ARTIFICIAL INTELLIGENCE IN BONE MARROW TRANSPLANTATION AND CELL THERAPY

Fernando Barroso Duarte*
Nelson Hamerschlak**

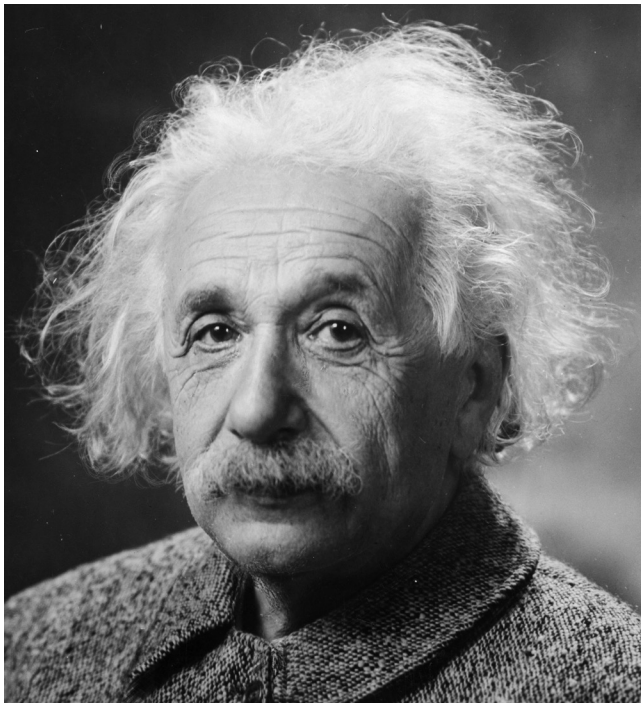
** President of SBTMO*
***Past president of SBTMO*

"The human spirit must prevail over technology"
Albert Einstein

Much has been said about the importance of artificial intelligence (AI) in our lives. What seemed to be the future is already present in our daily lives. Discussions on the subject permeate forums in all areas such as administration, IT, mathematics, law, engineering, science in general and as far as medicine and hematology are concerned.

We can divide AI into subsections: statistical models, machine learning (ML), simulation, and deep learning. In HCT, the most important utility of this is the ability to predict outcomes and better select donors, estimating the possibility of relapse, which is the main cause overall. Unfortunately, in Brazil, we must consider infection as the leading cause of death within 100 days post-HCT[1].

Another important concept that has emerged recently is Explainable Artificial Intelligence (XAI): a framework and tools to reveal predictions. All these tools together could improve the quality of patient care. This tool is especially important in predicting the efficacy of HCT in children, and we could use a dataset of statistical analysis using the "jamoving" application. ML to predict the efficacy of HCT in adult and pediatric patients and early death post-HCT. In the era of precision and personalized medicine, the use of AI methods, clinical support tools can improve patient care in complex clinical situations such as pediatric HCT. Donor and recipient age are crucial in HCT. The best chance of success is when the donor's age is between 18 and 35 years old, with 95% accuracy after using a chi-square test for feature selection. Optimization of Harris Hank appears to be the best technique. Additionally, four XAI techniques: SHAP, LIME, Qlattice, and Eli5, were used to make the models more accurate and interpretable. According to them, the most important parameters were relapse, donor age, recipient age, platelet recovery time, and presence of lymphoma[1].

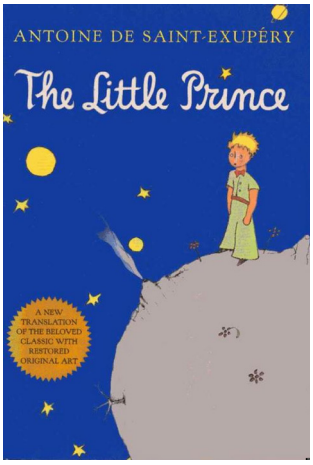


Albert Einstein, *German: (14 March 1879 – 18 April 1955) was a German-born theoretical physicist who is widely held to be one of the greatest and most influential scientists of all time. Best known for developing the theory of relativity,*

The concept of accumulating information to help solve and prevent complex problems is also part of the so-called natural intelligence (NI). It is common to discuss that older professionals are more experienced, perhaps due to the accumulation of important information in their memory that can eventually help resolve difficult situations. Often in discussions of clinical cases among health professionals, we ob-

serve examples of cases and situations experienced in the past resolving today's complex patients. On the other hand, we also witness the natural intelligence among some very gifted young professionals capable of not only citing articles they have read, but also the author, institution, scientific journal and, it would not be absurd, the publication page[2].

Artificial Intelligence (AI) has been developed for many years. Alan Turing wrote an incredible article in 1950 "Computing Machinery and Intelligency"[3]. AI is the ability of technological solutions to simulate human intelligence, carrying out certain activities autonomously and learning for themselves, thanks to the processing of a large volume of data they receive from their users.



- **Brave New World** *is a dystopian novel by English author Aldous Huxley, written in 1931 and published in 1932.[2] Largely set in a futuristic World State.*

- **The Little Prince** *is a novella written and illustrated by French writer, and military pilot, Antoine de Saint-Exupéry.*

In our opinion, natural and artificial intelligence are complementary and each benefits from the other. They are not competitive and artificial intelligence should not be frightening. It's here to stay. It's up to us to know how to make the most of it. In our area of Hematology, bone marrow transplantation and cell therapy, important resources and tools have already emerged that will certainly benefit our patients.

It is almost impossible for all of us health professionals to accumulate the scientific information published on a daily basis, medication leaflets, important lectures, data accumulated in patient records and decision support tools.

In the past, when the first computer resources appeared, one of the most heard phrases was "a good doctor is no longer the one who accumulates information, but the one who knows how to search for it". Today with artificial intelligence this has become easier[4].

One of the most interesting examples, for those who don't know, is "Isabel Active Intelligence". (www.isabelhealthcare.com). We learned from our teachers that one of the most assertive ways to correctly diagnose oneself is through the consideration of differential diagnoses. Well, this tool allows the professional to list, in order of probability, differential diagnoses from the most common to the rarest, based on signs, symptoms, laboratory and imaging test results. We also have other examples, such as image analysis through visual systems that help identify tumors and cell images for hematological diagnosis, among other applications.

Decision support tools and therapeutic guidance for diseases and treatment complications based on information from medical records, literature and genetic and environmental factors should also be mentioned. We know that people of different races can respond differently to the same treatments. How can we accumulate this information and properly treat our patients without assistance tools? All this without mentioning the increasing advent of robots that can assist in the handling of exams, diseases and patients[4,5].

Today tools sometimes contained in your smartphone can monitor patients remotely. Recently, we were introduced to one that monitors signs of cytokine release syndrome after cell therapy in outpatient treatment or even after discharge, such as temperature, blood pressure and oxygenation measurements, sending information to the medical team. Monitoring of this type is already widely used in geriatrics and cardiology with measurements of heart rate and rhythm [4].

In hematopoietic stem cell transplantation and cell therapy, numerous publications and initiatives have been taken. We highlight the so-called precision medicine defined as an emerging approach to the treatment and prevention of diseases that takes into account the individual variability in genes, environment and lifestyle of each person that influences several steps of the transplant from the selection of patients and donor, type of conditioning regimen, prevention and treatment of GVHD, VOD and infections. In this sense, artificial intelligence and "machine learning" initiatives permeate our day-to-day activities, helping us make decisions. Predictive models of death, viral infections, graft-versus-host disease and other complications as well as relapses are being widely used [6,7,8,9].

Fernando Pessoa *(13 June 1888 – 30 November 1935) was a Portuguese poet, writer, literary critic, translator, publisher, and philosopher, described as one of the most significant literary figures of the 20th century and one of the greatest poets in the Portuguese language.*

Charles Spencer Chaplin *(16 April 1889 – 25 December 1977) was an English comic actor, filmmaker, and composer who rose to fame in the era of silent film. He became a worldwide icon through his screen persona, the Tramp, and is considered one of the film industry's most important figures.*

In recent decades, humans have learned that emotional intelligence (EI) is crucial. We have seen psychologists, doctors, and the media all echoing the same truth: "This person is brilliant, but lacks EI, and that is the problem." At the same time, technological growth has been exponential, leading to innovations like electric cars, cloud-based information, numerous actions directly on smartphones, robotic surgeons, and precision medicine. Some actions are faster and more precise than humans can achieve.

We have many options and solutions, and perhaps we can do anything we set our minds to. However, all these possibilities bring the challenge of understanding where exactly humans and machines stand. It's impossible not to think of Charles Chaplin in "Modern Times," Aldous Huxley's "Brave New World," George Orwell's "1984," and even Antoine de Saint-Exupéry's "The Little Prince." We should value a quote from this classic of literature: "You can only understand the world after you have experienced it," or from the master of Portuguese literature, Fernando Pessoa, who said in "The Book of Disquiet" that "we cannot eat a piece of cake without losing it."

This is why we must improve our accessibility to everything that can make life better, such as AI. However, we must not forget that EI and the need to feel the wind on our faces or see the sun after the storm are essential. Nothing can separate us from our soul and breath.

Finally, but not exhausting the subject, instruments for patient education and real-time assistance have been developed. It's an incredible world and we, healthcare professionals, have to know how to make the most of this moment. This is not a competition between our practice and artificial intelligence. We will not be efficient if we do not know how to take advantage of it. To paraphrase Albert Einstein, "no matter how much technology advances, the human spirit will prevail"

PS. This text in Nelson Hamersclak part was originally written in Portuguese. It was translated into English by AI and then corrected by NI.

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ORIGINAL ARTICLE

MODELS OF HLA-DPB1 PERMISSIVENESS AND UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION

Nágila Taline Brotto[1, 2*]
Carmem Bonfim[2, #]
Alberto Cardoso Martins Lima[3, #]

1- Multiprofessional Residency Program in Hematology/Oncology – Complexo Hospital de Clínicas, Federal University of Paraná, Curitiba, PR, Brazil

2 - Instituto de Pesquisa Pelé Pequeno Príncipe, Faculdades Pequeno Príncipe, Curitiba, PR, Brazil

3 - Histocompatibility Laboratory – Complexo Hospital de Clínicas, Federal University of Paraná, Curitiba, PR, Brazil

**Current affiliation*

#Contributed equally as co-senior authors

Corresponding author: Alberto Cardoso Martins Lima, Ph.D. (E-mail: acml@ufpr.br)

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ABSTRACT

In current allo-HCT practice, a fully HLA-matched sibling donor is the best donor associated with improved transplant outcomes. When a matched sibling donor is unavailable, the second best available donor option is a matched unrelated donor (MUD), either HLA 8/8 or HLA 10/10. One notable characteristic in the MUD setting is that HLA-DPB1 mismatches are present in around 80/85% of unrelated donor/recipient pairs. This unique feature has an additional layer of complexity as these HLA-DPB1 incompatibilities may be further divided into permissive and non-permissive mismatches by two biological-driven permissiveness models, namely T-cell epitope (TCE) and DP expression. In the current review article, we described the basics of T-cell allorecognition, the unique HLA-DPB1 immunogenetics, the early conflicting results regarding HLA-DPB1 mismatching in allo-HCT, the development and the clinical impact of T-cell epitope and Expression models, the new indirect allorecognition algorithm of HLA-DPB1 permissiveness (PIRCHE model), the role of HLA-DPB1 in nonmalignant disease setting, and future perspectives on HLA-DPB1 permissiveness.

Keywords: HLA-DP beta-Chains. Hematopoietic Stem Cell Transplantation. Unrelated Donors.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a highly complex curative treatment for patients with malignant and nonmalignant diseases[1,2]. While several patient, donor, and transplant characteristics influence the HCT prognosis, the Human Leukocyte Antigen (HLA) genetic disparity between patient/donor pairs is a critical factor affecting HCT outcomes[3]. The HLA gene complex is highly polymorphic and located in the short arm of chromosome 6. It contains several genes with immunological functions, and the classical histocompatibility genes include HLA-A, -B, and -C in class I and HLA-DRB1, -DQB1, and -DPB1 in class II[4].

A major immunological feature of HSCT is the potent allorecognition of HLA mismatched proteins via T-cell receptors. Allorecognition occurs when T cells from one individual recognize and react to foreign HLA molecules from another individual[5]. This vigorous alloimmune response occurs bidirectionally in Host-versus-Graft (HvG) and Graft-versus-Host (GvH) directions[6]. In the HvG allorecognition, the

patient T-cell recognizes HLA-mismatched proteins expressed in donor cells. In turn, the donor T-cell recognizes HLA mismatches in the patient's cells in the GvH direction. Moreover, T-cell allorecognition may occur from three distinct pathways: direct, indirect, and semi-direct[5]. In direct T-cell allorecognition, T-cells recognize an intact allogeneic HLA molecule expressed by a distinct individual (Figure 1A). Indirect allorecognition occurs when T-cells recognize a self-HLA molecule presenting an allogeneic peptide derived from the foreign HLA molecule (Figure 1B). The semi-direct pathway has been described in solid organ transplantation but has not been investigated in the allo-HCT[5].

In the allo-HCT context, HvG and GvH alloreactivities lead to immune graft rejection and acute and chronic graft-versus-host disease (GVHD) [6]. The GvH alloreactivity may also be beneficial by mediating relapse control via the graft-versus-leukemia (GvL) effect[7]. Therefore, to minimize the deleterious T-cell allorecognition following allo-HCT, the best donor option is a 12/12 HLA-matched sibling[8]; however, depending on the patient's age and ethnicity, a fully matched sibling is available for only 13% to 51% of patients[9]. For the remaining patients, the second-best option is an 8/8 matched unrelated donor (MUD)[10]. However, selecting the best MUD can be challenging, as it is influenced by the unique characteristics of HLA-DPB1 immunogenetics[11].

HLA-DPB1 IMMUNOGENETICS

HLA-DPB1 is a classical transplantation antigen capable of eliciting GVH allorecognition[12]. Due to its unique exon 2 polymorphism, with six hypervariable regions (A, B, C, D, E, and F) and differential expression in 3-untranslated region (rs9277534 marker), the HLA-DPB1 locus presents distinct immunogenetic features compared to other classical histocompatibility genes[13,14].

The HLA-DPB1 gene is located 400 Mb away from the HLA-DRB1/DQB1 genes and is separated by a recombination hotspot[15]. This results in a significant variation in the HLA-DPB1 locus, leading to extensive mismatching in 80-85% of MUD[16,17] and 5-10% of HLA-matched siblings[18-20]. Moreover, the HLA-DPB1 antigens exhibit differential expression levels based on the single nucleotide polymorphism rs9277534 (G/A) in the 3' untranslated region[14]. Previous studies have demonstrated that HLA-DPB1 antigens associated with the rs9277534G variant have higher surface expression than those associated with the rs9277534A variant (Figure 2). Low-expression *HLA-DPB1* alleles include **02:01, *02:02, *04:01, *04:02, *17:01, 23:01, 24:01, 30:01, 31:01, 39:01, 40:01, 41:01*, while high-expression *HLA-DPB1* alleles *include *01:01, *03:01, *05:01, *06:01, *09:01, *10:01, *11:01, *13:01, *14:01, *15:01, *16:01, *18:01, *19:01*, and **20:01* [21].

Importantly, the two validated models of HLA-DPB1 permissiveness, T-cell epitope (TCE)[16] and HLA-DP expression[22], have been translated into clinical practice based on HLA-DPB1's exon 2 polymorphism and rs9277534G/A expression marker, respectively.

"EARLY ERA" OF HLA-DPB1 MISMATCHING

The impact of HLA-DPB1 mismatching was also assessed in the early era of bone marrow transplantation, showing controversial results. In 1993, Petersdorf et al. evaluated 129 patients who underwent bone marrow transplantation from 10/10 MUD and found no association between HLA-DPB1 mismatching and acute GVHD[23]. In a follow-up study, the Seattle group reassessed the role of HLA-DPB1 mismatching in a cohort of 205 patients receiving 10/10 MUD allo-HCT. Compared to the HLA-DPB1 match group, only two HLA-DPB1 mismatches were associated with increased odds of grade III/IV acute GVHD[24]. In this cohort, the survival was similar among the groups with and without HLA-DPB1 mismatches[24].

In 2002, a French group studied the impact of DP incompatibilities in 57 unrelated donor/recipient pairs matched for HLA-A, B, C, DRB1, DQB1, and DRB3/4/5. It was observed that two HLA-DPB1 mismatches were significantly severe acute GVHD and poor survival[25]. In 2003, the Anthony Nolan group studied 143 patients who underwent T-cell depleted 10/10 MUD allo-HCT. This study showed that the absence of DPB1 mismatches led to a lower risk of acute GVHD, albeit with a higher relapse risk[26]. In a subsequent study, the same group confirmed these findings with a larger group of 423 patients undergoing T-cell depleted allo-HCT with 10/10 MUD, demonstrating that HLA-DPB1 matching was significantly associated with an increased risk of disease relapse[27].

A multicenter study from the International Histocompatibility Working Group with 5929 recipient/MUD pairs who underwent allo-HCT between 1984 and 2005 revealed that HLA-DPB1 mismatching increased the risk of GVHD but decreased the risk of relapse without affecting overall survival[17]. The multicenter study by Lee et al., which included 3857 MUD transplants, also found no association between HLA-DPB1 mismatching and decreased overall survival[28]. Therefore, the National Marrow Donor Program (NMDP) guideline for unrelated donor selection pub-

lished in 2008 did not include HLA-DPB1 matching as a selection criterion due to the lack of association between HLA-DPB1 disparities and poorer survival[29].

As most HLA-8/8 or HLA-10/10 MUD have HLA-DPB1 mismatches[16,17], there was a need to distinguish clinically tolerable HLA-DP incompatibilities (permissive mismatches) from those associated with poorer outcomes (non-permissive mismatches). As novel evidence highlighting how the unique HLA-DPB1 immunogenetics differentially impact allo-HCT became available, it has led to the development of two biological-driven permissiveness models, namely TCE[16] and Expression[22], and the translation of these models into the clinical MUD allo-HCT practice[30]. Notably, these "intelligent" HLA-DP mismatch permissive algorithms provided a new reassessment of the role of HLA-DPB1 mismatching in allo-HCT with unrelated donors.

TCE PERMISSIVENESS MODEL

In 2001, Fleischhauer et al. reported a case of allograft rejection in a patient with chronic myeloid leukemia[31]. The patient received a transplant from a donor who was 10/10 matched, with only one HLA-DPB1*09:01 mismatch in the HvG direction. Remarkably, it was found that HLA-DPB1*0901–specific CD4+ T-cell clones with cytotoxic activity were present during the onset of graft rejection[31].

A milestone study led by Zino et al. has classified HLA-DPB1 alleles into three distinct immunogenicity groups based on the T-cell epitope reactivity patterns of two alloreactive HLA-DPB1*0901-specific T-cell clones[32]. The three HLA-DPB1 allele groups were divided in high immunogenicity (TCE1: HLA-DPB1*0901, *1001, *1701), intermediate immunogenicity (TCE2: HLA-DPB1 *0301, *1401, *4501) and low immunogenicity (TCE3: most other HLA-DPB1 alleles)[32]. Furthermore, the authors developed an algorithm for HLA-DPB1 mismatch permissiveness based on direct T-cell allorecognition. In this model, HLA-DPB1 mismatches are classified as permissive if they share the same immunogenicity group. Conversely, if the HLA-DPB1 mismatches have different immunogenicity groups, they are classified as non-permissive. Nonpermissive mismatches are further categorized as GvH or HvG, depending on whether the patient or the donor has the higher immunogenicity TCE group. Indeed, a retrospective evaluation of 118 MUD transplants revealed that the predicted nonpermissive HLA-DPB1 mismatches were significantly related to increased risks of grade II to IV acute GVHD and transplantation-related mortality[32]. In an Italian Registry study with 621 adult patients who received unrelated allo-HCT, Crocchiolo et al. proposed a new TCE model, considering the HLA-DPB1*02:01 as a separate immunogenicity group[33]. The TCE4 model also revealed that there was an association between nonpermissive HLA-DP mismatching and a higher risk of nonrelapse mortality as well as inferior overall survival[33].

Under the auspices of the International Histocompatibility Working Group in HCT, Fleischhauer et al. led a validation of the TCE model in a cohort of 5428 HLA 10/10 MUD transplants[16]. In the 10/10 setting, the study revealed that nonpermissive mismatches were associated with a higher incidence of severe aGvHD, increased non-relapse mortality, and inferior overall mortality when compared with permissive mismatches[16]. In a multicenter study conducted by the NMDP, Pidala et al. aimed to validate the TCE model in an independent cohort of 4710 HLA 8/8 matched cases. The study confirmed that nonpermissive HLA-DPB1 allele mismatch was associated with poorer survival outcomes than permissive HLA-DPB1 mismatches[34].

Although the clinical impact of TCE permissiveness was validated, only 72 HLA-DPB1 alleles had a defined TCE group, limiting the early practical application of this algorithm. Thus, Crivello et al. developed a “functional distance” score based on site-directed mutagenesis and its impact on T cell alloreactivity to overcome this limitation[35]. It was shown that “functional distance” scores ≤0.59, 0.6-1.99, and ≥2 were highly correlated with TCE groups 1, 2, and 3, respectively[35]. With this new approach, all HLA-DPB1 alleles can now be readily classified into the three TCE groups. Later, Arrieta-Bolaños et al. carried out a validation study of the "functional distance" TCE groups in a multicenter study with 2730 patients with malignancies[36]. Similar to the previous TCE version, they observed that nonpermissive HLA-DPB1 mismatches were significantly associated with poorer overall survival, increased transplant-related mortality, and higher incidence of acute and chronic GVHD[36].

A recent study by the Center for International Blood and Marrow Transplant Research, conducted by Arrieta-Bolaños et al., divided a cohort of 2216 TCE3 permissive mismatches into two sub-groups: 930 "core" (DPB1*02:01, 04:01, 04:02, and 23:01) and 1286 "non-core" (other TCE3 alleles)[37]. The study aimed to test the hypothesis that TCE3 DPB1 alleles with immunopeptidome overlap would be less immunogenic. The study found that "core" permissive mismatches had significantly lower grade II-IV acute GVHD and transplant-related mortality when compared to nonpermissive mismatches. In contrast, "non-core"

permissive mismatches had similar outcomes than nonpermissive mismatches[37].

HLA-DP EXPRESSION MODEL

Petersdorf et al. conducted a landmark study assessing the role of *rs9277534* expression marker in 1441 recipients of transplants from HLA-10/10 MUD with only one HLA-DPB1 mismatch[38]. They found that when the donor carried a low-expression HLA-DPB1 mismatch, the risk of grade II-IV acute GVHD was significantly higher in patients with high-expression HLA-DPB1 mismatches compared to those with low-expression HLA-DPB1 mismatches[38].

In 2018, Morishima et al. proposed the DP2/DP5 model, which included 19 common DPB1 alleles found either in the DP2 (rs9277534A) or DP5 (rs9277534G) evolutionary clade in the Japanese population[39]. This study revealed that grade 2-4 aGVHD risks were significantly higher in the DP5 (high expression) group than in the DP2 (low expression) group. It was also observed that within the TCE permissive mismatch group, DP5 (high expression) patients had an increasing incidence of acute GVHD when compared to the DP2 (low expression) recipients[39]. Later, Lorentino et al. replicated and validated the association of rs9277534A/G expression and DP2/DP5 models with higher risks of acute GVHD in 422 Italian patients with malignancies who had undergone MUD allo-HCT[40].

More recently, an International Histocompatibility Working Group in HCT study led by Petersdorf et al. aimed to confirm the impact of the expression model in acute GVHD in an independent cohort of 11318 HLA-10/10 unrelated donor/recipient pairs[22]. Among these pairs, 2047 were HLA-12/12, 5880 had one HLA-DPB1 mismatch (HLA-11/12), and 3391 had two HLA-DPB1 mismatches (HLA-10/12). As previously shown in other studies, patients with high-expression HLA-DPB1 mismatches had a significantly increased risk of grades II to IV and severe acute GVHD compared to those with low-expression HLA-DP mismatches[22]. This independent finding validated the clinical significance of the expression model in the MUD allo-HCT scenario.

Most recently, Ruggeri et al. hypothesized that a combination of TCE and Expression models, named TCE-permissive and high-expression HLA-DPB1 mismatches (TPHE), could act synergically to improve allo-HCT outcomes[41]. This contemporary registry study, which included 6627 8/8 MUD/patient pairs, found that TPHE mismatches had better relapse-free survival than non-TPHE mismatches and HLA-DPB1 matches. Further, compared to TPHE, non-TPHE mismatches showed poorer overall survival[41]. These findings suggest that applying the TPHE model could enhance MUD selection, especially for patients with high-risk malignant diseases. In this sense, a public web application called Expression of HLA-DP Assessment Tool (https://dpb1-tce-expression.nmdp.org/) was released to optimize the combined use of TCE and Expression models in unrelated donor selection (Figure 3)[42].

PREDICTED INDIRECTLY RECOGNIZABLE HLA EPITOPES (PIRCHE) MODEL

A new algorithm called Predicted Indirectly Recognizable HLA Epitopes (PIRCHE) has been developed to evaluate HLA permissiveness as an *in silico* measure of indirect alloreactivity[43]. In the 10/10 HLA MUD scenario, the patient's HLA-DP-mismatched peptides are presented by shared HLA-A, -B, and -C (PIRCHE I) or shared HLA-DR and -DQ (PIRCHE II) (Figure 4).

In 2014, Thus et al. performed the first study applying the PIRCHE model in the MUD allo-HCT setting, using a cohort of 88 patients receiving 10/10 unrelated donor allo-HCT[44]. Interestingly, this study found that patients with PIRCHE I or II have a higher risk of developing acute GVHD compared to those without any PIRCHE. In addition, considering only patients with TCE HLA-DPB1 permissive mismatches, it was shown that patients with PIRCHE I had a higher risk of acute GVHD when compared to those with no PIRCHE I. This initial evidence suggested that the PIRCHE model could refine the TCE permissive mismatches[44].

A recent study conducted by Buhler et al. examined the impact of PIRCHE I and II scores in a group of 909 recipient/MUD pairs[45]. The study revealed that GvH PIRCHE I was not associated with any outcomes, while GvH PIRCHE II significantly increased the risks of grade II-IV acute GVHD and lowered the risk of relapse. Thus, the authors suggested that prioritizing HLA-DPB1 mismatches with no PIRCHE II for patients with low relapse burden could help reduce the risks of acute GVHD[45].

Zou et al. investigated the impact of molecular mismatch approaches, including PIRCHE scores, in 1514 patients with malignancies receiving allo-HCT from unrelated donors matched at HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1[46]. The MD Anderson group found that high PIRCHE I and II scores in the GvH direction were significantly associated with an increased risk of grade 2-4 acute GVHD and higher

non-relapse mortality, although with a concomitant reduced risk of disease relapse[46].

Despite promising data, the PIRCHE model has not been included as a formal criterion in current NMDP guidelines for selecting unrelated donors[30].

HLA-DPB1 MISMATCHING AND PERMISSIVENESS IN NONMALIGNANT DISORDERS

The role of HLA-DPB1 mismatching and permissiveness models in MUD allo-HCT for nonmalignant disorders has been poorly reported. Few studies have been conducted in this setting, showing conflicting evidence.

Horan et al. conducted a large retrospective registry study with a cohort of 663 patients with various nonmalignant disorders. The study demonstrated that HLA-DPB1 mismatching did not impact clinical outcomes following MUD transplantation[47]. Similarly, the Japanese Marrow Donor Program evaluated the effect of HLA-DPB1 mismatching in 101 10/10 HLA-matched pairs and 69 9/10 single-allele mismatched pairs in 2011. The study also found that HLA-DPB1 mismatching did not predict any outcome following unrelated donor allo-HCT[48]. However, it's worth noting that TCE permissiveness was not assessed in these two retrospective registry studies[47,48].

In contrast, Fleischhauer et al. evaluated the role of TCE permissiveness in 72 patients with beta-thalassemia major who received 10/10 MUD[49]. The study revealed that TCE non-permissive mismatches in the HvG direction were associated with higher risks of graft rejection and lower thalassemia-free survival[49]. More recently, Lima et al. studied 106 patients who underwent 10/10 MUD allo-HCT with in vivo T-cell depletion for nonmalignant disorders, mainly acquired and inherited bone marrow failure[50]. This single-center study also found that the presence of TCE non-permissive HvG disparities significantly increased the incidence of graft rejection[50]. Furthermore, the impact of HLA-DP expression model on MUD allo-HCT for non-malignant diseases remains unclear .

Thus, further studies are required to confirm the clinical significance of HLA-DPB1 mismatching and TCE/Expression permissiveness after MUD allo-HCT for nonmalignant diseases.

CONCLUSION

In current allo-HCT practice with calcineurin inhibitor-based GVHD prophylaxis, the MUD allo-HCT survival outcomes are similar to those of HLA-matched sibling donors (8). Applying HLA-DPB1 permissive models may greatly enhance MUD selection and improve transplant outcomes, particularly when combined with HLA-A, -B, -C, -DRB1 matching and younger donor age[30].

The "intelligent" use of HLA-DPB1 (mis)matching, based on the patient's unique needs, may provide a tailored-based MUD selection, thereby optimizing allo-HCT results. For instance, if disease relapse is a major concern, as for high-risk Acute Leukemia patients, the MUD search should prioritize TPHE mismatches to increase the likelihood of the GvL effect, thereby improving relapse control and relapse-free survival[41]. In turn, if avoiding acute GVHD is the major goal, as for patients with nonmalignant disorders, the MUD search should first prioritize HLA-DPB1 matching and, when unavailable, a core permissive mismatch[37].

Further investigation is clearly warranted to examine the impact of HLA-DPB1 permissive mismatch models on MUD allo-HCT with innovative GVHD prophylaxis approaches, such as post-transplantation cyclophosphamide and abatacept[51,52].

FIGURE 1: **Pathways of T-cell allorecognition. A Direct allorecognition. B Indirect allorecognition.**

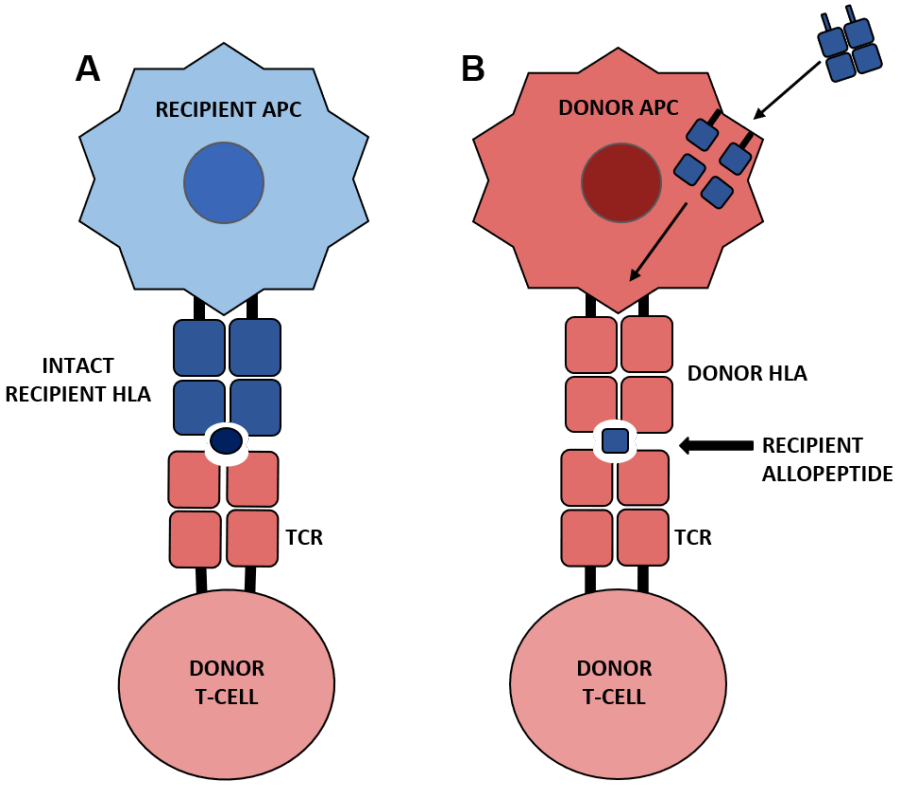


FIGURE 2: **HLA-DPB1 expression variants.**

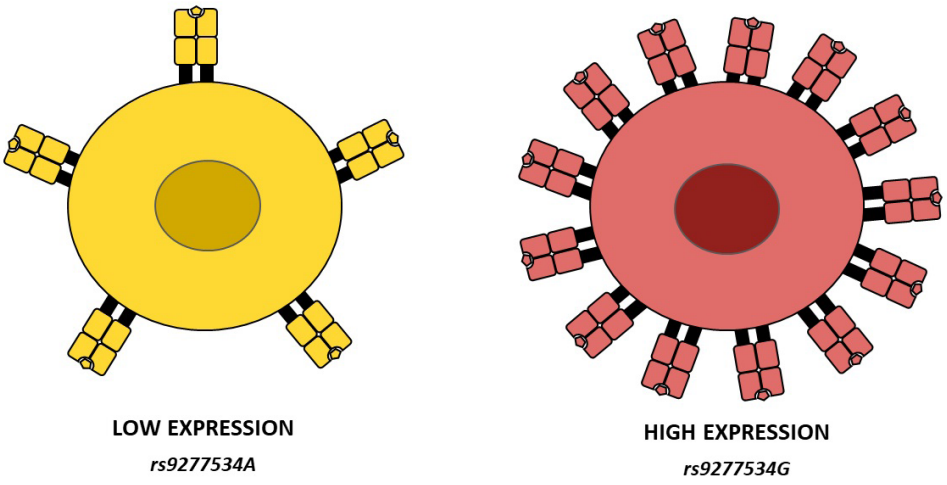


FIGURE 3: **Expression of HLA-DP Assessment Tool (https://dpb1-tce-expression.nmdp.org/).**

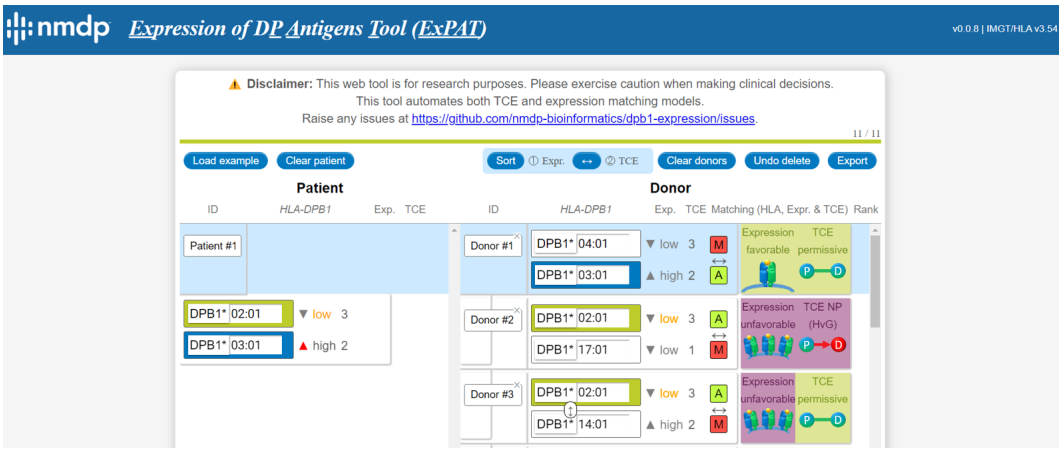
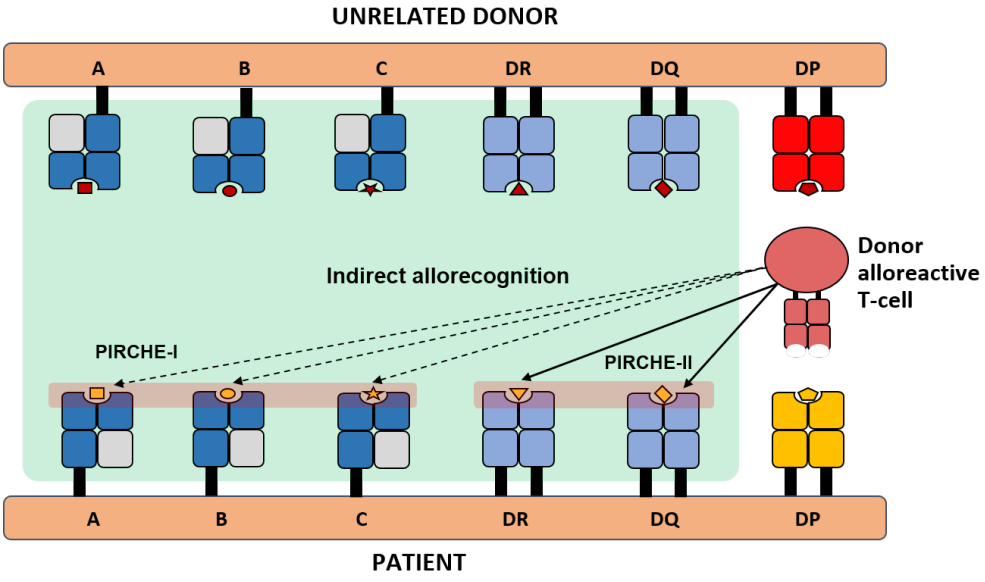


FIGURE 4: **The Predicted Indirect Recognizable Human Leukocyte Antigen (PIRCHE) Algorithm.**



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ORIGINAL ARTICLE

OVERALL SURVIVAL IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH PROTOCOL CALGB 9511 AT A TERTIARY HOSPITAL IN THE NORTHEAST OF BRAZIL

Paulo Henrique Mariano de Alencar[1], Lívia Andrade Gurgel[2], Lara Facundo de Alencar Araripe[1], Hércules Amorim Mota Segundo[1], Ana Vitoria Magalhães Chaves[1], Fernando Barroso Duarte[3]

1 - Hematology and Hemotherapy Program at the Federal University of Ceará (UFC).

2 - Hematology and Hemotherapy Service at Walter Cantídio University Hospital.

3 - Hematology and Bone Marrow Transplant Service at Walter Cantídio University Hospital of UFC.

Corresponding author: Paulo Henrique Mariano de Alencar (E-mail: phm.alencar@gmail.com)

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is the most common neoplasm in childhood and has high survival rates. In adults, due to the biological characteristics of the disease and chemotherapy-related toxicity, survival is lower. CALGB 9511 is a chemotherapy protocol based on pediatric regimens with high remission rates after induction. **Objectives**: To evaluate the survival of patients with ALL undergoing the CALGB 9511 protocol at Walter Cantídio University Hospital (HUWC); to describe the impact of risk factors: presence of measurable residual disease, BCR-ABL fusion gene status, and allogeneic bone marrow transplant (BMT) on the survival of this group. **Methodology**: Retrospective evaluation of medical records of patients with ALL treated with this protocol between 2011 and 2022. Statistical analysis was performed using the Kaplan-Meier method to estimate survival probability. **Results**: 79 patients were eligible; 19% were BCR-ABL positive; the mean 2-year overall survival was 44%; The 2-year survival rate for patients undergoing HSCT was approximately 78%.. **Conclusion**: The survival curves of the study conducted at HUWC are similar to those described in the literature and corroborate the severity of the disease. Accessibility to new therapeutic modalities is a strategy that can improve the survival of these patients.
Keywords: Leukemia. Disease. Drug Therapy.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common hematologic neoplasm in childhood, with an overall five-year survival rate of approximately 90%. Survival in adults is lower due to the biological characteristics of the disease itself and the toxicity of chemotherapy regimens.[1,2,3]

Multiple induction regimens have been developed for the treatment of ALL in adults, many of which are based on pediatric protocols that include the use of corticosteroids, anthracyclines, alkylating agents, asparaginase, and central nervous system prophylaxis.[4,5,6]

Around 80% of patients undergoing intensive induction regimens achieve complete remission, however more than half will experience disease recurrence during or after chemotherapy, leading to reduced overall survival. Risk stratification is essential to define which patients should be referred to a specialized bone marrow transplant center after the first remission.[7]

The CALGB 9511 protocol was developed based on intensive pediatric regimens. This protocol is divided into the phases of Induction, Intensifi-

cation, Central Nervous System Prophylaxis, and Maintenance. The results demonstrated high rates of complete remission after Induction and progression-free survival, especially in younger patients without comorbidities[8].

The treatment of ALL in adults remains challenging, particularly within the public health system. Early access of patients to a specialized oncology-hematology center, with support for possible complications during treatment and adequate infrastructure, are still obstacles to be overcome.

This retrospective study aims to report the outcome of adult patients with ALL treated with the CALGB 9511 protocol at an oncology-hematology center in the state of Ceará.

MATERIALS AND METHODS

Study design and patients

This is a descriptive retrospective observational study aimed at evaluating the group of patients diagnosed with Acute Lymphoblastic Leukemia treated at the Hematology Service of Walter Cantídio University Hospital (HUWC-UFC). Adult patients aged 18 years or older diagnosed with Acute Lymphoblastic Leukemia were evaluated from March 1, 2011, to December 31, 2022. Patients under 18 years of age, diagnosed with biphenotypic acute leukemia or mixed lineage leukemia, and those with a previous diagnosis of Chronic Myeloid Leukemia were excluded from the study.

High-risk criteria were based on the CALGB 8811 protocol. High-risk patients were those with a white blood cell count greater than 30,000/mm^3 for ALL-B and greater than 100,000/mm^3 for T lineage; age greater than 35 years, BCR-ABL positive, and complex karyotype (more than 3 chromosomal alterations).

Indications for allogeneic bone marrow transplantation were high-risk ALL and patients with relapsed ALL.

Disease assessment

The definition of ALL was based on the 2016 WHO classification. Lineage identification was performed through flow cytometry. BCR-ABL analysis was conducted by PCR, and karyotype analysis was performed through classical cytogenetics in Giemsa.

Patients in complete remission after induction had <5% blasts in bone marrow aspirate. Measurable residual disease (MRD) was assessed at the end of induction by flow cytometry in BCR-ABL negative ALL patients and by flow cytometry and PCR in BCR-ABL positive ALL.

Statistics

For descriptive statistics, the mean, median, and standard deviation were calculated for continuous quantitative variables, and relative and absolute frequency were calculated for qualitative variables. Data analysis was performed using the R program. Results with $p < 0.05$ were considered statistically significant. Survival probability estimation was conducted using the Kaplan-Meier method, and a log-rank test was performed to compare the observed differences between the survival curves of the groups.

RESULTS

Between March 2011 and December 2022, a total of 79 patients were eligible (Table 1). The average age at diagnosis was 36 years, with 48.1% (38/79) being female and 51.9% (41/79) being male. Regarding the immunophenotype at diagnosis, 82.3% (65/79) had markers defining them as B-lineage, and 17.7% (14/79) were classified as T-lineage.

As for the mutational status of BCR-ABL, analyzed only in acute lymphoblastic leukemias of B-lineage, 50.6% (40/79) did not have the fusion gene, and 19% (15/79) tested positive for the gene in question. Additionally, 30.4% (24/79) did not undergo mutational status evaluation due to reasons such as early death or unavailability of molecular biology assessment at the time. Of the patients, 69% (55/79) were classified as high-risk ALL, and 30.4% (24/79) as standard-risk.

After the completion of induction chemotherapy, during the follow-up assessment with bone marrow aspiration, 78.5% (62/79) were in remission, and 21.5% (17/79) were refractory or had early death. Among those who achieved remission, 14.8% (9/62) had positive measurable residual disease post-induction, and 41% (25/69) had negative MRD; 10.1% of patients (8/69) had central nervous system infiltration at diagnosis or during the course of treatment.

Of the patients who achieved remission after induction chemotherapy (Table 2), 45.2% (28/62) experienced disease recurrence during treatment (relapse), and 31.6% (27/79) of patients underwent bone marrow transplantation.

Regarding the primary outcome (Table 2), 65.8% (52/79) deceased and 34.2% (27/79) survived. The overall survival at 2 years was 44% (95% CI 0,34 – 0,56), and the median survival was 1.4 years (Figure 1). Progression-free survival at 1 year was 67.3%

(95% CI 0.575 – 0.787) and at 2 years was 40.1% (95% CI 0.302 – 0.532) (Figure 2).

Regarding the secondary outcome, the median survival of patients diagnosed as having the BCR-ABL positive gene showed a survival rate above 75%, while BCR-ABL negative patients had a median survival of 19.9 months (p=0.06) and an overall survival at 2 years of 50% (Figure 3).

The probability of survival at 2 years for patients undergoing allogeneic bone marrow transplant was 78% (95% CI 0.62 – 0.97), while for those who were not transplanted, it was 27,5% (95% CI 0,17 – 0,43) (Figure 3). Regarding the reasons for not undergoing transplantation, 73% of patients were due to treatment refractoriness, 6% due to being classified as standard risk, 4% due to patient's preference, 8% due to lack of a donor, and 9% due to clinical comorbidities contraindicating the procedure.

The presence of measurable residual disease was assessed after 100 days post-transplant, with negative results in 29,6% of patients, positive in 3.7%, inconclusive in 7.4%, not performed due to early post-transplant relapse in 11.1%, and not performed due to unavailability of the test in the facility in 48,2%.

DISCUSSION

Acute lymphoblastic leukemia is the most common cancer in children, with survival rates exceeding 90%. Beyond this age range, adolescents and young adults have poorer outcomes compared to the pediatric population, with a five-year overall survival between 54% and 74%. The use of pediatric protocols has improved survival rates; however, in older adults, outcomes remain discouraging, with cure rates below 20%.This is possibly due to increased therapy-related toxicity, leading to dose reductions and treatment delays. Additionally, adverse genetic risk characteristics are more common in this population, resulting in shorter remissions and frequent relapses.[1,2,3]

The CALGB protocol is based on pediatric regimens and includes high doses of glucocorticoids, asparaginase, and vincristine, along with frequent central nervous system prophylaxis. Conventional protocols for adults use more myelosuppressive drugs, and central nervous system prophylaxis is delayed. When compared to traditional protocols, CALGB shows a median event-free survival of 78.1 months versus 30 months and a three-year overall survival of 73% (95% CI, 68%-78%) in patients under 30 years old.[1,2,3]

In this study, patients diagnosed with ALL and undergoing chemotherapy at a tertiary hospital in Northeast Brazil were evaluated. Regarding the primary outcome, the overall survival at 2 years was 44% with a median survival of 1.4 years. These results confirm the severity of the disease and the more unfavorable prognosis in patients over 50 years old, where overall survival is reduced to less than 25%. The two-year progression-free survival was 40%, which is comparable to other historical cohorts in the literature, confirming that despite high rates of remission post-induction, the incidence of relapse during treatment remains high, leading to a worse prognosis in those patients who relapse.[9,10]

Risk factors such as age, leukocyte count, complex karyotype, and some genetic alterations, such as the BCR-ABL fusion gene status, are known markers of poor prognosis. The Philadelphia chromosome t(9;22) is present in approximately 25 to 30% of ALL cases in adults. Historically associated with adverse prognosis, the development of targeted therapies such as tyrosine kinase inhibitors (TKIs) has resulted in prolonged remissions in young adults and older patients, negating their adverse prognosis.[1,2,3] In this study, the two-year overall survival of BCR-ABL positive ALLs was above 75%, while that of BCR-ABL negative ALLs was below 50%, with a median survival of 19.9 months, corroborating with the most current literature data even when using first-generation tyrosine kinase inhibitors (Imatinib) due to the difficulty of accessing second or third-generation TKIs.

Central nervous system infiltration in ALL is common both at diagnosis and relapse and indicates a worse prognosis. Pediatric protocols tend to perform central nervous system prophylaxis earlier to reduce the incidence of this event, preventing future CNS relapses. Central nervous system prophylaxis in this study was administered to 68.4% of patients, an important step in the treatment course and a pre-transplant strategy due to the unavailability of total body irradiation as pre-HSCT conditioning.

Despite the emergence of new targeted therapies, bispecific antibodies, and CAR-T cells, allogeneic bone marrow transplantation remains an important tool for durable remissions and cure in ALL, especially in a scenario of unavailability of these new therapies within the public healthcare system.

Indications for allogeneic transplantation in first remission vary according to the literature. Measurable Residual Disease positivity is one of the main prognostic markers currently and is the main transplant indicator in first remission. MRD post-induction is

related to long-term survival, and MRD post-consolidation is related to early relapse and chemotherapy refractoriness. At Walter Cantídio University Hospital, the transplant service is linked to the hematology service, allowing for communication and facilitated access to patients who are candidates for transplant in the service.

In this study, the overall survival of patients undergoing HSCT was compared to those who did not undergo this consolidation therapy. Our results showed a survival rate above 75% in the HSCT arm and approximately 25% in those who did not undergo transplantation. This strengthens the need for early referral of patients in first remission for evaluation by the transplant team and the search for alternative donors in the absence of matched donors.

Access to healthcare in the public service in developing countries like Brazil, especially in the Northeast region, is still precarious. Difficulty in obtaining medical care, particularly in rural areas, is still a reality, and many patients receive specialized care late, contributing to delayed diagnosis, early death, and poorer outcomes compared to first-world countries.

The results in this study were comparable to other historical cohorts, confirming the impact of using pediatric protocols on the survival of patients with ALL and better survival after the development of targeted therapies for BCR-ABL positive ALL patients. Allogeneic HSCT is an important consolidation tool, reducing mortality and increasing the chances of cure for these patients.

Despite many advances, such as increased access to measurable residual disease testing, which is a known important prognostic factor, there are still obstacles to be overcome: the difficulty of conducting comprehensive mutational profiling to identify characteristics of higher risk that may predict non-response to induction chemotherapy or early relapse, the availability of hematological beds for adequate treatment, and access to new drugs, especially in the setting of refractory disease.

CONCLUSION

Significant progress has been made in the treatment of ALL. Treatment in the public health system in developing countries remains challenging due to difficulties in accessing specialized services, bed availability, and access to new therapies. The results of this study reinforce the severity of the disease and the need for increased resources that can lead to improved survival in this patient population.

TABLE 1: Baseline characteristics of study patients. (Data expressed as absolute frequency (n) and relative frequency (%) for categorical variables and mean, standard deviation, and range for quantitative variables)

VARIABLES	N(%)
Age	36 ± 15 (33)*
Sex	
Female	38 (48,1%)
Male	41 (51,9%)
Risk Stratification	
High	55 (69,6%)
Standart	24 (30,4%)
Immunophenotype	
B ALL	65 (82,3%)
T ALL	14 (17,7%)
BCR-ABL	
Negative	40 (50,6%)
positive	15 (19%)
Not avaliable	24 (30,4%)
Karyotype	
Complex	10 (12,6%)
Hypoploidy	1 (1,2%)
Hyperploidy	1 (1,2%)
Normal	6 (7,6%)
Not performed	61 (77,2%)
***Mean ± Standard Deviation (Median); n (%); Range**	

TABLE 2: Summary of Primary Outcome (Data presented as absolute frequency (n) and relative frequency (%) for categorical variables)

VARIABLES	N(%)
Remission post-Induction	
Yes	62 (78,5%)
No	17 (21,5%)
MRD post-induction	
Positive	9 (14,5%)
Negative	25 (40,3%)
Not performed	28 (45,2%)
Central Nervous System Prophylaxis	
Yes	54 (68,4%)
No	9 (11,4%)
Not performed due to early demise	16 (20,3%)
Central Nervous System Infiltration	
Yes	8 (10,1%)
No	71 (89,9%)
Relapse	
Yes	28 (45,2%)
No	34 (54,8%)
Bone Marrow Transplant	
Yes	27 (31,6%)
No	14 (20,3%)
Not due to therapeutic refractoriness	38 (48,1%)
MRD D+100	
Inconclusive	2 (7,4%)
Positive	1 (3,7%)
Negative	8 (29,6%)
Not performed due to early demise	3 (11,1%)
Not available	13 (48,2%)
Decease	
Yes	52 (65,8%)
No	27 (34,18%)
Decease post-HSCT	
Yes	10 (37%)
Due to post-HSCT relapse	4/10 (40%)
Infeccion	5/10 (50%)
Other causes	1/10 (10%)
No	17 (63%)

FIGURE 1: **Overall survival at 2 years for patients with ALL undergoing protocol CALGB**

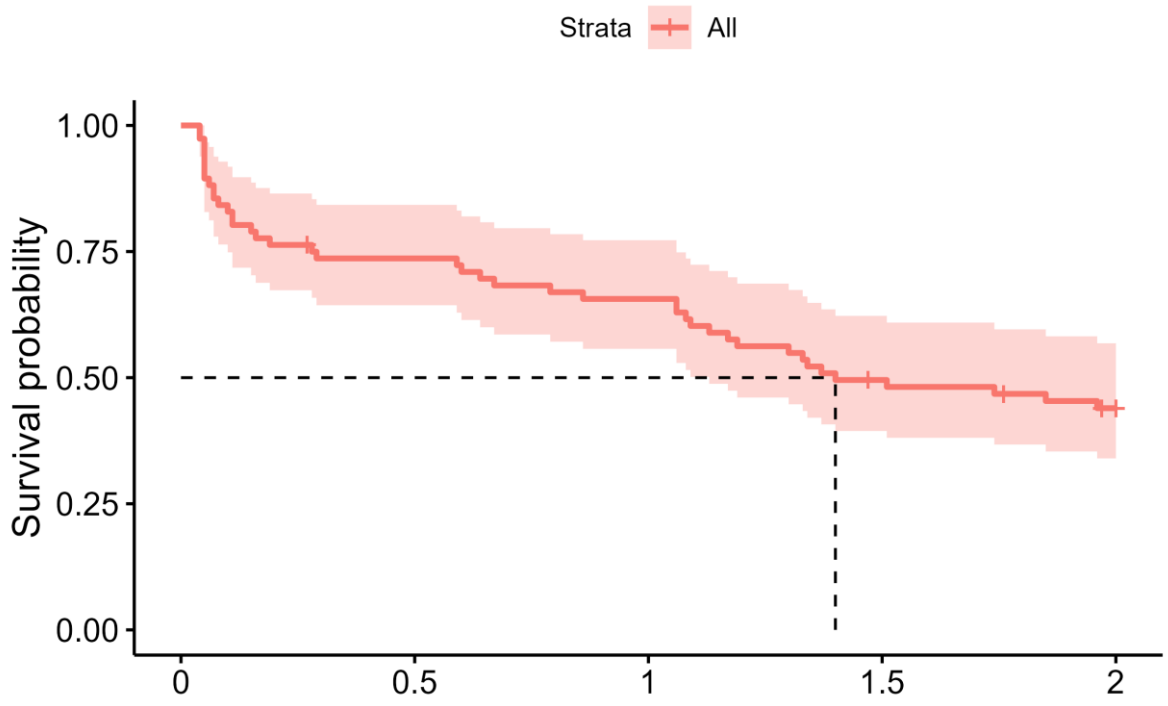


FIGURE 2: **Progression-free survival at 2 years**

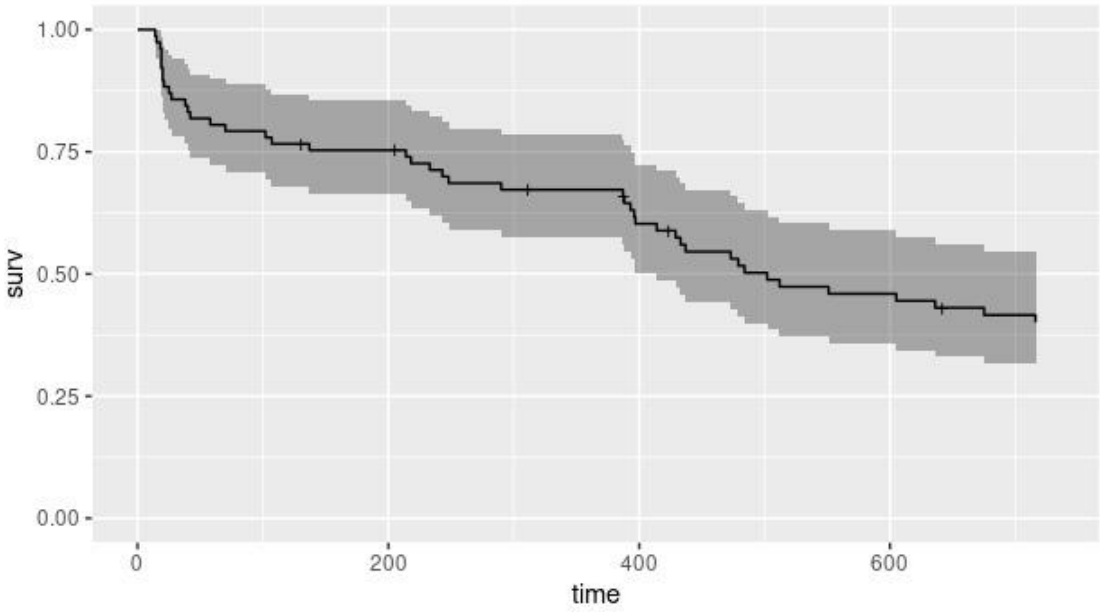


FIGURE 3: Probability of survival according to BCR-ABL fusion gene mutational status

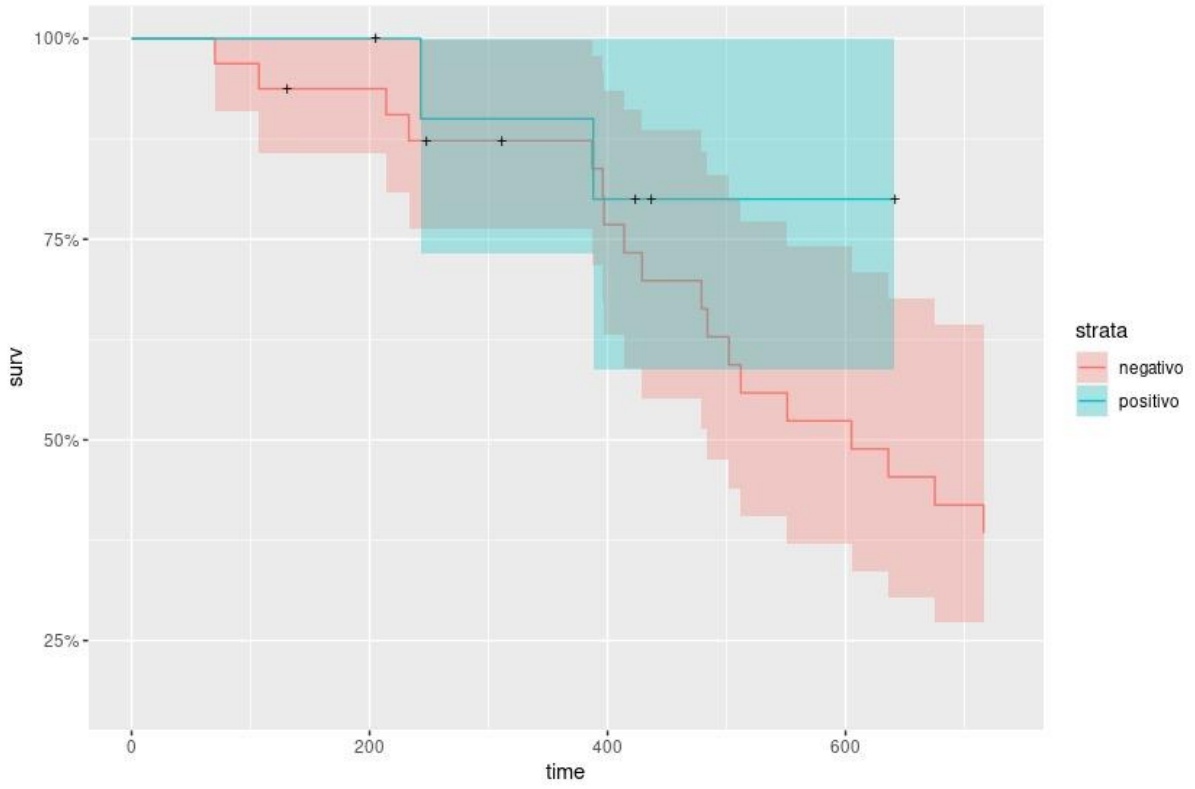
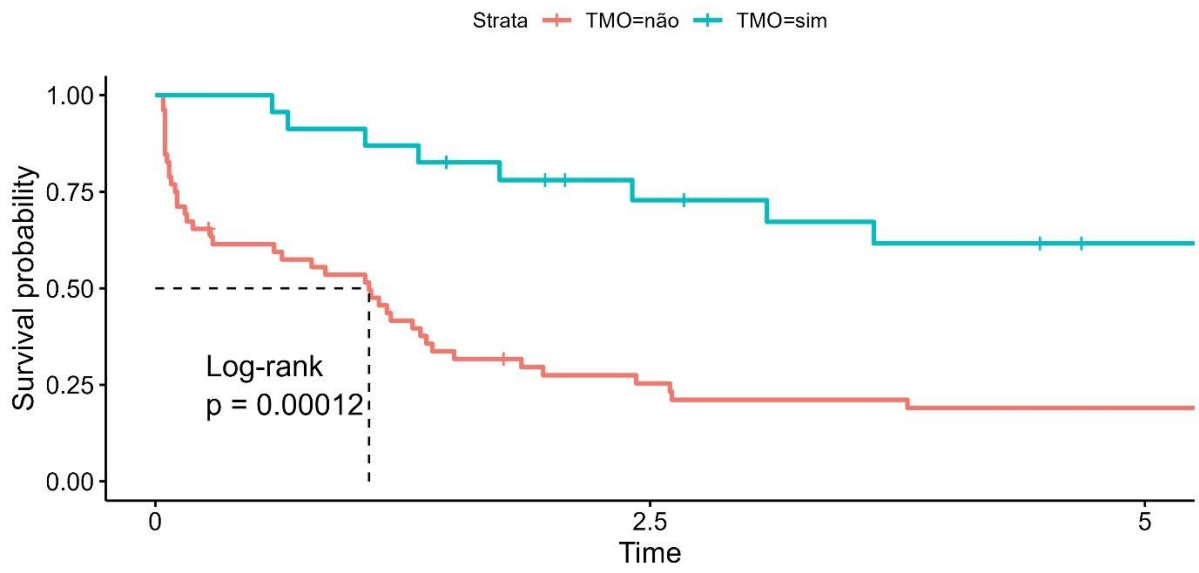


FIGURE 4: Overall survival in patients undergoing HSCT



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ORIGINAL ARTICLE

CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: BRAZILIAN SUMMARY SLIDES – 2024

Anderson João Simione[1], Cinthya Corrêa da Silva[2], Paula Moreira da Silva Sabaini[3], Antonio Vaz de Macedo[4], Heliz Regina Alves das Neves[5,28], Bruna Letícia da Silva Santos Geraldo[6,18], Monique Ammi[7], Flavia Ferreira Costa[8], Valeria Viana[9], Adriana Mendes de Quadros Cavilha[5], Rosana Rocha Concilio[10], Vergilio Antonio Rensi Colturato[1], Phillip Scheinberg[10], Samir Kanaan Nabhan[5], Decio Lerner[11], Nelson Hamerschlak[2], Marcos Paulo Colella[12], George Maurício Navarro Barros[3], Alexandre Silvério[13], Adriana Seber[6,8,14], Yana Augusta Sarkis Novis[15], Vanderson Geraldo Rocha[16], Maria Claudia Rodrigues Moreira[17], Claudia Caceres Astigarraga[18], Liane Esteves Daudt[19], Maria Cristina Martins de Almeida Macedo[20,21,22], Ricardo Chiattone[8], Juliana Folloni Fernandes[2,23], Volney Assis Lara Vilela[24,44], Rodolfo Daniel de Almeida Soares25, Gustavo Machado Teixeira[26], Celso Arrais-Rodrigues[27], Roberto Luiz da Silva[22], Vaneuza Araújo Moreira Funke[5,28], Afonso Celso Vigorito[12], Leonardo Javier Arcuri[2,11], Jayr Schmidt Filho[29], Vinicius Campos de Molla[30], João Samuel de Holanda Farias[31], Ricardo Pasquini[5,28], Carmem Maria Sales Bonfim[32], Abrahão Elias Hallack Neto[33], Rodolfo Froes Calixto[34], Luis Fernando Bouzas[35], João Victor Piccolo Feliciano[36], Rafael Dezen Gaiolla[37], Marcelo Capra[38], Angelo Atalla[39], Milton Alexandre Ferreira Aranha[40,41,42,] Rony Schaffel[9], Gianne Donato Costa Veloso[43], Gustavo Bettarello[45], Andresa Lima Melo[46], Simone de Castro Resende Franco[47], Marcelo C. Pasquini[48], Fernando Barroso Duarte[49]

1 Hospital Amaral Carvalho, Jaú, SP,

2 Hospital Israelita Albert Einstein, São Paulo, SP,

3 Barretos Cancer Hospital, Barretos, SP,

4 Hospital da Polícia Militar, Belo Horizonte, MG,

5 Hospital de Clínicas – Universidade Federal do Paraná, Curitiba, PR,

6 Associação da Medula Óssea, São Paulo - AMEO , SP,

7 Center for International Blood and Marrow Transplant Research (CIBMTR), Minneapolis, MN, USA,

8 Hospital Samaritano Higienópolis - Américas, São Paulo, SP,

9 Hospital Universitário Clementino Fraga Filho, Univ. Fed. RJ,

10 Real e Benemérita Sociedade de Beneficência Portuguesa de São Paulo, São Paulo, SP, 11 Instituto Nacional do Câncer (INCA), Rio de Janeiro, RJ,

12 Universidade Estadual de Campinas, Campinas, SP,

13 CEPON – Centro de Pesquisas Oncológicas, Florianópolis, SC,

14 Instituto de Oncologia Pediátrica – Grupo de Apoio ao Adolescente e à Criança com Câncer (GRAACC) – Universidade Federal de São Paulo, São Paulo, SP,

15 Sociedade Beneficente de Senhoras Hospital Sírio Libanês, São Paulo, SP,

16 Hospital das Clínicas da Universidade de São Paulo, São Paulo, SP,

17 Complexo Hospitalar de Niterói, Niterói, RJ,

18 Associação Hospitalar Moinhos de Ventos, Porto Alegre, RS,

19 Hospital de Clínicas de Porto Alegre, Porto Alegre, RS,

20 Hospital Leforte Liberdade SA, São Paulo, SP,

21 Biosana's, São Paulo, SP,

22 IBCC – Instituto Brasileiro de Controle de Câncer, São Paulo, SP,

23 ITACI - Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, SP,

24 Instituto de Cardiologia do Distrito Federal – Unidade Pietro Albuquerque, Brasília, DF,
25 Hospital Natal Center, Natal, RN,
26 Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, MG,
27 Universidade Federal de São Paulo, São Paulo, SP,
28 Hospital Nossa Senhora das Graças – Instituto Pasquini, Curitiba, PR,
29 A.C. Camargo Cancer Center, São Paulo, SP,
30 Centro De Pesquisa Clínica Hospital 9 De Julho, São Paulo, SP,
31 Hospital Erasto Gaertner, Curitiba, PR,
32 Hospital Pequeno Príncipe – Curitiba, PR,
33 Hospital Universitario da Universidade Federal de Juiz de Fora, Juiz de Fora, MG,
34 Real Hospital Português, Recife, PE,
35 Hospital Unimed Volta Redonda, Rio de Janeiro, RJ,
36 Fundação Faculdade Regional de Medicina de São José do Rio Preto (FUNFARME), SP,
37 Hospital das Clínicas - Faculdade de Medicina de Botucatu, UNESP, SP,
38 Hospital Mãe de Deus, Porto Alegre, RS,
39 Hospital Monte Sinai, Juiz de Fora, MG,
40 IBCC Oncologia – São Camilo, SP,
41 Hospital São Camilo - Pompéia, SP,
42 Hospital São Camilo – Santana, SP,
43 Santa Casa de Montes Claros, MG,
44 Hospital Sírio Libanês em Brasília, Brasília, DF,
45 Hospital DF Star, Brasília, DF,
46 Hospital Brasília, Brasília, DF,
47 Hospital da criança de Brasília, José Alencar, Brasília, DF,
48 Center for International Blood and Marrow Transplant Research (CIBMTR) and Medical College of Wisconsin, Milwaukee, WI, USA,
49 Hospital Universitário Walter Cantídio, Fortaleza, CE

Corresponding author: Anderson João Simione (E-mail: ambtmo.anderson@amaralcarvalho.org.br)

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ABSTRACT

The development of the Brazilian Registry of Hematopoietic Cell Transplantation (HCT) in collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR) allowed for an assessment of the activity and general outcomes of transplants in Brazil. Here, we report an updated activity. Brazilian transplant centers report their data to the CIBMTR, using the FormsNet3 platform. Information returns to Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) through the Data Back to Centers (DBtC) tool. Data from patients who received an HCT from 2012 to 2023 from Brazilian centers were extracted from CIBMTR. Descriptive analysis was carried out by patient-, disease- and transplant-specific variables and overall survival analysis using Kaplan Meyer. A total of 12,230 patients were eligible for this study (5,573 autologous and 6,657 allogeneic transplants). The number of reporting centers increased from 40 to 44 during the period. The most common HCT indication in Brazil is AML for allogeneic HCT with 152 transplants year and multiple myeloma for autologous HCT with 245 transplants per year. Among allogeneic HCT, in the last 4 years, mismatched related donor was the main source of donors. Regarding the graft source for allogeneic transplants, BM was the most frequent among pediatric transplants, while PBSC was the most used in adults. Infections were the leading cause of death in the first 100 days after all types of transplants. Patients with acute leukemia who underwent HCT with advanced stage disease had lower survival rates compared to those at other stages. Despite the differences in the number of cases and follow-up time, the results in this study were similar to those presented in the United States (US) Summary Slides.

Keywords: Data Management. Hematopoietic Stem Cell Transplantation. Brazil.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is often the only curative option for several malignant and non-malignant hematologic diseases, as well as for prolonging the survival of a number of patients[1]. Brazil has a large number of HCT centers, with 126 transplant programs in 86 centers recognized by the Brazilian Ministry of Health.

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

The Brazilian Association of Organ Transplant (ABTO), created in 1995, quarterly collects and publishes the annual activity of transplants in Brazil without HCT-related complication information. Reporting to ABTO is not mandatory. This activity is carried out voluntarily by those centers that are interested in having their production published. In addition to HCT-related data, also collected and published data on solid organ transplants. According to ABTO, 4,262 transplants were performed in 2023: 1,694 allogeneic and 2,568 autologous[5].

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the NMDP (formerly National Marrow Donor Program), which captures activity and outcomes of transplants in the US. Also, several centers outside the US contribute information to the CIBMTR, and Brazilian centers started to report to then the IBMTR since 1989. The number of Brazilian CIBMTR-reporting centers varied over the years, making it difficult to assess the actual activity of transplants in the region. In 2016 with collaboration between SBTMO and CIBMTR, a program to train professionals for data collection initiated and the number of reporting centers steadily increase[d6]. Also, this collaboration led to the development of the Brazilian Transplant Registry, as data reported from Brazilian centers is combined and returned to the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO). The HCT activity from Brazilian centers is now published annually in the SBTMO website as a resource to transplant community[7,8,9].

OBJECTIVE

The objective of this report is to report trends in HCT activity from Brazilian transplant centers from the last decade.

METHODS

Data Sources

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

Selection

Data from 12,416 transplants performed between 2012 and 2023 were extracted from the CIBMTR portal using the DBtC, gathering information from the 44 Brazilian centers that had sent their HCT data to the CIBMTR. However, only 12,230 transplant records had complete data for analysis (comprising 5,573 autologous and 6,657 allogeneic transplants). For this reason, this was the total number of HCTs considered in the analyses herein.

The analysis of overall survival (OS) included 8,182 patients who underwent a 1st HCT between 2012-2022, and those without follow-up data after transplantation or undergoing a 2nd HCT were excluded (Table 1).

There were considered complete those patients with information about type of transplant, diagnosis and graft source.

The spreadsheet was imported into Power BI Desktop (PBI). Functions were updated to count the number of transplants performed and the number of participating centers, to translate columns into Portuguese, to categorize and classify diseases, to group variables, and for performing global survival analyses.

Definitions and Outcomes

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

Allogeneic transplants were categorized as matched related donor, mismatched related donor (including haploidentical and related donors with one mismatch), and unrelated donor.

Grafts were classified as bone marrow (BM), peripheral blood stem cells (PBSC) and umbilical cord blood (UCB).

The disease stage for acute leukemias was classified as 1st remission, 2nd or further remission and patients who underwent HCT with active disease.

Patients with Myelodysplastic Syndrome (MDS) were divided into early disease, comprising refractory anemia (RA); refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia (RCMD); and MDS with del(5q) alone, or Advanced disease, including refractory anemia with excess blasts (RAEB) and Chronic Myelomonocytic Leukemia (CMML).

Patients with Lymphoma were categorized as chemosensitive and chemoresistant disease by the response to treatment prior to HCT.

Classification of conditioning regimens was based on the agents and doses used, as follows: myeloablative conditioning (MAC) for patients who received total body irradiation (TBI) ≥500 cGy in a single dose or >800 cGy in fractionated doses; busulfan >9 mg/kg oral or ≥7.2 mg/kg IV or melphalan >150 mg/m^2 as a single agent or in combination with other drugs. The conditioning regimens that did not fill the criteria for MAC were classified as reduced intensity/non-myeloablative (RIC/NMA)[10,11].

Causes of death were classified using the standard classification from DBtC. The main causes of death between 2018-2022 were separated between deaths 0-100 days and deaths >100 days up to 3 years after HCT.

Statistical analysis

Descriptive statistics were used to describe categorical data with number of cases and percentage, to numerical variables were used median and ranges. Overall survival was estimated by the Kaplan Meier method, and the log-rank test was used to compare survival between groups. Graphics were generated by PBI and exported to Microsoft PowerPoint for publication. Survival analyses were performed using R Statistical Software (Version 4.2.1).

Ethical considerations

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

RESULTS

Between 2012 and 2023, 12,230 transplants were reported from 44 Brazilian centers (Table 2), of which 21 (48%) were located in the state of São Paulo; 5 in Distrito Federal, 4 in Paraná, 4 in Minas Gerais, 3 in Rio de Janeiro; 3 in Rio Grande do Sul; and 1 in each of the following states: Ceará, Rio Grande do Norte, Pernambuco and Santa Catarina.

The number of active CIBMTR centers increased over the last few years, reaching 36 active centers in 2022 and 35 in 2023 (Figure 1), which has greatly contributed to the increase in the number of Brazilian transplants registered in the CIBMTR since 2016, reaching more than 1,900 transplants per year in the last two years (Figure 2).

Between 2012 and 2023, 39.8% of the allogeneic transplants performed in Brazil used a matched related donor, followed by a mismatched related donor (31.6%) and an unrelated donor (28.7%). In the last 4 years, the main type of allogeneic transplant performed in the country used a mismatched related donor (Figure 3).

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

Mismatched related donors were used to treat Acute Myelogenous Leukemia (AML; 32.8%), followed by Acute Lymphoblastic Leukemia (ALL; 23.9%) and non-malignant diseases (22.8%); 53.3% of them used MAC, and 46.7% used RIC/NMA.

The main global indications for HCT in Brazil in 2023 were Multiple Myeloma (MM; 505; 26%), followed by AML (288; 15%), Non-Hodgkin Lymphoma (NHL; 204; 11%), ALL (201; 10%) and Hodgkin Disease (HD; 173; 9%) (Figure 4). In pediatric allogeneic HCT, the main diseases were other non-malignant (37%), ALL (25%), and Aplastic Anemia (14%). In adults, the main indications for allogeneic transplants were AML (37%), ALL (18%) and MDS (12%).

Even though acute leukemias continue to be the main indication for allogeneic transplantation in the country, an increase was observed, from 2016 on, in transplants performed for non-malignant diseases and MDS/Myeloproliferative Neoplasms (MPN). The main indications for autologous HCT remain MM and lymphomas.

In patients with acute leukemias, 52% of those with AML and 49% with ALL were in 1st remission. Most HCTs were from a matched related donor in both AML (43%) and ALL (36%) (Table 4).

Infections were the leading cause of death in the first 100 days after all types of transplants: autologous (68%), matched related donor (52%), unrelated donor (55%), and mismatched related donor (54%). The most common cause of death for more than 100 days after HCT was the primary disease: autologous (66%), matched related donor (46%),

unrelated donor (45%) and mismatched related donor (45%) (Figure 5).

For survival analyses, the median follow-up was 24 months in allogeneic and 22 months in autologous HCT. Patients with acute leukemia who underwent transplantation with advanced stage disease had lower survival rates compared to those at other stages (Table 5).

Adults had higher survival rates after HCT from matched sibling donors when having HCT for AML (p=0.029; Figure 6), ALL (p=0.007; Figure 7), MDS (p=0.022; Figure 8) and aplastic anemia (p<0.001; Figure 9), but donor type had no impact in pediatric patients with acute leukemias and aplastic anemia.

The 2-year OS for MDS was similar despite disease risk and donor type (Figure 10). Patients with CML had a 2-year OS of 63.6% with a matched related donor, 54.4% with a mismatched related donor, and 57.0% with an unrelated donor (p=0.354; Figure 11). Patients with myelofibrosis had a survival of 59.0% in 2 years (Figure 12).

Patients undergoing autologous HCT to treat chemosensitive lymphomas had a significantly better 2-year OS than those with chemoresistant disease: 87.8% versus 75.7% in HD (p=0.023) and 75.9% versus 57.9% in NHL (p=0.001) (Figure 13). The 2-year OS was 83.2% for patients with MM (Figure 14). Age at HCT had no impact on 2-year OS (p=0.206; Figure 15).

DISCUSSION

The analyses presented herein showed an increase in the number of Brazilian CIBMTR participating centers compared to what was seen in the first publications. Forty-four centers contributed with the information regarding new transplants between 2012 and 2023. In 2023, 35 centers reported new HCT data to the CIBMTR. Despite the lower number of active centers last year, 44 centers were active throughout the whole period analyzed. This shows that, over the years, centers have intermittently started and paused data reporting.

We observed an increase in the number of transplants with a mismatched related donor since 2012 and a decrease in unrelated UCB transplants in the same period, most likely due to the use of haploidentical donors with post-transplantation cyclophosphamide.

Comparing our data with those of the US Summary Slides published in the CIBMTR website[12], matched related donor HCTs are the main type of transplants performed in Brazil, followed by those using a mismatched related donor, while unrelated BM/PBSC transplants predominate in the United States (USA).

Among pediatric patients, the main source was BM in Brazil, following the same trend in the USA; on the other hand, there was an increase in PBSC use over the years, and it has been the main choice of graft source for adult recipients in Brazil since 2018 and, since 2000, in the USA, for all types of allogeneic HCT.

In 2023, the main indications for adult HCTs in Brazil were MM, AML, NHL, HD, and ALL, while in the USA, in 2021, those were MM, AML, NHL, MDS/MPN and ALL. For pediatric patients, the main indications in Brazil were other non-malignant disease, other malignancy, ALL, aplastic anemia and AML, as compared to other non-malignant disease, other malignancy, ALL, AML and aplastic anemia in the USA.

Another important comparison between these countries was the cause of early death, 0 to 100 days after transplantation: in Brazil, infection was the main cause of early mortality for autologous, matched related donor, mismatched related and unrelated donors, while organ failure was the main cause of early death for the same types of transplants in the USA.

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

The Brazilian Summary Slides are fully available to active centers in the HCTBR through the SBTMO data request flow (Figure 16).

CONCLUSION

The partnership between the SBTMO and the CIBMTR has made the HCTBR possible. The Brazilian HCT data analyses shown here have resulted in these updated Brazilian Summary Slides, which contributes to a better understanding of our nationwide HCT outcomes, by making the results available to centers as a both national and international benchmark. The Brazilian Summary Slides are updated once a year and published at the SBTMO website. Despite the differences in the number of cases and follow-up time, the results in this study were similar to those presented in the US Summary Slides, as discussed above.

Consolidating the HCTBR has yielded positive results, as witnessed by the increase in the number

of Brazilian centers affiliated to the CIBMTR and the higher qualification of DMs across the country. Nonetheless, there is still a lot to be done. It is necessary to improve the commitment of the HCT centers toward data reporting, in order to optimize the registry of transplants, the accomplishment of long-term follow-up and the continuing education of DMs, thus stimulating good quality data retrieval within the national registry. Government support (through resources, infrastructure and qualification) is also essential to achieve such goals. Continual and tireless efforts in this regard may help in the constant improvement of the HCTBR, and, in the long run, result in the provision of better care to patients.

ACKNOWLEDGEMENTS

The accomplishment of this work was only possible thanks to the efforts of many invaluable professionals throughout Brazil's HCT history: Dr. Ricardo Pasquini, one of the pioneers in HCT in Latin America; SBTMO, for the support provided to Brazilian data managers, along with different incentives, especially during the formalization of the data managers working group; Dr. Nelson Hamerschlak, Dr. Vergilio Antonio Rensi Colturato and Dr. Fernando Barroso Duarte, both of whom encouraged this movement in the country since 2016; Dr. Marcelo Pasquini, who facilitates direct contact with CIBMTR and has brought and keep bringing updates and teachings from the research record; Monique Ammi, who has always been active in the Brazilian centers' affiliation process, and DM education and ongoing support; HCT multidisciplinary teams across the country, all of which directly or indirectly enables the continuing development of this work; all the patients who underwent this treatment modality and contribute to scientific research by making their data available.

TABLE 1. Exclusion criteria for overall survival

Exclusion criteria	n
Patients without follow-up update	1,191
≥2nd HCT	935

TABLE 2. HCT centers

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

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

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Patients <18 Years												
Matched Related Donor (N=505)												
PBSC	2%	4%	2%	3%	9%	5%	9%	6%	3%	13%	14%	10%
BM	93%	88%	96%	94%	91%	93%	85%	92%	97%	87%	78%	88%
UCB	5%	8%	2%	3%	0%	2%	6%	2%	0%	0%	8%	2%
Unrelated Donor (N=857)												
PBSC	5%	3%	16%	12%	7%	7%	12%	4%	23%	28%	26%	27%
BM	53%	72%	78%	75%	85%	87%	81%	88%	74%	60%	68%	71%
UCB	42%	25%	6%	12%	7%	6%	7%	8%	3%	13%	6%	2%
Mismatched Related Donor (N=786)												
PBSC	24%	10%	27%	14%	25%	21%	34%	26%	26%	23%	23%	16%
BM	76%	90%	73%	86%	75%	79%	66%	74%	74%	77%	77%	84%
Patients ≥18 Years												
Matched Related Donor (N=2,142)												
PBSC	49%	47%	43%	50%	46%	52%	53%	57%	65%	65%	74%	73%
BM	51%	53%	57%	50%	54%	48%	47%	43%	35%	35%	26%	27%
UCB	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Unrelated Donor (N=1,051)												
PBSC	35%	29%	38%	51%	51%	46%	58%	55%	62%	83%	77%	76%
BM	38%	59%	62%	46%	49%	54%	42%	44%	35%	17%	23%	24%
UCB	27%	12%	0%	3%	0%	0%	0%	1%	4%	0%	0%	0%
Mismatched Related Donor (N=1,316)												
PBSC	18%	33%	43%	34%	40%	44%	63%	65%	72%	76%	78%	81%
BM	82%	67%	57%	66%	60%	56%	37%	35%	28%	24%	22%	19%

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

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
AML												
Disease Stage												
1st complete remission	35%	43%	47%	44%	59%	51%	53%	55%	52%	54%	54%	55%
2nd or subsequent complete remission	36%	28%	38%	40%	31%	30%	28%	25%	31%	20%	24%	24%
Relapsed disease/Never in CR	29%	28%	15%	16%	10%	19%	19%	20%	17%	26%	22%	21%
Donor Type												
Matched Related Donor	50%	54%	66%	49%	50%	50%	44%	42%	43%	37%	38%	31%
Mismatched Related Donor	16%	6%	10%	17%	23%	23%	33%	33%	42%	47%	45%	49%
Unrelated Donor (BM/PBSC)	28%	26%	20%	33%	27%	27%	22%	25%	15%	15%	17%	20%
Unrelated Donor (UCB)	6%	14%	4%	1%	0%	0%	1%	0%	0%	1%	0%	0%
ALL												
Disease Stage												
1st complete remission	45%	40%	56%	58%	52%	41%	52%	39%	44%	44%	50%	61%
2nd or subsequent complete remission	49%	54%	37%	40%	39%	51%	34%	48%	46%	45%	37%	33%
Relapsed disease/Never in CR	6%	6%	7%	2%	9%	8%	15%	13%	10%	11%	13%	6%
Donor Type												
Matched Related Donor	43%	52%	52%	44%	40%	36%	38%	31%	34%	29%	28%	33%
Mismatched Related Donor	7%	3%	2%	8%	16%	25%	26%	28%	39%	47%	49%	47%
Unrelated Donor (BM/PBSC)	29%	34%	45%	42%	42%	38%	34%	36%	26%	23%	23%	20%
Unrelated Donor (UCB)	21%	11%	1%	6%	1%	1%	2%	5%	1%	1%	0%	0%

TABLE 5. Overall survival of AML/ALL patients

A. AML

	N	OS in 2 years (%)	p
AML			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	78	48.9% (37-60)	
Mismatched Related Donor	87	58.7% (46-69)	0.506
Unrelated Donor	80	55.3% (43-66)	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	568	55.6% (51-60)	
Mismatched Related Donor	316	47.1% (41-53)	0.029
Unrelated Donor	244	53.2% (46-60)	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	36	58.2% (40-73)	
2nd or subsequent complete remission	24	50.3% (28-69)	0.520
Relapsed disease/Never in CR	18	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	387	62.5% (57-68)	
2nd or subsequent complete remission	103	45.7% (35-56)	<0.001
Relapsed disease/Never in CR	78	34.6% (23-46)	
Mismatched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	30	71.6% (51-85)	
2nd or subsequent complete remission	37	68.3% (48-82)	<0.001
Relapsed disease/Never in CR	20	28.6% (11-49)	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	173	55.8% (47-64)	
2nd or subsequent complete remission	84	52.9% (40-64)	<0.001
Relapsed disease/Never in CR	59	12.8% (5-25)	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	33	76.3% (56-88)	
2nd or subsequent complete remission	28	56.1% (36-72)	0.063
Relapsed disease/Never in CR	19	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	100	67.2% (56-76)	
2nd or subsequent complete remission	94	54.2% (43-64)	<0.001
Relapsed disease/Never in CR	50	23.6% (12-37)	

B. ALL

	N	OS in 2 years (%)	p
ALL			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	128	57.2% (47-66)	
Mismatched Related Donor	147	53.0% (43-62)	0.632
Unrelated Donor	250	60.9% (54-67)	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	327	56.0% (50-62)	
Mismatched Related Donor	175	48.7% (40-57)	0.007
Unrelated Donor	186	45.1% (37-53)	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	38	69.5% (51-82)	
2nd or subsequent complete remission	69	49.7% (36-62)	0.203
Relapsed disease/Never in CR	21	57.1% (27-79)	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	243	63.2% (56-69)	
2nd or subsequent complete remission	69	36.9% (25-49)	<0.001
Relapsed disease/Never in CR	15	-	
Mismatched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	33	71.0% (48-85)	
2nd or subsequent complete remission	102	50.8% (39-61)	0.135
Relapsed disease/Never in CR	12	-	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	111	56.6% (46-66)	
2nd or subsequent complete remission	55	38.5% (25-52)	0.018
Relapsed disease/Never in CR	9	-	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
1st complete remission	76	73.1% (61-82)	
2nd or subsequent complete remission	147	57.5% (49-65)	0.008
Relapsed disease/Never in CR	27	45.7% (24-65)	
Patients Age ≥18 Years			
Disease Stage			
1st complete remission	112	49.7% (39-59)	
2nd or subsequent complete remission	59	44.5% (31-57)	0.272
Relapsed disease/Never in CR	15	-	

TABLE 6. Comparison of overall survival – Brazil and USA

A. Acute leukemia

	Brazilian Registry (2012-2022)		US Summary Slides (2010-2020)	
	N	OS in 2 years (%)	N	OS in 3 years (%)
AML				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	36	58.2% (40-73)	371	69% (64-74)
2nd or subsequent complete remission	24	50.3% (28-69)	141	66% (58-75)
Relapsed disease/Never in CR	18	-	68	28% (18-42)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	387	62.5% (57-68)	5,340	57% (56-59)
2nd or subsequent complete remission	103	45.7% (35-56)	1,182	53% (50-56)
Relapsed disease/Never in CR	78	34.6% (23-46)	1,594	31% (29-34)
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	33	76.3% (56-88)	388	64% (59-70)
2nd or subsequent complete remission	28	56.1% (36-72)	210	66% (60-73)
Relapsed disease/Never in CR	19	-	109	37% (29-48)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	100	67.2% (56-76)	8,066	55% (54-56)
2nd or subsequent complete remission	94	54.2% (43-64)	1,966	53% (51-55)
Relapsed disease/Never in CR	50	23.6% (12-37)	2,417	30% (28-32)
Mismatched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	30	71.6% (51-85)	176	62% (54-72)
2nd or subsequent complete remission	37	68.3% (48-82)	96	60% (49-73)
Relapsed disease/Never in CR	20	28.6% (11-49)	64	34% (24-49)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	173	55.8% (47-64)	2,189	50% (48-53)
2nd or subsequent complete remission	84	52.9% (40-64)	595	53% (49-58)
Relapsed disease/Never in CR	59	12.8% (5-25)	629	27% (23-31)
ALL				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	38	69.5% (51-82)	296	79% (74-84)
2nd or subsequent complete remission	69	49.7% (36-62)	459	70% (66-75)
Relapsed disease/Never in CR	21	57.1% (27-79)	37	62% (48-80)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	243	63.2% (56-69)	2,281	64% (62-66)
2nd or subsequent complete remission	69	36.9% (25-49)	629	45% (41-49)
Relapsed disease/Never in CR	15	-	222	37% (31-45)
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	76	73.1% (61-82)	300	77% (72-82)
2nd or subsequent complete remission	147	57.5% (49-65)	451	65% (61-70)
Relapsed disease/Never in CR	27	45.7% (24-65)	37	69% (55-86)
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	112	49.7% (39-59)	2,652	63% (61-65)
2nd or subsequent complete remission	59	44.5% (31-57)	783	46% (42-50)
Relapsed disease/Never in CR	15	-	248	37% (32-44)
Mismatched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
1st complete remission	33	71.0% (48-85)	124	70% (62-80)
2nd or subsequent complete remission	102	50.8% (39-61)	223	64% (57-71)
Relapsed disease/Never in CR	12	-	20	-
Patients Age ≥18 Years				
Disease Stage				
1st complete remission	111	56.6% (46-66)	771	69% (65-73)
2nd or subsequent complete remission	55	38.5% (25-52)	344	47% (42-54)
Relapsed disease/Never in CR	9	-	99	28% (20-39)

B. MDS and Aplastic Anemia

	Brazilian Registry (2012-2022)		US Summary Slides (2010-2020)	
	N	OS in 2 years (%)	N	OS in 3 years (%)
MDS (Adults)				
Matched Related Donor				
Disease Stage				
Early disease	115	54.1% (44-63)	720	50% (47-54)
Advanced disease	106	54.5% (44-64)	1,611	46% (43-48)
Unrelated Donor				
Disease Stage				
Early disease	54	47.4% (33-61)	1,385	48% (45-51)
Advanced disease	52	47.4% (33-61)	3,044	44% (42-46)
Aplastic Anemia				
Patients Age 0-17 Years				
Donor type				
Matched Related Donor	62	84.9% (73-92)	487	98% (96-99)
Mismatched Related Donor	67	73.8% (60-83)	101	86% (79-93)
Unrelated Donor	70	80.7% (69-88)	358	91% (88-94)
Patients Age ≥18 Years				
Donor type				
Matched Related Donor	154	84.1% (77-89)	603	85% (82-88)
Mismatched Related Donor	52	72.5% (58-83)	200	80% (73-86)
Unrelated Donor	81	57.1% (45-67)	627	76% (73-80)

FIGURE 1. Active Brazilian centers in the CIBMTR by year

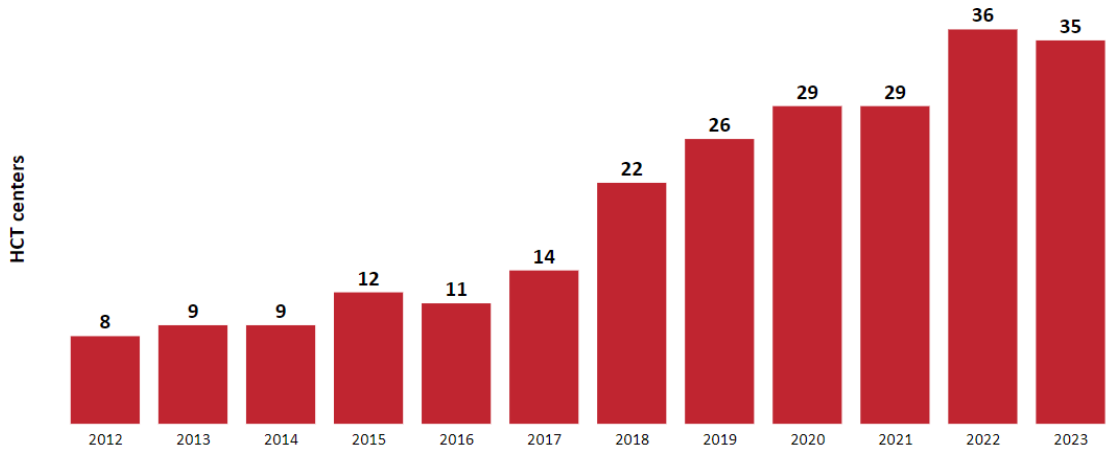


FIGURE 2. Transplants performed in Brazil and reported in the CIBMTR

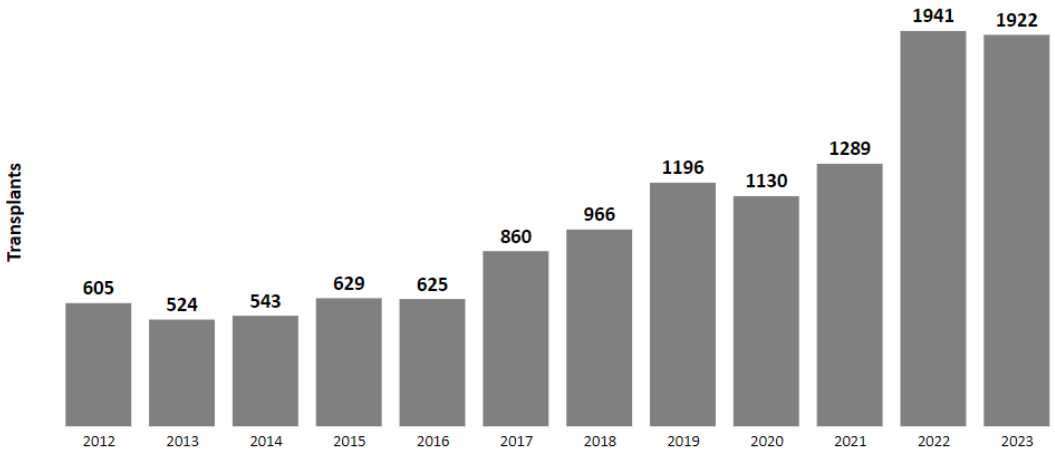


FIGURE 3. Relative proportion of allogeneic HCTs in Brazil by donor type

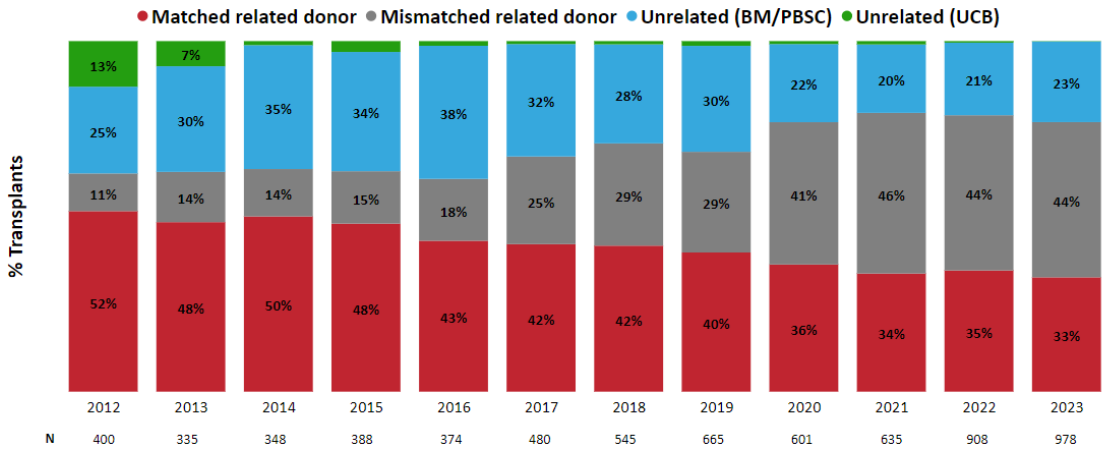


FIGURE 4. Global indications for HCT in Brazil, 2023 (n=1,922)

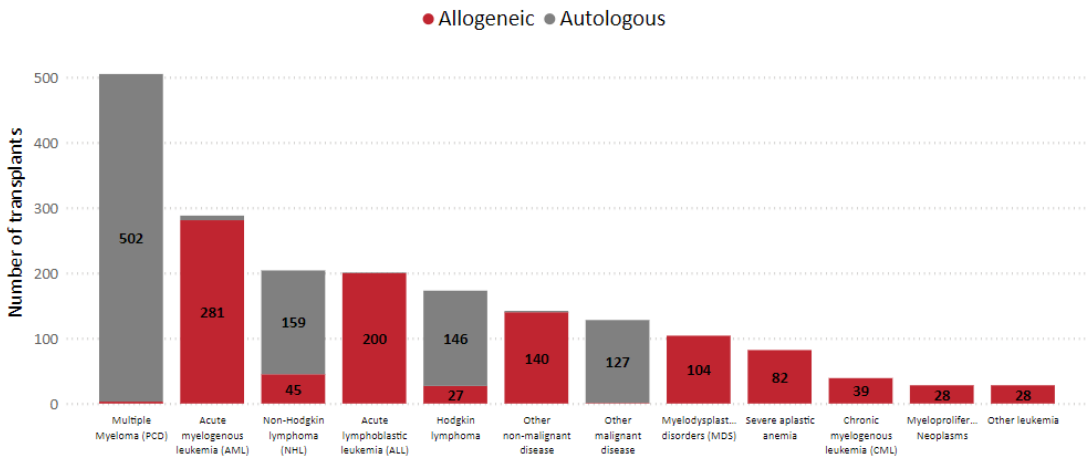
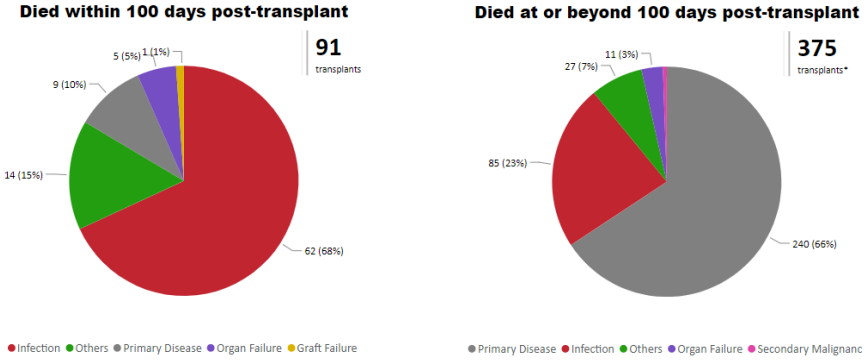
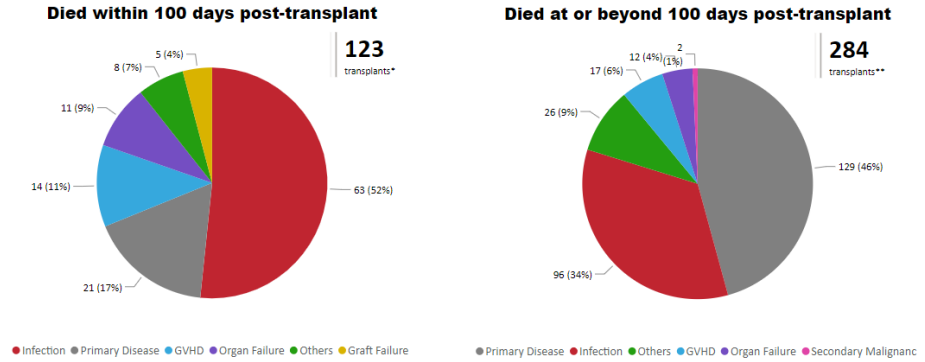


FIGURE 5. Causes of Death after HCT in Brazil, 2018-2022

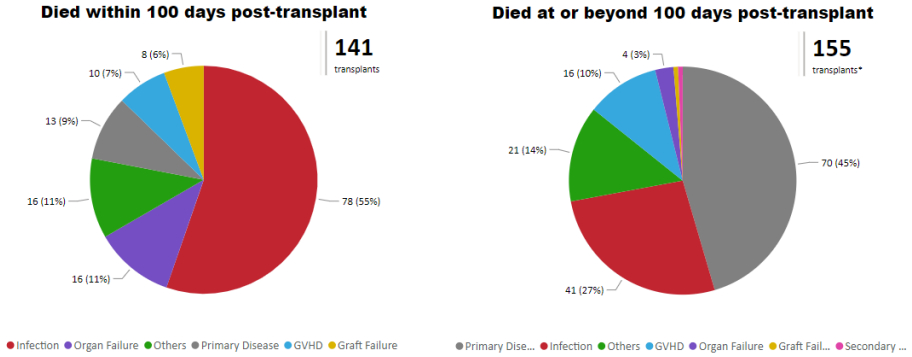
A. Autologous



B. Matched related donor



C. Unrelated donor



D. Mismatched related donor

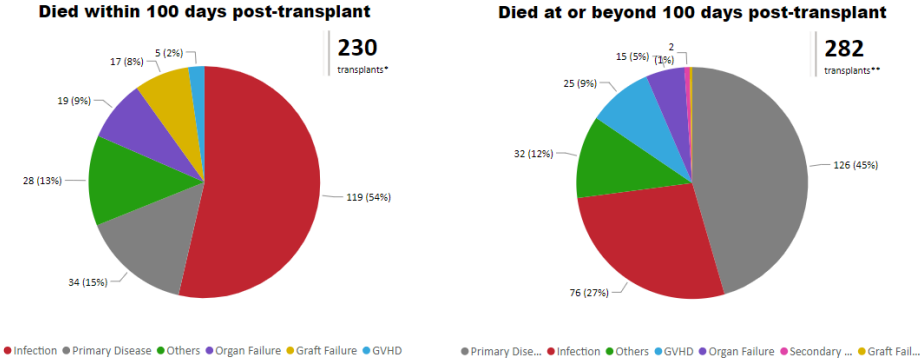


FIGURE 6. AML, overall survival after 1st allogeneic HCT by donor type

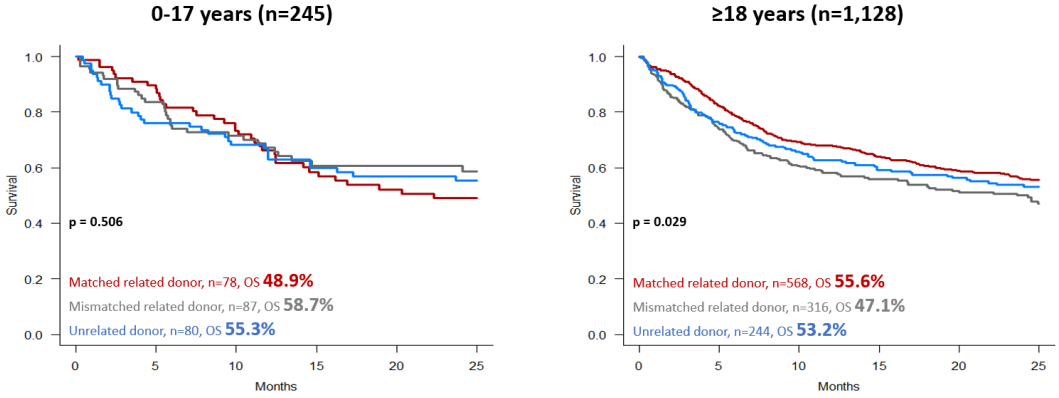


FIGURE 7. **ALL, overall survival after 1st allogeneic HCT by donor type**

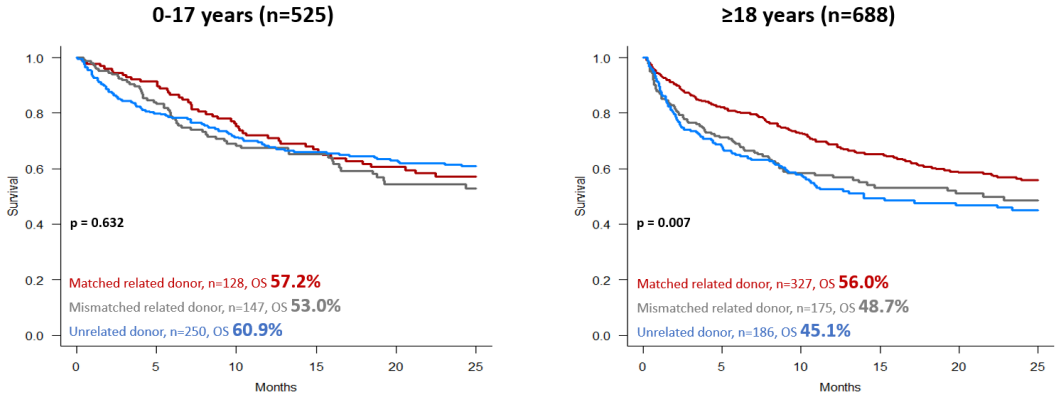


FIGURE 8. **MDS, overall survival after 1st allogeneic HCT by donor type**

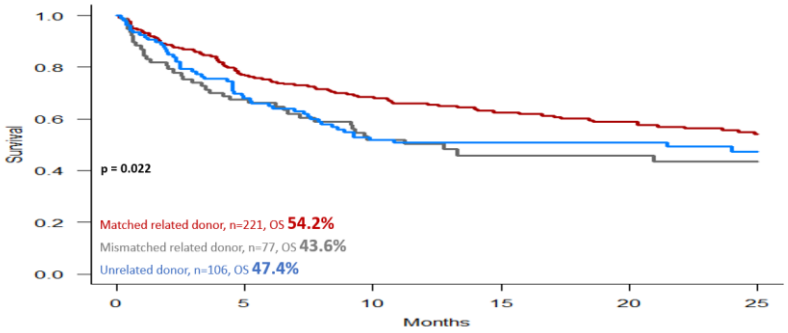


FIGURE 9. **Aplastic Anemia, overall survival after 1st allogeneic HCT by donor type**

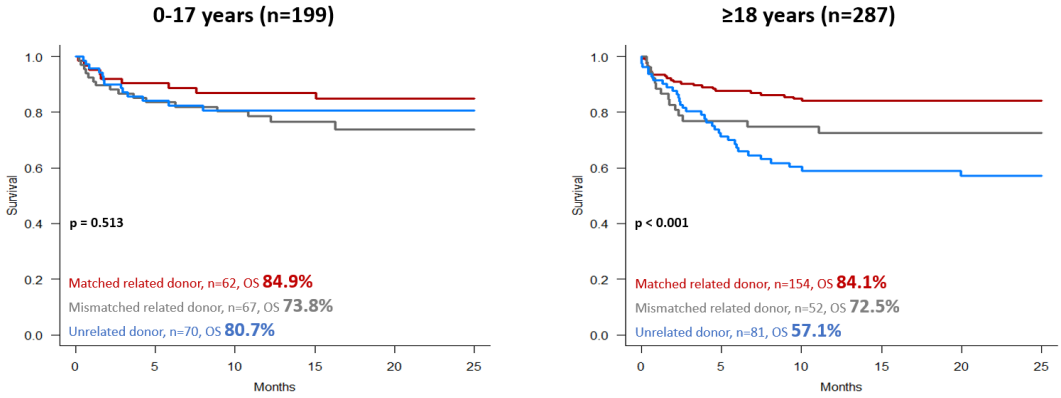


FIGURE 10. **MDS, overall survival after 1st allogeneic HCT by disease stage**

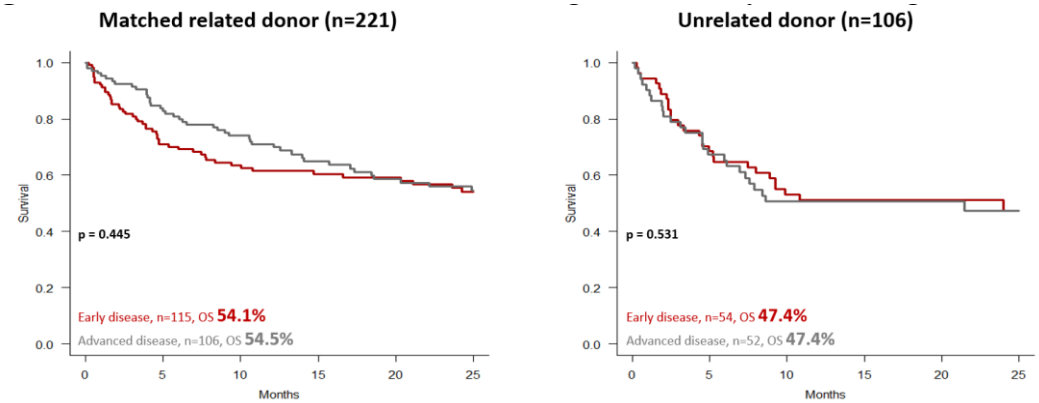


FIGURE 11. **CML, overall survival after 1st allogeneic HCT by donor type**

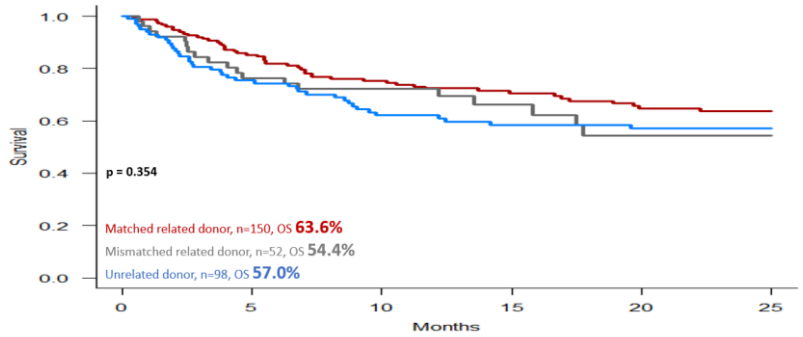


FIGURE 12. **Myelofibrosis, overall survival after 1st allogeneic HCT**

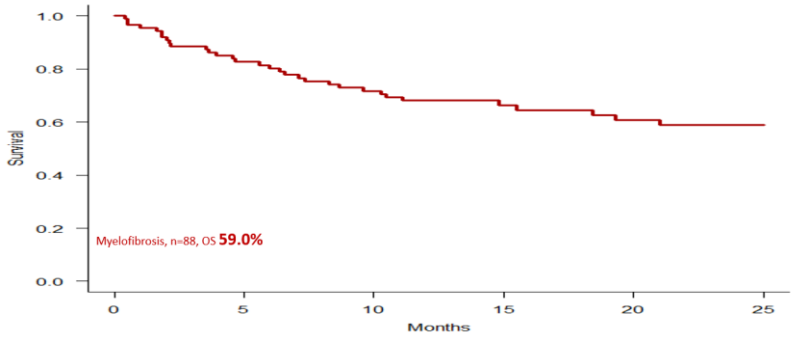


FIGURE 13. **Lymphomas, overall survival after 1st autologous HCT**

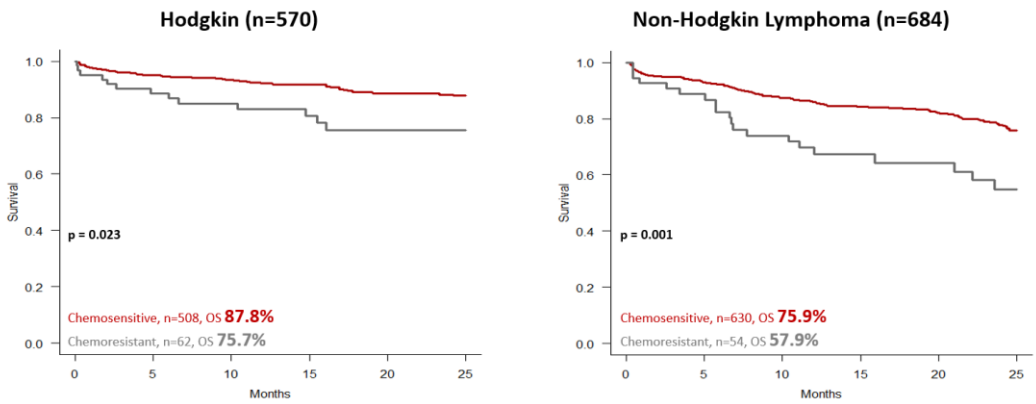


FIGURE 14. **Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HCT**

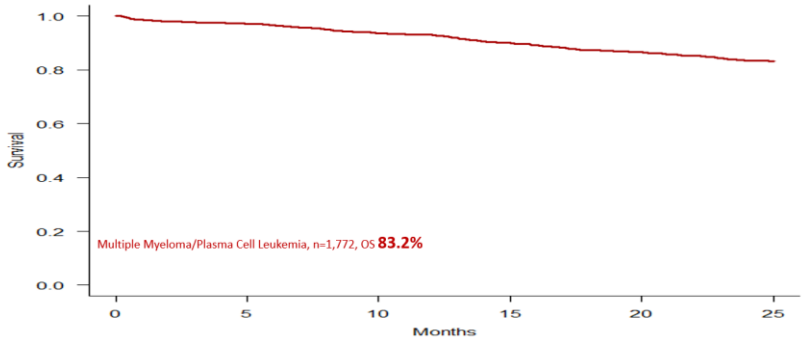


FIGURE 15. **Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HCT by age at HCT**

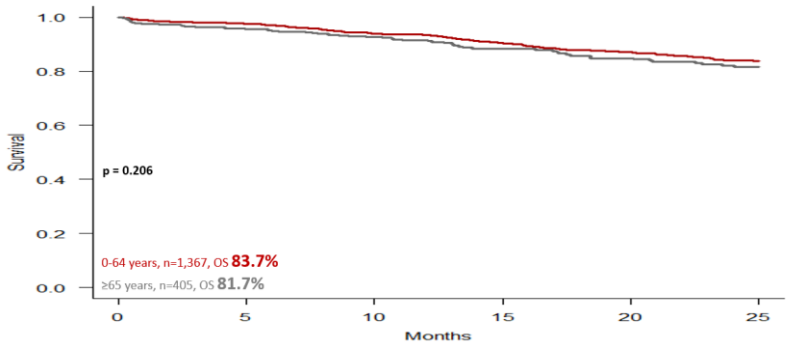
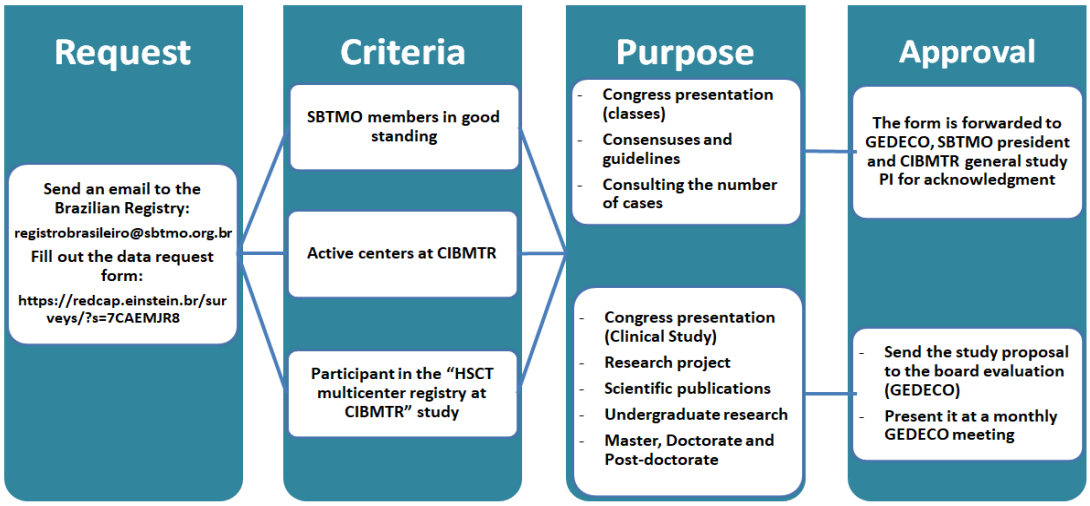


FIGURE 16. **Data request flow**



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ORIGINAL ARTICLE

FLT3-MUTATED ACUTE MYELOID LEUKEMIA OUTCOMES IN A NORTHEAST BRAZILIAN UNIVERSITY HOSPITAL

Hercules Amorim Mota Segundo[1]
Lara Facundo de Alencar Araripe[1]
Ana Vitoria Magalhães Chaves[1]
Paulo Henrique Mariano de Alencar[1]
Fernando Barroso Duarte[2]

1 - Hematology and hemotherapy resident at Walter Cantídio University Hospital (HUWC-UFC).

2 - Chief of the Hematology and Bone marrow transplantation division at Walter Cantídio University Hospital (HUWC-UFC).

Corresponding author: Hercules Amorim Mota Segundo (E-mail: hmotasegundo@gmail.com)

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ABSTRACT

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene occur in approximately 25-45% of new diagnoses of Acute Myeloid Leukemia. The addition of FLT3 inhibitors to conventional protocols improves overall survival in this condition. Objectives: To assess the incidence of FLT3 gene mutation among patients diagnosed with AML at Walter Cantídio University Hospital; Describe access to FLT3 inhibitors and bone marrow transplantation (BMT), and the overall survival of this group. Methodology: Retrospective evaluation of medical records of patients treated for AML between 2020 and 2022. Statistical analysis was performed using the Kaplan-Meier method to estimate survival probability. Results: 47 patients were diagnosed with AML during this period, of whom 17% had FLT3+ mutation. 3/8 patients accessed FLT3 inhibitors. The median survival with FLT3+ mutation was 9.1 months vs. 12.9 months in FLT3- (p = 0.196). The overall survival of AML patients was 30.9% at 2 years. 11/47 patients underwent allogeneic BMT. Conclusion: The addition of targeted therapies and BMT may contribute to reduce mortality in AML. Elderly patients and those not undergoing HSCT have worse outcomes.

Keywords: Leukemia, Myeloid, Acute. Bone Marrow Transplantation. Genetics. Mortality.

INTRODUCTION

Acute Myeloid Leukemia (AML) is a neoplasm originating from hematopoietic stem cells, marked by aggressiveness, where medullary occupation by myeloid precursors leads to hematopoietic dysfunction and severe cytopenias. It typically manifests with dyspnea, asthenia, severe infections, and bleeding. International data estimate a median age of diagnosis of 65 years and an overall 5-year survival rate of approximately 24%[1].

Cytogenetic and molecular evaluation demonstrated significant heterogeneity among patients, due to recurrent mutations or germline predisposition, as well as acute leukemia secondary to myelodysplasia and therapy related.

Mutations in the FMS-like tyrosine kinase 3 (FLT3) receptor are the most frequent genetic alteration associated with AML[2], present in all FAB subtypes (more prevalent in subtype M3). This transmembrane receptor is located in CD34+ precursor cells with potential for myeloid and lymphoid differentiation and is activated through the FLT3 ligand (FL) expressed in cells of the tumor microenvironment. Its auto-

phosphorylation leads to the activation of multiple intracellular signaling pathways responsible for regulating apoptosis, proliferation, and differentiation.

Approximately 30% of AML cases exhibit abnormal expression of the FLT3 receptor. Mutations of the internal tandem duplication (ITD)[3] type result from an in-frame duplication in the juxtamembrane domain, as well as missense mutations of a single amino acid in the tyrosine kinase domain (TKD). These mutations lead to constitutive activation of the receptor and dysregulation of auto-inhibitory mechanisms, causing proliferative and survival gains through activation of the Ras and STAT5 pathways[4,5].

Epidemiological studies have shown that FLT3-ITD mutation is associated with a higher relapse rate, being an independent predictor of worse event-free survival (EFS) and overall survival (OS)[6]. These data supported the inclusion of this genetic marker as a defining intermediate risk factor[7], independent of allelic ratio. Its identification led to the development of targeted therapies, consisting of FLT3 inhibitors (e.g., sorafenib, midostaurin, gilteritinib, and quizartinib).

Randomized clinical trials demonstrated the efficacy of midostaurin (RATIFY trial)[8] and quizartinib (QUANTUM-FIRST trial)[9] inhibitors in newly diagnosed patients when added to intensive chemotherapy (daunorubicin and cytarabine). The ADMIRAL trial[10] showed the efficacy of gilteritinib monotherapy in relapsed and refractory patients, with or without previous exposure to FLT3 inhibitors.

MATERIALS AND METHODS

This is a descriptive retrospective observational study aiming to evaluate patients diagnosed with Acute Myeloid Leukemia (AML) treated in either inpatient or outpatient settings at the Hematology Service of Walter Cantídio University Hospital (HUWC-UFC).

Adults (aged 18 years or older at the time of diagnosis) diagnosed according to the European LeukemiaNet[3] criteria between January 1, 2020, and December 31, 2022, were evaluated.

Data collection was performed through chart review and consultation of the mortality registry. The project was approved by the Research Ethics Committee (CEP-HUWC) under approval number 6,177,086.

This work aimed to define the incidence of FLT3 mutation in this center, describe demographic data, access to bone marrow transplantation and FLT3 inhibitors, and conduct survival analysis of this population.

The R software (version 4.3.2) was used for statistical analysis and graph generation. Survival analysis employed the Kaplan-Meier method, and comparison was performed using the Logrank test.

RESULTS

During the period analyzed in this study, 65 cases of Acute Myeloid Leukemia (AML) were diagnosed. Of these, 18 were classified as Acute Promyelocytic Leukemia and were therefore excluded from the analysis.

The median age was 49.3 years (range: 18-76 years), with a predominance of females (57.4%). Most patients came from the countryside of the state of Ceará (55.3%). Hypertension, type 2 diabetes mellitus, smoking, and alcoholism were the most frequent comorbidities (see Table 1).

Regarding the characterization of AML, 70.2% of patients were classified as "Not otherwise specified[11], while 21.3% received the clinical diagnosis of "AML secondary to myelodysplasia" due to the lack of access to molecular markers for characterizing related mutations. There were also diagnoses of chronic myeloid leukemia in myeloid blast crisis (6.4%) and therapy-related AML (2.1%).

Using the risk classification established by the European LeukemiaNet in 2022, 70.2% of patients were classified as Intermediate risk, 10.6% as Favorable risk, and 19.1% as High risk.

Cytogenetic and molecular evaluation showed 17% of cases with FLT3 mutation (n=8, FLT-TKD = 1, FLT3-ITD = 7). The most frequent findings in the karyotype were deletion 7q, t(8;21), and complex karyotype. 12.8% of patients had a normal karyotype, and evaluation was not possible in 21.3% due to the absence of metaphase growth.

The median time between diagnosis and the start of treatment was 8 days (range 1 to 127 days). Most patients underwent induction with anthracycline-based regimens (76.6%) in the first line. Approximately 10% underwent supportive therapy. The complete response rate was 53.1% among these patients, with 17% dying during induction therapy.

Of the patients with FLT3 mutation (n=8), 3 accessed FLT3 inhibitors, as shown in the Swimmer plot (Figure 1).

Hematopoietic stem cell transplantation (HSCT) was performed in 23.4% of patients, with matched

sibling donors (54.5%), unrelated donors (18.2%), and haploidentical donors (27.3%). Most patients underwent reduced-intensity conditioning (54.5%). The main reasons for not transplanting were lack of sustained response (38.9%), therapy-related death (25%), and clinical contraindication (19.4%).

Disease progression was the main cause of death (83%), followed by infectious and hemorrhagic complications (34% and 11%, respectively). The early death rate (within 60 days after diagnosis) was 20.8%.

Overall survival of this patient group (Figure 2) was 51.1% at 1 year (CI 38.6-67.6%) and 30.9% at 2 years (CI 19.7-48.7%), with a median survival of 12.2 months (CI 7.6-22.7 months). Comparison between subgroups showed no statistically significant difference in survival (Figure 3) between mutated and non-mutated FLT3 (median of 9.1 vs. 12.9 months, $p = 0.49$). There was better survival (Figure 4) in patients under 60 years of age ($p = 0.004$) and those undergoing HSCT ($p = 0.0001$).

DISCUSSION

Acute myeloid leukemia (AML) continues to pose a significant mortality burden in low- and middle-income countries[12]. This study revealed complete response rates and survival times comparable to other Brazilian centers but notably lower than data from high-income countries[13,14]. Early mortality remains a challenge[15], with deaths primarily attributed to infectious complications and delayed access to specialized centers.

Access to bone marrow transplantation is another limiting factor for AML patient outcomes, with only 23.4% of patients able to undergo the procedure at this center. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the mainstay in treating patients with adverse and intermediate-risk AML[16]. Patients who underwent HSCT achieved a 2-year overall survival of 79.5%, demonstrating the efficacy of the procedure in this cohort.

The slow incorporation of new drugs within the public healthcare system also hampers outcome improvement[12]. In this study, we observe that recent advancements resulting from the approval of FLT3 tyrosine kinase inhibitors (FLT3-TKIs) have not been routinely incorporated, with access limited to 3 out of 8 patients with mutated FLT3.

Patients aged 60 years or older had significantly inferior outcomes, with a median overall survival of 1.4 months. This data is similar to previous decades and may be related to the limited therapeutic arsenal available within the Brazilian Unified Health System (SUS). At the time that this article was written, only low-dose cytarabine (LDAC) and hydroxyurea were provided as low-intensity therapies. Advances such as BCL-2 inhibitors, hypomethylating agents, and CPX-351[17] remain unavailable in the Brazilian public sector.

This study has limitations, including the short analysis period, lack of access to diagnostic tests and risk stratification (notably among patients with early death), as well as incomplete chart records due to its retrospective nature.

CONCLUSION

AML remains a high-mortality disease. Patients not undergoing allogeneic transplantation and elderly patients had worse survival in this center. Increasing access to new drugs, such as FLT3-TKIs, may improve its outcomes. Further epidemiological studies, encompassing other oncology treatment centers, are necessary to accurately describe the real-world scenario of this condition.

TABLE 1. Demographic data of patients diagnosed with non-promyelocytic acute myeloid leukemia at Walter Cantídio University Hospital, between 2020-2022

	N (%)
Age group	
18-29 years	9 (19,1)
30-39 years	9 (19,1)
40-49 years	6 (12,7)
50-59 years	14 (29,8)
60-69 years	8 (17)
70-79 years	1 (2,1)
Median age in years (range)	49,3 (18-76)
Sex	
Male	20 (42,6)
Female	27 (57,4)
Hometown	
Fortaleza	21 (44,7)
Other cities	26 (55,3)
Comorbidities	
Hypertension	11 (23,4)
Diabetes mellitus	9 (19,1)
Smoking	6 (12,7)
Alcoholism	6 (12,7)
Illicit drugs addiction	3 (6,4)
Obesity	2 (4,2)
Cardiopathy	2 (4,2)
Other neoplasia	1 (2,1)
No comorbidity	22 (46,8)
Classification	
AML, NOS	33 (70,2)
AML secondary to myelodysplasia	10 (21,3)
CML in myeloid blast crisis	3 (6,4)
Therapy-related AML	1 (2,1)

FIGURE 1: **Swimmer's plot of patients diagnosed with FLT3-mutated AML**

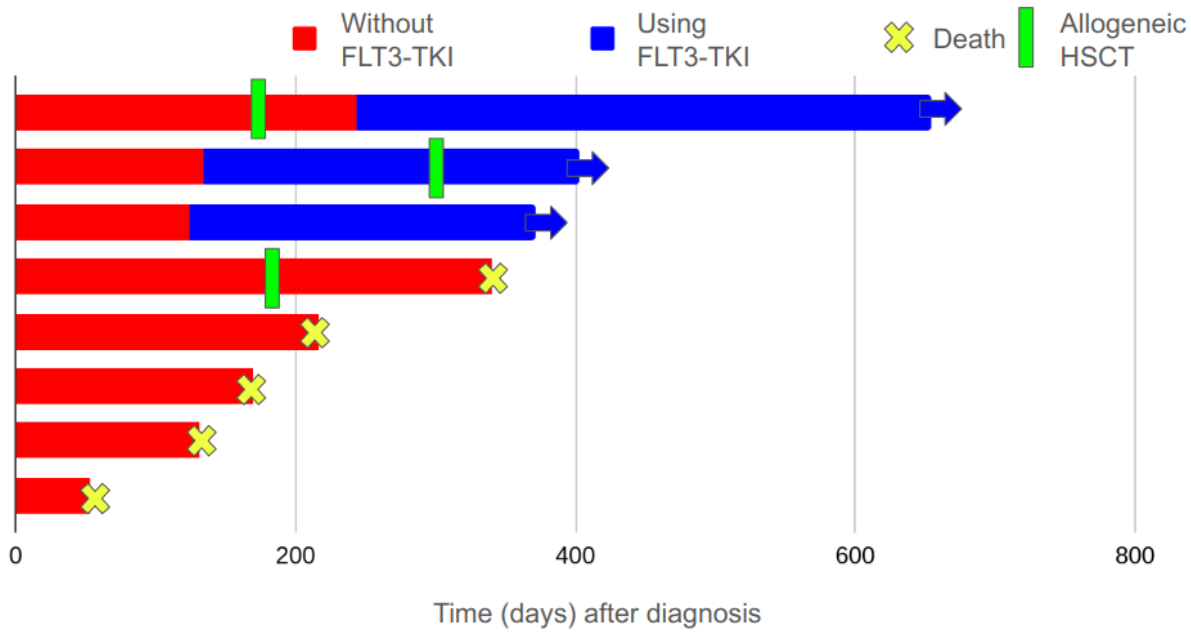


FIGURE 2: **2-years overall survival**

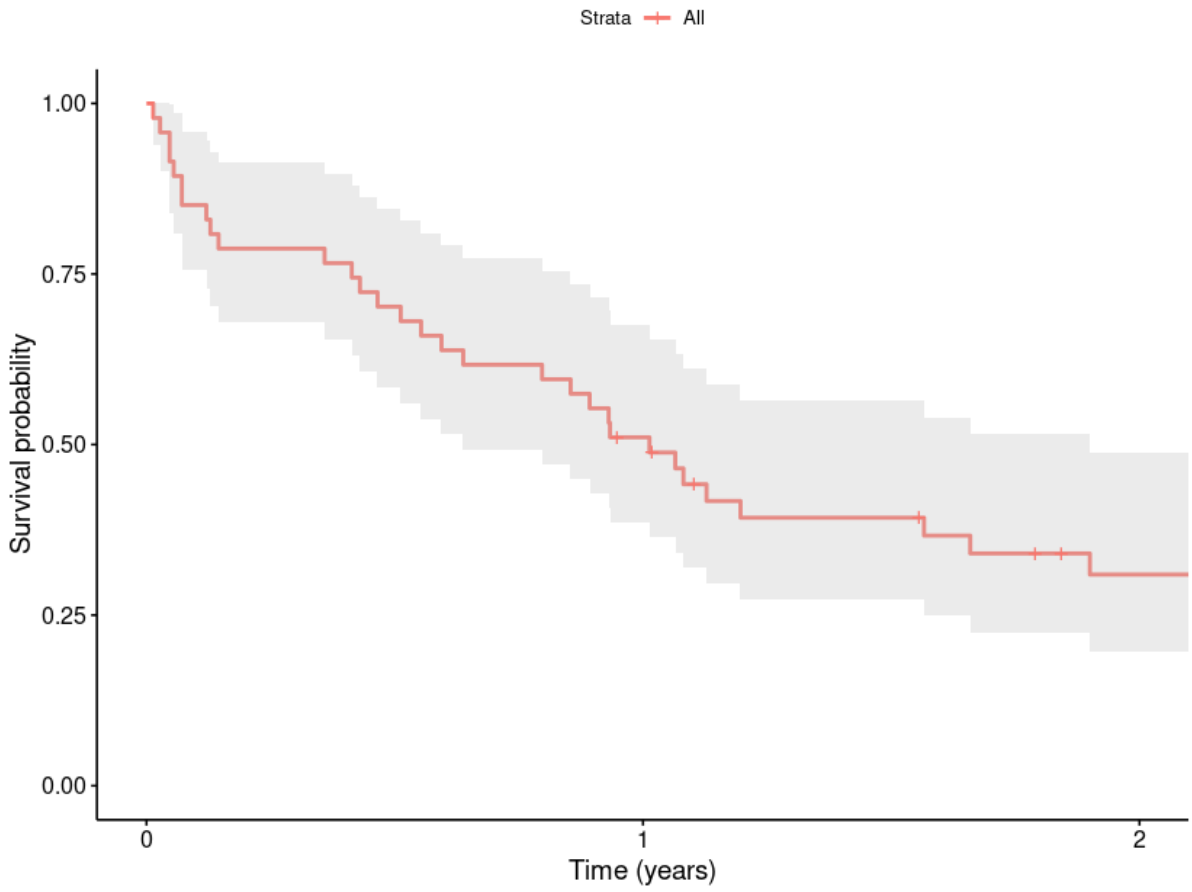


FIGURE 3: Overall survival by FLT3 mutational status

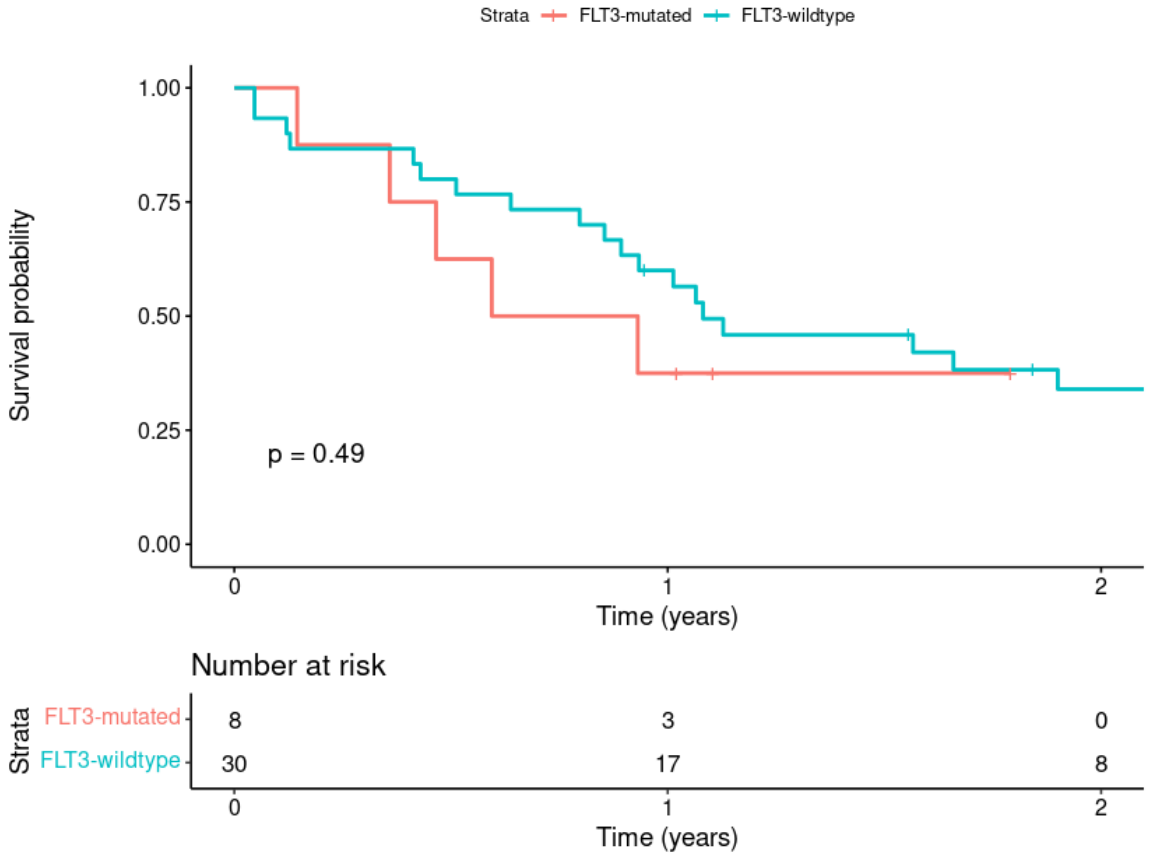
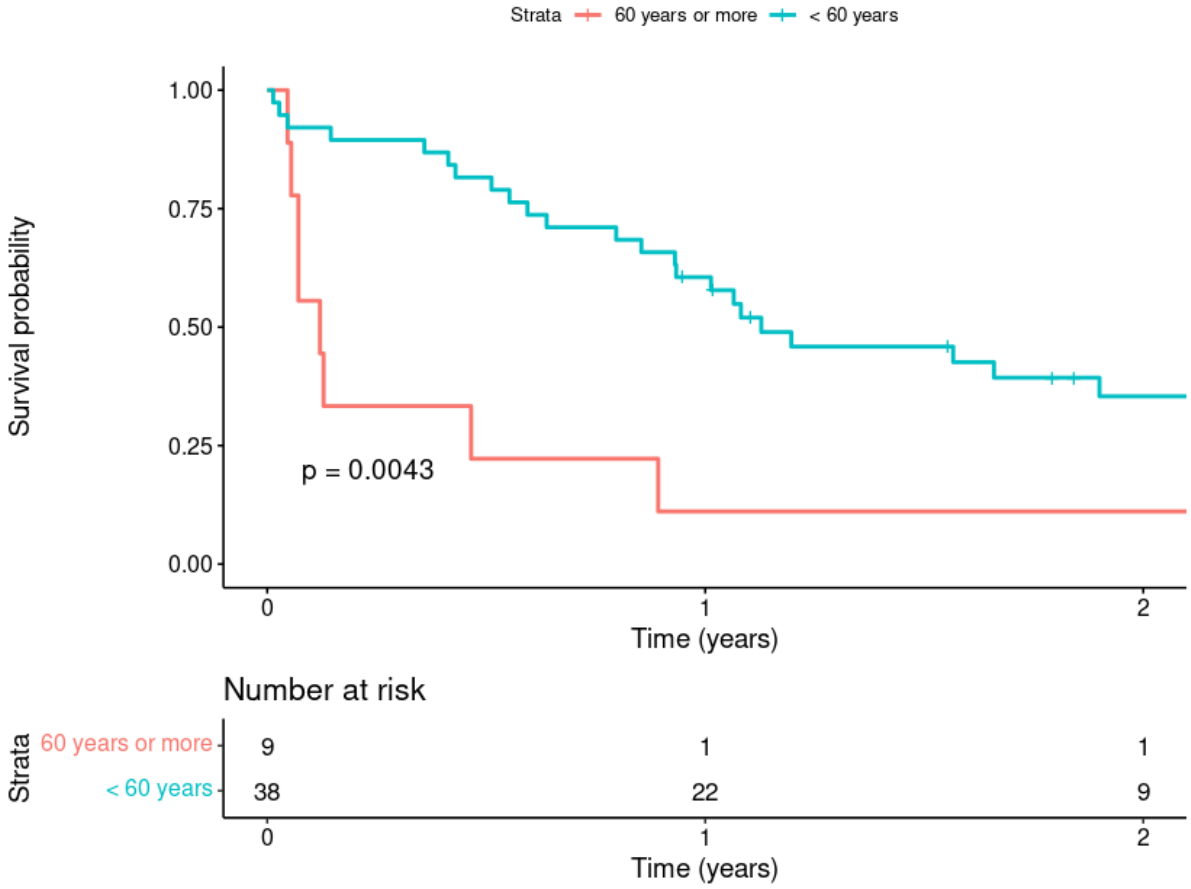


FIGURE 4: Overall survival by age group



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ORIGINAL ARTICLE

DESENSITIZATION THERAPY FOR ELEVATED DONOR-SPECIFIC ANTIBODY LEVELS IN HAPLOIDENTICAL TRANSPLANTATION IN CHILEAN PATIENTS

Sarmiento M[1], Salinas J[1], Rojas P[1], Gutierrez C[1], Vidal M[1], Jara V[1], Garcia MJ[1], Campbell MJ[1], Flores Y[1] Sandoval V[1], Vergara M[1], Palacios F[1], Ocqueteau M[1]

1 - Programa de trasplante hematopoyético del adulto. Red de Salud Christus UC - Pontificia Universidad Católica de Chile.

Corresponding author: Mauricio Sarmiento (E-mail: msarmiento@ucchristus.cl)

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ABSTRACT

Allogeneic stem cell transplantation (ALOSCT) is curative for several hematological diseases. Unrelated donors and cord blood stem cells are valid options but haploidentical donors (HAPLO) have been considered the main source of stem cells in several countries, partly due to easy access and low cost of the transplantation process. Unfortunately, some patients have antibodies against the HLA epitopes from family haploidentical donors (donor-specific antibodies [DSA]) which are associated with engraftment failure and lethality. A few strategies exist to reduce or eliminate HLA antibodies that bind to these receptors. In this study, we present our experience with DSA desensitization by retrospectively examining a cohort from our hospital program. Between 2012 and 2023, we performed 243 ALOSCTs, of which 142 were from HAPLO and 56 were from unrelated donors. Nine patients (7%) had elevated DSA levels, most of which were female patients and mostly HAPLO. The median fluorescence intensity for these patients was 22,490 (19,000-28,560). Most of these high DSA patients (80%) received a desensitization procedure that involves plasmapheresis, rituximab, and immunoglobulin. The remaining 20% had severe infections during transplantation, and received rituximab monotherapy instead. The median dose of stem cells infused was 6.5 x 10^6 CD34/kg. Graft-versus-host disease (GVHD) preventative measures for all patients involved post-transplantation cyclophosphamide. Primary graft failure was observed in 45% of DSA elevated patients. For the remaining patients, median granulocyte and platelet engraftment were 14 d (12-16) and 16 d (13-18), respectively. Mortality in patients who did not receive engraftment was 100%. The incidence of mild, chronic GVHD was 15%. In conclusion, the desensitization of DSA in patients provided a 55% rate of engraftment and survival. However, a 45% rate of primary graft failure continued to pose a challenge in patients with DSA and required the development of improved strategies to reduce elevated transplant-related mortality.

Keywords: Stem Cell Transplantation. Allogeneic Cells. Desensitization, Immunologic. Antibodies.

INTRODUCTION

Allogeneic stem cell transplantation (ALOSCT) is a curative treatment option for many diseases[1]. Before the year 2000, patients without family donors or access to cord blood grafts could not receive stem cell transplants. Over the last few decades, haploidentical donors (HAPLO) have emerged as a relevant source of stem cell precursors, providing access to transplantation for many patients (1). However, since the development of the HAPLO platform and unrelated donors (URD) availability, primary graft failure (PGF) has been a frequent challenge[2-3]. Cut-off values for donor-specific antibodies (DSA),

which are measured by median fluorescence intensity (MFI) >10,000, were established as a risk factor for PGF. Ciurea et al. reported DSA as contributors to PGF and provided a desensitization strategy with a 50% success rate[4]. Similarly, reports suggest that patients who receive a pre-transplant plasmapheresis, followed by rituximab and high-dose IVIG, have a 50% reduction in DSA levels. Based on this data, our adult transplantation program began with HAPLO in 2012 and utilizes this desensitization procedure in patients with high titers of DSA. Here, we report our experience with patients from a Latin American transplantation center.

PATIENTS AND METHODS

Patients

Since 2012, our institution started using HAPLO donors for adult allogenic hematopoietic stem cell transplantation. The cyclophosphamide post-transplantation strategy was adopted according to validated protocols[5]. For this study, we performed a retrospective analysis of all patients transplanted since 2012 and collected data regarding demographics, transplantation procedures and clinical outcomes.

Conditioning

Our institutional guidelines offer myeloablative transplantation in fit patients under 45 years of age. Cyclophosphamide/total body irradiation or fludarabine/total body irradiation were used. Patients unfit for myeloablation were treated with reduced-intensity conditioning such as fludarabine in combination with melphalan, busulfan, or cyclophosphamide.

Transplantation procedures

All patients received a detailed pre-transplant evaluation measuring global functions. Our program performs hospitalized transplantations. Immunosuppressor monitoring and the administration of granulocyte-colony stimulating factor (G-CSF), antibiotics, antifungals, antiviral prophylactics, and related treatments are standardized according to institutional guidelines and were reported previously[6].

DSA testing

In all HAPLO patients, DSA tests were performed during pre-transplantation screening. According to the Luminex technique, blood samples with EDTA were processed with the fluorometric, solid phase immunoassay for individualized HLA-purified class I and II antigens. A MFI >10,000 DSA units was designated as positive for graft failure risk.

Desensitization strategy

In patients with DSA-positive tests, a desensitization protocol with the standard desensitization therapy was administered (Figure 1). The procedure started one week before conditioning and consisted of three sessions of plasmapheresis with 1× to 1.5× plasma volume (replaced with either fresh or frozen plasma) followed by rituximab 375 mg/m^2 and administration of immunoglobulin 2 gr/kg over two days.

Graft-versus-host disease (GVHD) prophylaxis

In all HAPLO patients, post-transplantation cyclophosphamide was administered at a dose of 50 mg/kg on days 3 and 4. Subsequently, tacrolimus and mycophenolate were administered and progressive discontinuation started at 4 months post-transplantation, for those who tolerated the treatment.

GVHD treatment

Institutional guidelines for GVHD treatment start with the adjustment of immunosuppressors, topical corticosteroids, and systemic methylprednisolone. If there was no response, ruxolitinib, vedolizumab, ibrutinib, or extracorporeal photopheresis were available[7].

Ethics aspects

The studies involving human participants were reviews and approved by clinical ethic committee of the Hospital Universitario de la Pontificia Universidad Católica de Chile. All patients provided written, institutional informed consent permitting the collection of anonymous data and transplantation outcomes. The institutional ethics board approved publication of this data.

Statistical methods and outcome definitions

The demographic and baseline characteristics were presented using mean, percentage, and ranges. Transplantation outcomes are analyzed in a frame of competitive risk and cumulative incidence. The comparisons between the variables were made with the Chi-square method. The survival probabilities were estimated with the Kaplan–Meier method. Engraftment was defined was defined as the first of three consecutive days of achieving a sustained peripheral blood neutrophil count of >500 × 10^6 /L and independence from platelet transfusion for at least 7 days with a platelet count of more than >20 × 10^9/L Primary graft failure was established when there was no evidence of neutrophil and platelet engraftment at +30 d. The effects of the events that occurred during the follow-up and after transplantation, such as acute GVHD or relapse, were analyzed as a time-dependent covariate. The SPSS version 15 (IBM Software, USA) and Prisma Software version 6.0.1 (GraphPad Software, USA) were used for analysis. The differences were considered significant for values of $p < 0.05$, with 95% confidence intervals (CIs).

RESULTS

Patients, diseases, and characteristics

Between 2012 and 2023, we performed 243 ALOSCTs, of which 142 were from HAPLO and 52 from full match unrelated donors (URD). Of those, 133 HAPLO and 49 URD patients without elevated DSA levels, did not experience PGF. The remaining 9 patients (7%, DSA >10,000 MFI) were mostly females. In Table 1, demographic and basal characteristics of patients with high DSA levels are summarized.

DSA test and desensitization

The median MFI of patients with high DSA level was 22,490 (12,000-28,560). In (n = 7) 80% of these patients, desensitization therapy involved plasmapheresis, rituximab, and immunoglobulin. In two patients with severe fungal (mucormycosis and aspergillar sp infections respectively) infection at transplantation, desensitization involved rituximab monotherapy (Table 2). There was no correlation between MFI positivity and PGF. The median MFI of the successful engraftment group was 19,283 and in the PGF group was 20,886 (p = 0.9).

Transplantation outcomes

The median stem cell engraftment count (CD34/kg) post-transplant, was 6.5 x 10^6 CD34/kg. PGF was observed in 45% of the patients with high DSA levels. In patients with successful engraftment (55%), granulocyte and platelet engraftment levels reached 66% at medians of 14 d (range 12-16) and 16 d (range 13-18), respectively (Table 2). Acute GVHD grade 3-4 was reported in one patient who was refractory to all treatments. Chronic GVHD was reported in two patients and was limited to mild cutaneous symptoms.

Transplant-related mortality and overall survival

Overall survival at 3 years was 55% with the median not reached (Figure 2). Mortality was 45% (n = 4) all of which were transplant related. Three of the reported deaths were associated with PGF (two with previous AML and one with T-ALL, all heavily treated), and one (previous T-ALL) had hematologic complete recovery but with acute intestinal GVHD, refractory to corticosteroids, ruxolitinib, tocilizumab, mesenchymal stem cells, extracorporeal photopheresis, fecal microbiota transplantation, and infliximab. In patients with PGF, mortality was associated with fungal infections that were unresponsive to medical treatment.

DISCUSSION

Haploidentical donors for allogeneic transplantation have become a cornerstone of hematology, allowing transplantations for patients who would not have qualified decades ago. Since the release of the Luznik et al. HAPLO protocol[8], transplantation institutions worldwide, have successfully adopted HAPLO for transplantation[9]. However, PGF is a frequent occurrence with HAPLO and cord blood transplantations[10]. Reports suggest the incidence of PGF is variable and ranges from 30% to 56%. Our data shows that in a cohort of Chilean patients, mainly with acute leukemia, high DSA levels were associated with PGF and mortality even after desensitization. In our analysis, the MFI intensity was not associated with PGF; however, some patients with a strongly positive MFI had successful engraftments. One disadvantage to our analysis is the retrospective nature of our data and the small sample size. However, when reviewing available data from other previous studies, most were also retrospective and had small patient numbers[4,11,12]. Due to the scarcity of evidence, a meta-analysis was conducted and reported a total of 2,436 patients from 15 studies. This meta-analysis reported that the presence of DSA before ALLOSCT had a 7.47-fold increased risk of PGF failure compared to patients without anti-HLA DSA (OR 7.47; 95% confidence interval, 4.54 to 12.28, P < 0.001; I^2 = 28.91%, P = 0.13). The authors also reported that mean fluorescence intensity cutoff, primary disease, graft source, conditioning, and pre-transplantation desensitization did not affect the rate of PGF. Nonetheless, this meta-analysis included patients with both cord blood and HAPLO transplants, and analyzed mostly non-randomized studies, making it difficult to conclude with certainty[10]. Better quality evidence from randomized studies is difficult to obtain due to ethical considerations; since it would be problematic to propose a study in a control group with DSA and without desensitization. There is no definition of the best desensitization strategy with the same uncertainty. Recently, Ciurea et al. updated data on desensitization with the same strategy used in our program. In a matched case-control study, 37 patients, with a median age of 51 years, were treated with this desensitization protocol and compared to a control group of HAPLO patients without DSAs (n = 345). Mostly in women receiving stem cells from their child, the mean DSA decreased on average from 10,198 to 5,937 MFI. This study also reports that patients with DSA levels at >20,000 MFI and persistent positive C1q after desensitization had a significantly lower engraftment rate, higher non-relapse mortality, and worse overall survival than in the control group[13]. Regarding desensitization, there is a consensus promoting B-cell lymphodepletion. Since starting rituximab in this clinical scenario, several medications have been developed for other diseases related to the proliferation of

B lymphocytes. For example, there are many excellent medications that are used to treat myeloma that consistently reduce antibody production and have attractive mechanisms of action, with a possible use in DSA reduction. The use of daratumumab[14], bortezomib[15], or even other monoclonal antibodies have emerged as possible methods for achieving better desensitization rates in patients with DSA.

CONCLUSION

In our experience, desensitization provides a better chance at successful transplantation in patients with elevated DSA levels. However, ALLOSCT patients still frequently experience PGF and further investigations to identify new strategies to reduce mortality in this group of patients are necessary.

TABLE 1. Patient characteristics

Sex female/male	n = 6 (66%)/ n = 3 (34%)
Age median (range)	40 years (21-47)
Diagnosis (sex)	Acute myeloid leukemia CR 2: n = 3 (female = 2) Acute T lymphoblastic leukemia CR2: n = 2 (female = 1) Acute B lymphoblastic leukemia Philadelphia + CR1: n = 1 (female = 1) Severe aplastic anemia: n = 2 (female = 2) Myelodysplastic syndrome: n = 1 (male = 1)
Pre-transplant treatment	In AML/MDS patients 7/3: n = 1 FLAGIDA: n = 3 Venetoclax/azacytidine: n = 3 In ALL patients BFM: n = 1 HyperCVAD: n = 2 HyperCVAD + Dasatinib: n = 1 ATG/Eltrombopag/Cyclosporine: n = 2
Donor type	Unrelated matched donor n = 3 Haploidentical n = 6
Median fluorescence intensity of donor-specific antibodies (range)	22,490 (12,000-28,560)
Conditioning	Cyclophosphamide/total body irradiation: n = 1 Fludarabine/cyclophosphamide/ATG: n = 3 Fludarabine/melphalan: n = 4 Fludarabine/busulfan: n = 1
AML: acute myeloid leukemia. CR: complete response. ALL: lymphoblastic acute leukemia. MDS: myelodisplastic syndrome. FLAGIDA: fludarabine, citarabine, idarrubicine. BFM: Berlin/Frankfurt/Munster protocol. 7/3: daunorrubicine/cytarabine. ATG: antithymocyte globulin. HyperCVAD: cyclophosphamide, vincristine, doxorrubicina, dexamethasone, citarabine, methotrexate.	

TABLE 2. Transplantation characteristics and outcomes

Median CD34 x 10^6 CD34/kg infused (range)	9 (3.8-11)
Engraftment % and day (range) Granulocytes Platelets	 66% at median day 12 (12-18) 66% at median day 15 (13-18)
Primary graft failure	n = 3 (34%)
Acute graft versus host disease 3-4/100 days	n = 1
Chronic graft versus host disease	n = 2 cutaneous, mild
Mortality and causes primary graft failure refractory acute graft versus host disease	n = 4 (45%) n = 3 n = 1
3-year overall survival	n = 5 (55%)

FIGURE 1. Desensitization strategy.

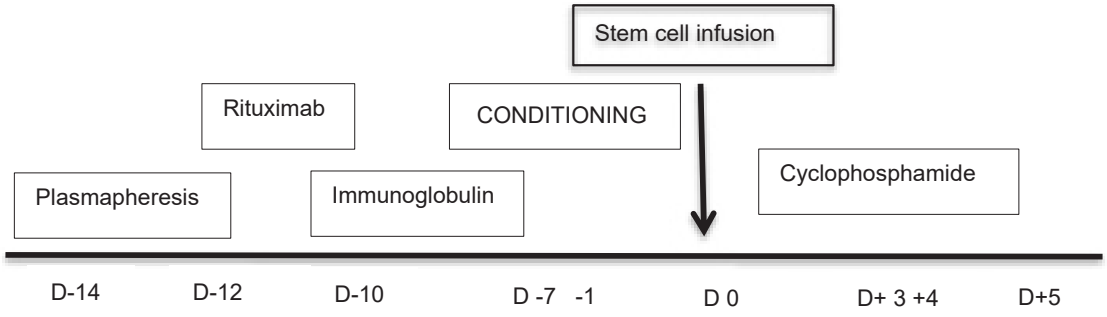
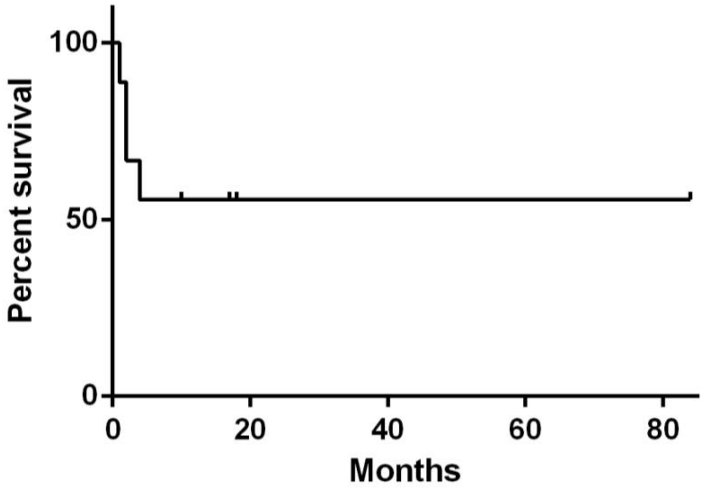


FIGURE 2. Overall survival of patients with DSA who received desensitization therapy



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ORIGINAL ARTICLE

PROJECT OF A DASHBOARD FOR BRAZILIAN CENTERS AFFILIATED WITH CENTER FOR INTERNATIONAL BLOOD AND MARROW RESEARCH

Heliz Regina Alves das Neves[1,2] Anderson João Simione[3], Cinthya Corrêa da Silva[4], Paula Moreira da Silva Sabaini[5], Bruna Letícia da Silva Santos Geraldo[6,7], Cristiano de Oliveira Ribeiro[2], Flavia Ferreira Costa[8], Adriana Mendes de Quadros Cavilha[1], Indianara Rotta[1], Leonardo Otuyama[9], Joaquim Gasparini dos Santos[9], Rafael de Oliveira[9], Simone Ojima Ferreira[10], Jessica di Chiara Salgado[11], Monique Ammi[12], Marcelo C. Pasquini[13], Vergilio Antonio Rensi Colturato[3], Samir Kanaan Nabhan[1], Nelson Hamerschlak[4], Vaneuza Araújo Moreira Funke[1,2], Yana Augusta Sarkis Novis[10], Vanderson Geraldo Rocha[9], Decio Lerner[11], Carmem Maria Sales Bonfim[14], Antonio Vaz de Macedo[15], Ricardo Pasquini[1,2], Fernando Barroso Duarte[16]

1 - Complexo Hospital de Clínicas – Universidade Federal do Paraná, Curitiba, PR,
2 - Hospital Nossa Senhora das Graças – Instituto Pasquini, Curitiba, PR,
3 - Hospital Amaral Carvalho, Jaú, SP,
4 - Hospital Israelita Albert Einstein, São Paulo, SP,
5 - Barretos Cancer Hospital, Barretos, SP,
6 - Associação da Medula Óssea, São Paulo - AMEO, SP,
7 - Associação Hospitalar Moinhos de Ventos, Porto Alegre, RS,
8 - Hospital Samaritano Higienópolis - Américas, São Paulo, SP,
9 - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, SP,
10 - Sociedade Beneficente de Senhoras Hospital Sírio Libanês,
11 - Instituto Nacional do Câncer (INCA), Rio de Janeiro, RJ,
12 - Center for International Blood and Marrow Transplant Research (CIBMTR), Minneapolis, MN, USA,
13 - Center for International Blood and Marrow Transplant Research (CIBMTR) and Medical College of Wisconsin, Milwaukee, WI, USA,
14 - Hospital Pequeno Príncipe – Curitiba, PR,
15 - Hospital da Polícia Militar, Belo Horizonte, MG,
16 - Hospital Universitário Walter Cantídio, Fortaleza, CE

Corresponding author: Heliz Regina Alves das Neves (heliz.neves@hc.ufpr.br)

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ABSTRACT

Since the first hematopoietic stem cell transplantation (HSCT) was performed at the Federal University Hospital (Curitiba, PR) in 1979, the number of centers offering this modality of treatment has increased. However, accessing comprehensive HSCT outcomes has become a challenge due to lack of an official Brazilian registry. The partnership between the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) and the Center for International Blood and Marrow Research (CIBMTR) was an important milestone in the establishment of the HSCT Brazilian registry (HSCTBR). By using CIBMTR's Data Back to Center (DBtC) tool, we have gained insights into HSCT outcomes through the Brazilian Summary Slides. While understanding the country's transplant scenario is crucial, it is equally important for each center to assess their own outcomes. In order to help the Brazilian centers with the CIBMTR, the data manager of SBTMO working group has developed a business tool solution to facilitate this important task.

Keywords: Data Management. Hematopoietic Stem Cell Transplantation. Dashboard Systems.

INTRODUCTION

Since 2016, various strategies have been implemented to improve the transplant scenario in the country. These strategies include efforts to increase the number of Brazilian centers for affiliation with CIBMTR, the creation of training programs in HSCT for data managers, and the partnership between the SBTMO and the CIBMTR. These collective efforts have made the official registry in Brazil possible. According to the Brazilian Summary Slides – 2023[1], forty centers are now affiliated with CIBMTR and reporting data to it. While the Brazilian Summary Slides provides valuable insights, it is also possible for each affiliated center to know its individual results. However, not all centers have qualified personnel with expertise in data analysis, particularly in the IT field. A way used by centers to learn about some results is presented in a visual format on the CIBMTR portal. Nonetheless, Brazilian researchers need to know other results, including survival analysis with comparative curves. To address this need, the data manager of the SBTMO working group developed a dashboard utilizing data extracted from the DBtC and Power Business Intelligence (PBI). This solution, along with a manual of instruction, will be distributed to all centers affiliated with CIBMTR.

OBJECTIVE

The aim of this project was to create a dashboard template incorporating comparative survival analysis in Power Business Intelligence (PBI) and share it with HSCT/CT centers affiliated with CIBMTR. This initiative enables users to interactively visualize their results.

MATERIAL AND METHODS

The initial step involved creating a dashboard template in PBI utilizing data fields of data extracted from the DBtC on the CIBMTR portal. In this first version, survival curves were created using R script visual in PBI, including p value for comparison curves and risk table. This version was published and tested on a website by two Centers, which have developed the project (Table 1). The second step was to create a comprehensive dashboard template with some reports on eight pages, including graphs using innate statistical and graphs using R script visual in PBI. This version featured a menu navigation (Figure 1), descriptive graphs by disease and transplant type (Figure 2), graphs categorized by age group, event date, donor type and tissue source (Figure 3), overall survival comparing allogeneic and autologous HSCT (Figure 4), acute leukemia survival comparing adult and pediatric curves (Figure 5), acute and chronic leukemia survival comparing disease status curves (Figure 6 and 7), and a report by disease classification according to the Latin-American BMT (LABMT) from the Worldwide Network for Blood & Marrow Transplantation (WBMT), facilitating this registration in the country (Figure 8). All dashboard reports are interactive and include filters by transplant type, age category (adult and pediatric), disease, year of the event and disease status for leukemias. The final step was to create a manual containing software requirements, PBI configuration instructions (data source settings and R statistical folder), and guidance on downloading the DBtC file from the CIBMTR Portal and navigating on the dashboard. The manual and the complete dashboard were distributed via email to seven data managers (DM) from different Brazilian centers and to a North American center (Table 1).

RESULTS

The DBtC allowed the standardized collection and data analysis for Brazilian centers affiliated with CIBMTR using business intelligence tools. In the initial phase of this project, survival graphs with comparative curves were successfully generated using R scripts. Following the inclusion of necessary R software packages to run survival curves, tests of the published dashboard yielded positive outcomes. This progress was presented at the Transplantation & Cellular Therapy Meeting of ASCTC and CIBMTR in 2023[2] and was awarded the second place in the IT category. In the final phase, six centers participated in this project, two as developers and four receiving the instruction manual via email. Challenges related to PBI and R software installation, as well as downloading the DBtC file were effectively solved. Additional assistance for DM, was provided via WhatsApp and virtual meeting. Two centers have successfully implemented the developed dashboard. The full presentation of this project is available at the 2024 Tandem Meetings Session Recordings website[3].

CONCLUSION

Expertise, particularly in R scripting and business intelligence, is essential for effective implementation of this project. An important advantage of this project lies in the utilization of an open-source software. Another advantage is that DMs need to setup PBI and R software only once. Fol-

lowing configuration in PBI, the DM must import the DBtC file in PBI and the dashboard is updated. Subsequent updates require only importing the new DBtC file, replacing the old one. The next step for this project is to present it to the SBTMO coordinator for approval to share the template with all CIBMTR- affiliated centers in Brazil. Future perspectives include incorporating new outcome analysis such as relapse, GVHD and cellular therapy following the DBtC updates. Additionally, there is potential to provide an interactive dashboard of HSCT/CT results on the SBTMO website and to utilize the BI tool to develop strategies for improving long-term follow-up in Brazil.

TABLE 1. Participating Centers

PARTICIPATING CENTERS	PARTICIPATION
Complexo Hospital de Clínicas – Universidade Federal do Paraná, Curitiba, PR	Developers
Hospital Amaral Carvalho, Jaú, SP	
Hospital Israelita Albert Einstein, São Paulo, SP	Received manual and the complete dashboard
Barretos Cancer Hospital, Barretos, SP	
Hospital Nossa Senhora das Graças – Instituto Pasquini, Curitiba, PR	
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, SP	
Hospital Pequeno Príncipe, Curitiba, PR	
Instituto Nacional do Câncer (INCA), Rio de Janeiro, RJ	
Hospital Sírio Libanês em Brasília, Brasília, DF	
BMTCT Database & Systems - Bone Marrow Transplantation and Cellular Therapy - St. Jude Children's Research Hospital, Memphis, TN - USA	

FIGURE 1. Menu navigation.

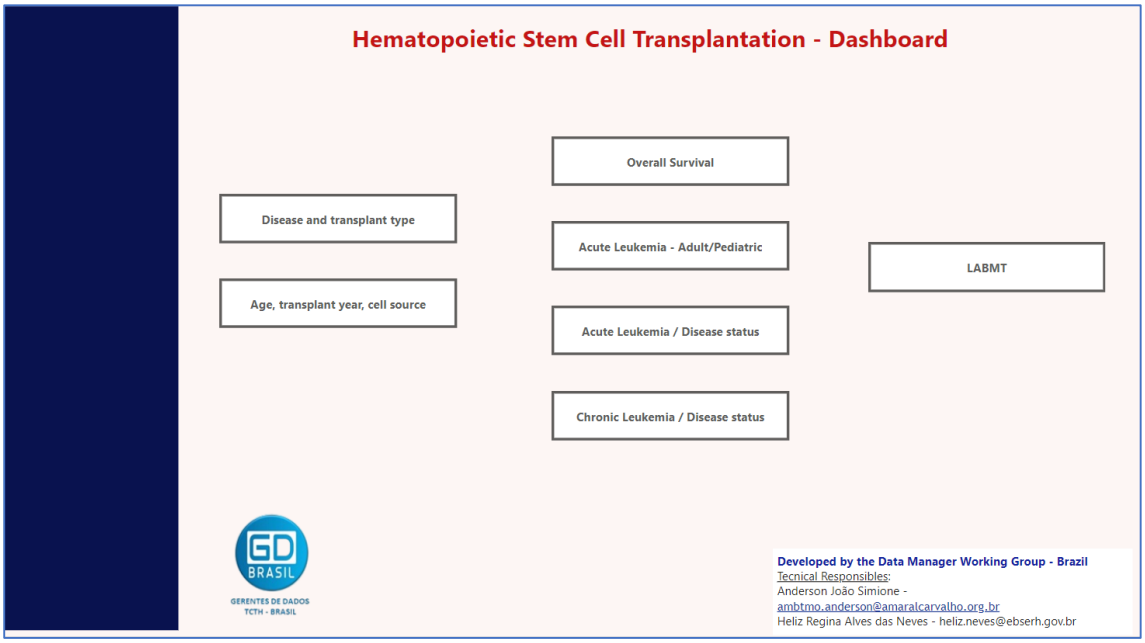


FIGURE 2. **Descriptive graphs by disease and transplant type.**

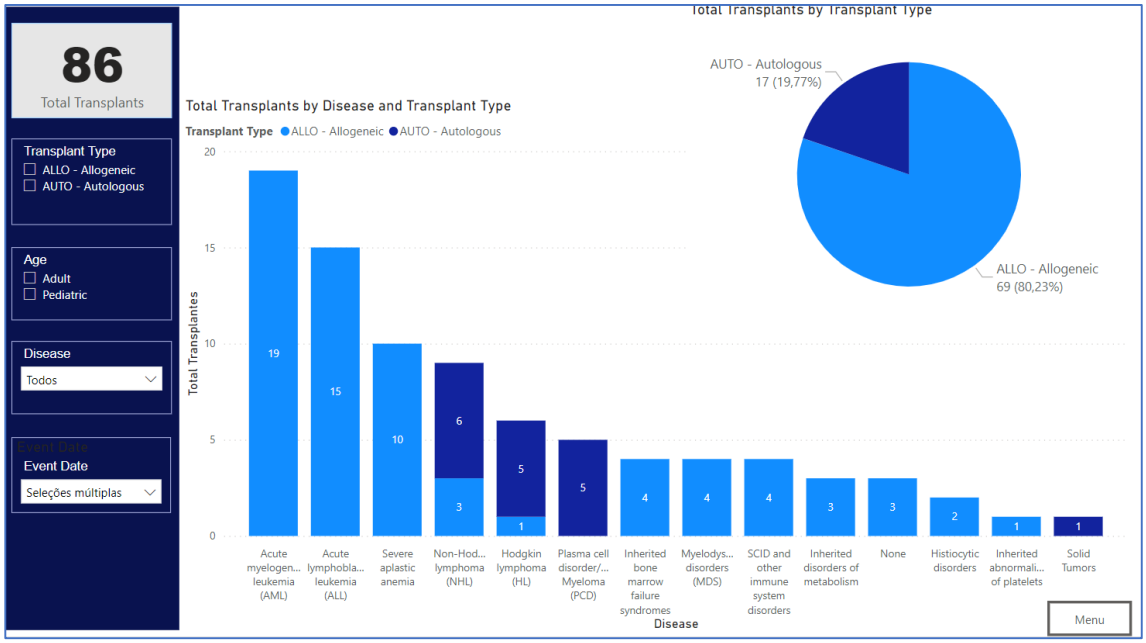


FIGURE 3. **Graphs by age group, event date, donor type and tissue source.**

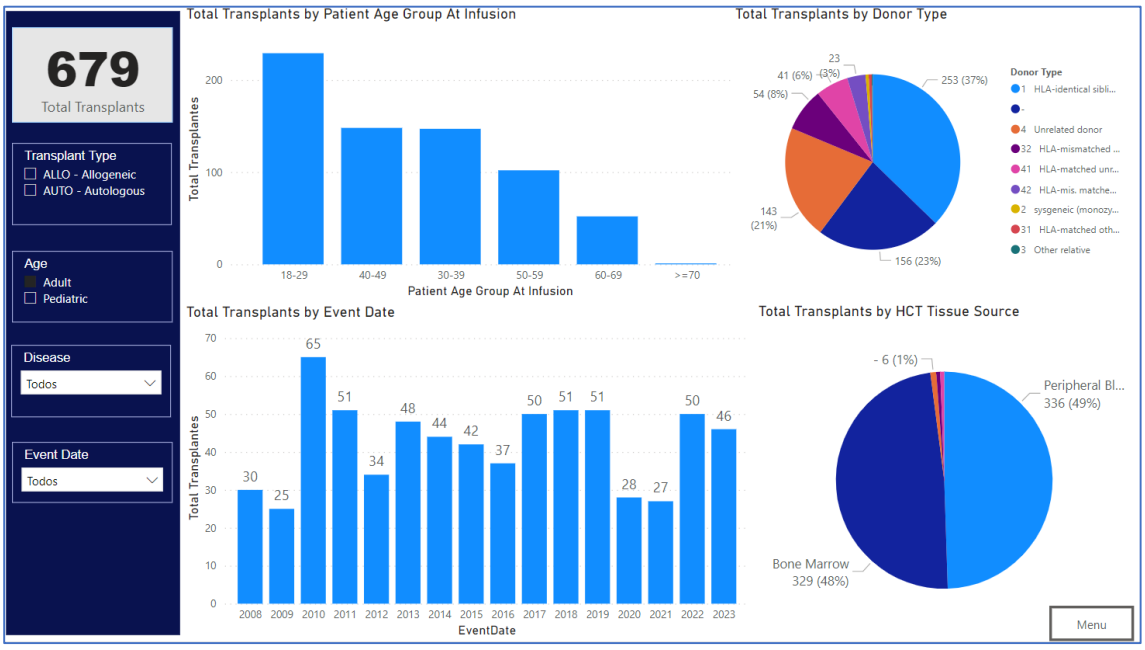


FIGURE 4. **Overall survival comparing allogeneic and autologous HSCT.**

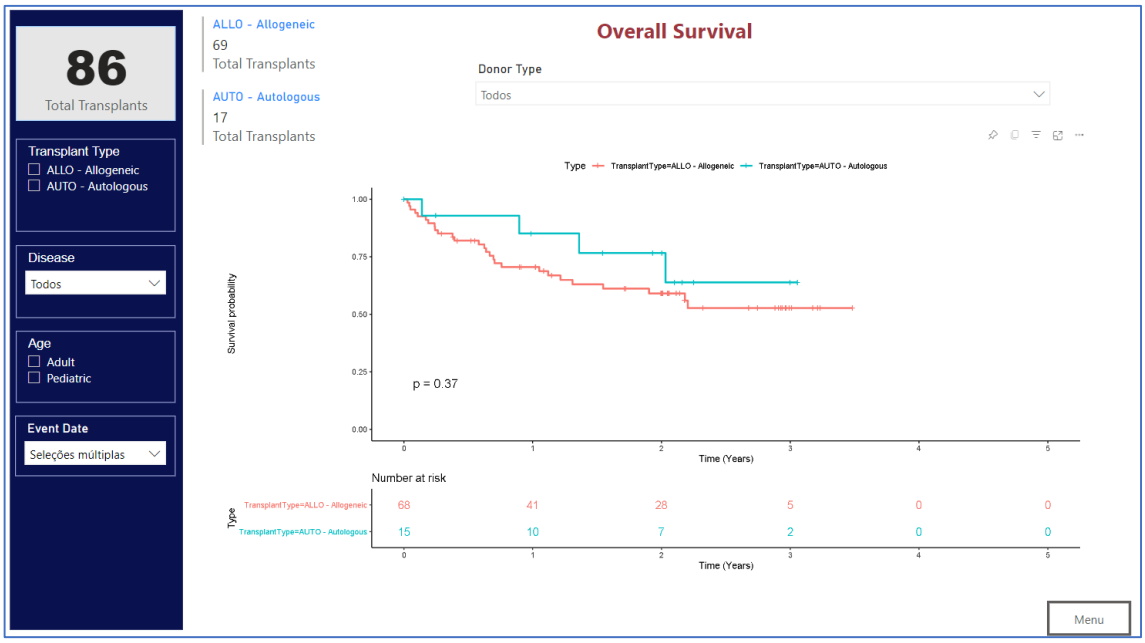


FIGURE 5. **Acute leukemia survival comparing adult and pediatric curves.**

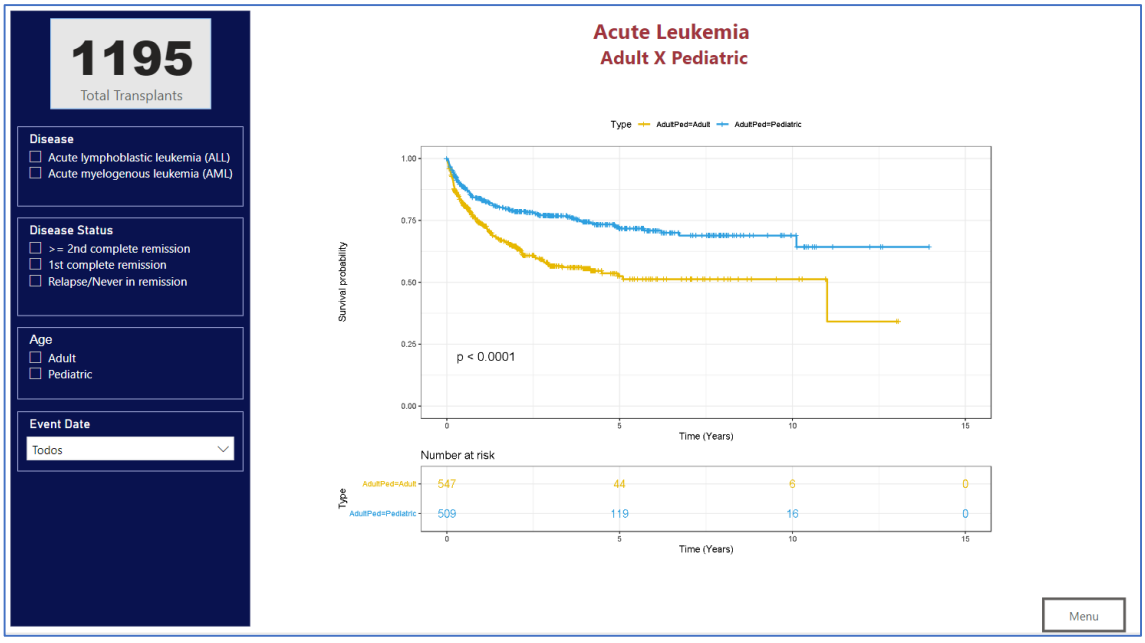


FIGURE 6. **Acute leukemia survival comparing disease status curves.**

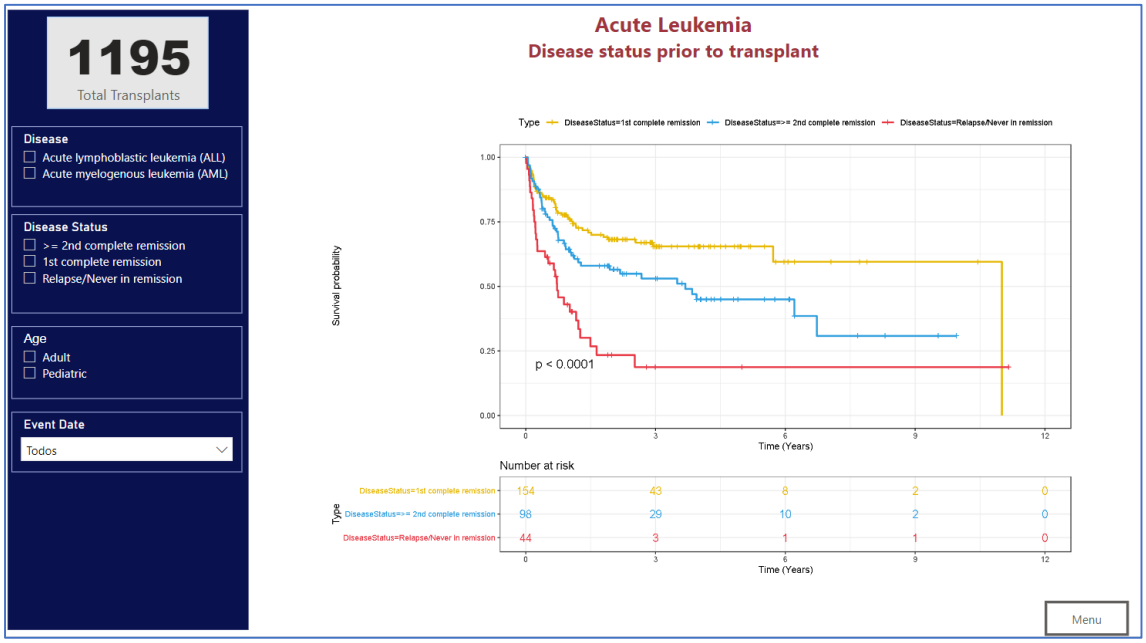


FIGURE 7. **Chronic leukemia survival comparing disease status curves.**

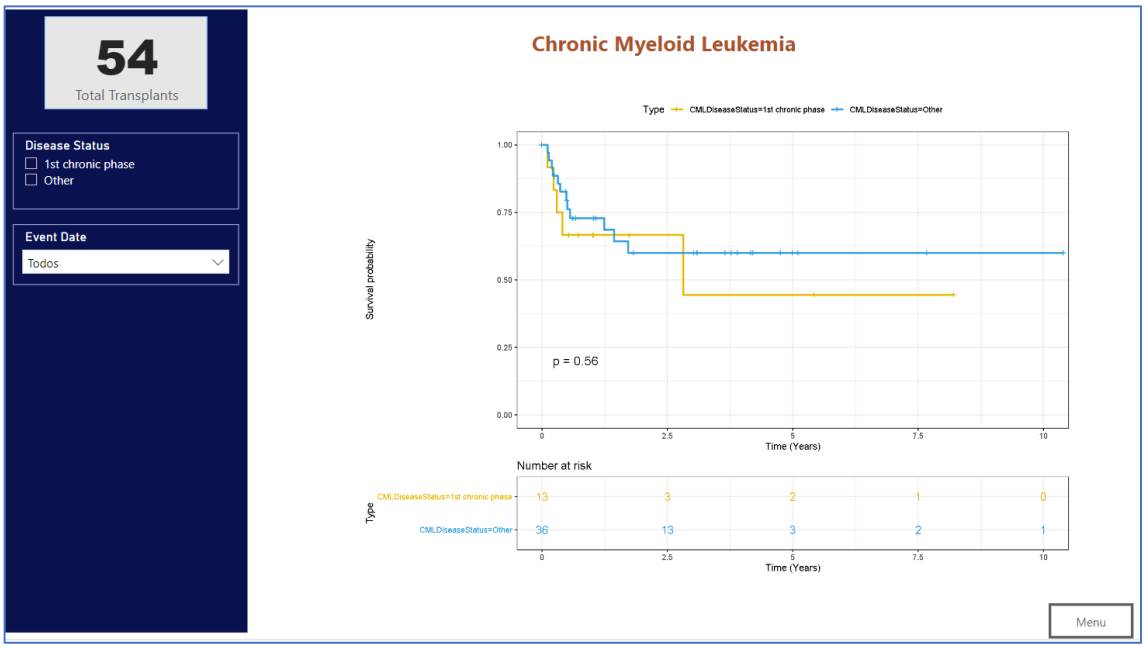
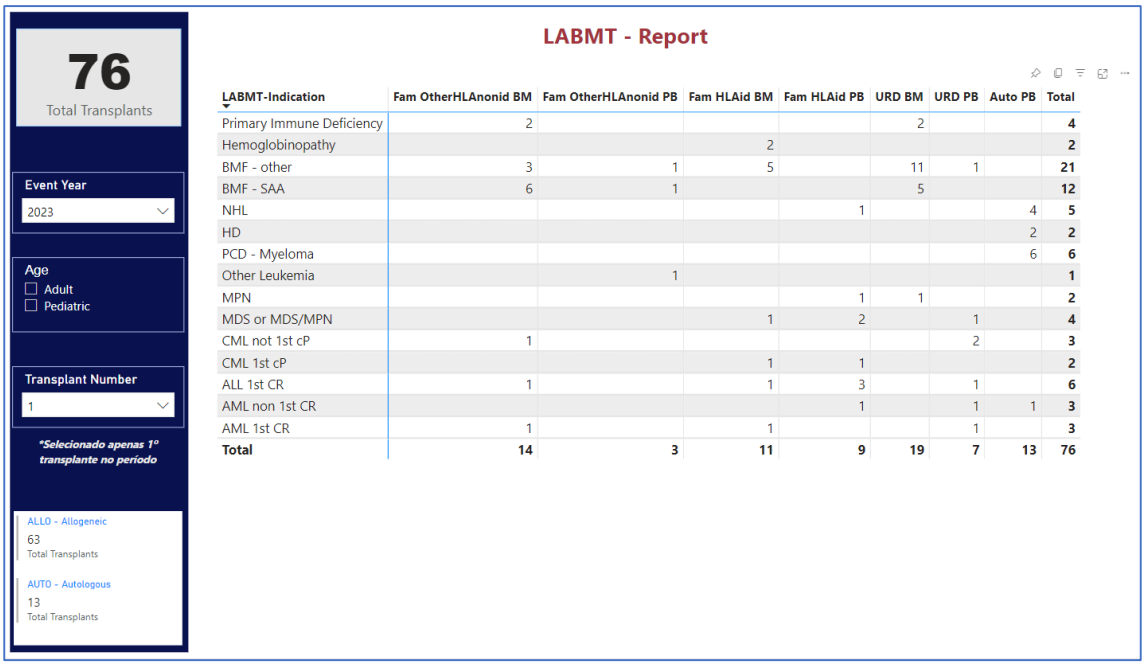


FIGURE 8. **Report by disease classification according to LABMT from WBMT.**



LABMT-Indication	Fam OtherHLAnonid BM	Fam OtherHLAnonid PB	Fam HLAid BM	Fam HLAid PB	URD BM	URD PB	Auto PB	Total
Primary Immune Deficiency	2				2			**4**
Hemoglobinopathy			2					**2**
BMF - other	3	1	5		11	1		**21**
BMF - SAA	6	1			5			**12**
NHL				1			4	**5**
HD							2	**2**
PCD - Myeloma							6	**6**
Other Leukemia		1						**1**
MPN				1	1			**2**
MDS or MDS/MPN			1	2		1		**4**
CML not 1st cP	1					2		**3**
CML 1st cP			1	1				**2**
ALL 1st CR	1		1	3		1		**6**
AML non 1st CR				1		1	1	**3**
AML 1st CR	1		1			1		**3**
Total	**14**	**3**	**11**	**9**	**19**	**7**	**13**	**76**

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SHORT COMMUNICATION

GATA GENOTYPE AND FY*B(-67T>C) POLYMORPHISM AS A CHEAP AND RELIABLE TOOL TO EVALUATE ETHNICITY IN BRAZILIAN PATIENTS SUBMITTED TO AUTOLOGOUS TRANSPLANTATION

Luciana Tucunduva[1,2], Carla Luana Dinardo[3], Leonardo Jun Otuyama[1], Karen Chinoca Ziza[3], Celso Arrais Rodrigues[4,5], Yana Novis[2], Silvia Figueiredo Costa[6,7], Vanderson Rocha[1,8,9]

1 - Laboratorio de Investigação Médica (LIM) 31, Hospital das Clínicas Faculdade de Medicina, Universidade de São Paulo (HCFMUSP), São Paulo, Brazil

2 - Hospital Sírio-Libanês, São Paulo, SP, Brazil

3 - Fundação Pró-Sangue Hemocentro de São Paulo, São Paulo, SP, Brazil

4 - Division of Hematology – UNIFESP, São Paulo, Brazil

5 - Hospital Nove de Julho – DASA, São Paulo, Brazil.

6 - LIM-49 Instituto de Medicina Tropical da Universidade de São Paulo, São Paulo, Brazil

7 - Infectious Diseases Department, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

8 - Hospital Vila Nova Star-Rede D'Or, São Paulo, SP, Brazil

9 - Churchill Hospital, Oxford University Hospitals, Oxford, UK

Corresponding author: Luciana Tucunduva (E-mail: luciana.tucunduva@gmail.com)

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INTRODUCTION

Although race and ethnicity are socially constructed concepts, collecting high quality data on these characteristics is crucial for clinical research.[1] Notably, in genetic association studies, a particular potential confounding factor is different ethnic background among patients, that can be related both to the genes and the outcome of interest – a bias referred to as population stratification.[2]

In Brazil, to describe race we commonly use the National Institute of Geography and Statistics (IBGE) classification, so-called "self-declared color", referring to individuals declaring their own racial or ethnic identity. The classification is divided in five categories (white, black, brown, yellow and indigenous), but it is acknowledged that defining ancestry by phenotypic characteristics, especially in countries with highly mixed population like Brazil, can be misleading and imprecise.[3]

The association between FY*B(-67T>C) polymorphism (rs2814778) in the GATA-box erythroid promoter region of Duffy antigen receptor chemokine gene and African ancestry is well known, defining the Duffy-null genotype.[4]

At the present study we aimed to evaluate the relationship between the GATA FY*B(-67T>C) polymorphism and self-declared race in Brazilian patients undergoing autologous transplantation and verify the feasibility of using this test as a more reliable tool to evaluate ethnicity in this population.

MATERIAL AND METHODS

We conducted a study to evaluate the association of candidate-gene polymorphisms and toxicities after autologous stem-cell transplantation (ASCT) in adult patients with lymphoma or myeloma. All patients submitted to ASCT in two Brazilian transplant centers (Hospital das Clinicas, Faculdade de Medicina University of São Paulo and Hospital Sirio-Libanes) from 2015 to 2021 with available DNA to study genetic polymorphisms were included. This study was approved by Ethics Committe of both institutions (CAPPesq and CEP) and carried out according to the criteria established by the Declaration of Helsinki with its modifications.[5] Considering our population,

it was imperative to properly eliminate the potential bias of population stratification and we decided to use GATA polymorphism besides self-declared race with this aim.

This cohort includes patients with available data on self-declared race and GATA polymorphism. Demographics and clinical data were collected from the transplant unit databases by investigators blind to the results of polymorphisms analysis. GATA genotyping was performed using commercial antisera (Lorne Laboratories, Danehill, UK) and DNA was extracted from blood or marrow samples using commercial kits (PureLink® Genomic Invitrogen, Carlsbad, CA, USA) following manufacturer's instructions. FY*B(-67T>C) allele genotyping was performed as described elsewhere.[6]

STATISTICAL ANALYSIS

Self-declared race was compared to GATA genotype (T/T, T/C and C/C) and the presence of GATA FY*B(-67T>C) polymorphism using Chi2 and Fisher tests. The departure from Hardy-Weinberg equilibrium (HWE) was tested by Chi2. Patients self-declared as black, brown, yellow or indigenous according to IBGE classification were grouped as "non-white patients". Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to assess differences between curves. For neutrophil and platelet engraftment, cumulative incidence function was estimated by the Aalen-Johansen method and compared using the Gray test. Statistically significant levels were set at p≤.05. Analyses were held on STATA software, version 18.0.

RESULTS

A total of 217 patients were included in this analysis. Median age at transplantation was 56 years (21-79) and 130 patients (59.9%) were male. Most patients were self-declared white (n=175, 80.6%) and the most common genotype was GATA67T/T (wild type/wild type) (n=142, 65.4%). There was no deviation from HWE in this population (p=0.129). Patients' demographic and clinical characteristics are described in Table 1.

Among the self-declared white patients, 73.1% were genotyped as GATA67T/T and 4.0% as GATA-67C/C, while among the non-white patients 21.4% were genotyped as GATA-67C/C (p<.0001). The allele FY*B(-67T>C) frequency was 0.22 in the whole population; it was identified in 26.9% of the self-declared white patients and in 66.6% of the non-white (p<.0001). Table 1 presents data regarding GATA genotype and GATA FY*B(-67T>C) allele frequency according to self-declared race.

Cumulative incidence of neutrophil and platelet engraftment in 30 days were 98.6% and 88.6%, respectively. Twelve-month overall survival was 86.6% (95% CI 79.9 - 91.2%), with no difference according to self-declared race (86.8% *vs* 85.5% for white and non-white patients, respectively, p=0.81) or the presence of the allele FY*B(-67T>C) (85.2% *vs* 89.9% for non-mutated and mutated patients, respectively, p=0.27).

DISCUSSION

This study shows that GATA FY*B(-67T>C) polymorphism is more prevalent in the non-white population among Brazilians submitted to ASCT. While two thirds of self-declared non-white patients presented the polymorphism, it was identified in a minority of white patients. GATA-67C/C genotype, meaning the presence of GATA FY*B(-67T>C) polymorphism in homozygosis, was identified in 21.4% of self-declared non-white patients, while it was very rare in the self-declared white group.

The presence of GATA FY*B(-67T>C) is a marker of African ancestry. This polymorphism prevents the expression of FY*B on erythrocytes' surface, leading to Fy (a-b-) phenotype, which induces protection against malaria infection.[7] Our group previously described that GATA-67C/C genotype, a simple and low-cost test, is more accurate than self-declared race in diagnosing benign ethnic neutropenia, a condition also associated to African ancestry.[4] The global GATA FY*B(-67T>C) allele frequency described at dbSNP (rs2814778) varies from 0 to 0.98 depending on the population, with very low frequencies in populations of North-Europe and high frequencies in Middle-East and Africa, as expected.[8] In Brazil, GATA FY*B(-67T>C) allele frequency is 0.18.[9]

Most studies of genetic association in the field of hematopoietic stem cell transplantation don't properly address differences on ethnicity among patients, probably because most of them are white of European ancestry and in this scenario population stratification is unlikely .[10–12] Also, collecting data on race or ethnicity is illegal in some countries.[13] However, in mixed populations like Brazilians, self-reporting race is inaccurate. According to recent data, 42.8% of Brazilians are self-declared white, 10.6% black and 45.3% brown with huge differences according to the region. Besides the risk of presenting misleading results, collecting proper data on race or ethnicity is important to guide health policies also regarding

HSCT. The Center for International Blood and Marrow Transplant group demonstrated that Hispanics and non-Hispanic blacks had lower stem cell transplantation utilization rate compared with non-Hispanic whites.[14]

No differences in clinical outcomes following ASCT were noted based on self-declared race or the presence of the GATA FY*B(-67T>C) polymorphism in this study, similar to the findings of a recent study that investigated the influence of race on outcomes after ASCT in multiple myeloma patients.[15]

In conclusion, our study shows that GATA FY*B(-67T>C) polymorphism is associated to self-declared race in Brazilian patients submitted to ASCT. Given the importance of correctly evaluating ancestry in genetic association studies in transplantation, GATA FY*B(-67T>C) polymorphism can be used as a more accurate tool in populations with mixed ethnic/racial background.

Table 1. Patients' demographic and clinical characteristics, GATA genotype and presence of FY*B(-67T>C) according to self-declared race*

	White n=175		Non-white n=42		p- value
	n	%	n	%	
Median age in years (range)	55 (20-79)		57 (27-71)		
Gender					
Male	101	57.7	29	69.0	
Female	74	42.3	13	31.0	
Diagnosis					
Gamopathy	92	52.6	29	69.0	
Lymphoma	83	47.4	13	31.0	
GATA Genotype					
GATA67T/T	128	73.1	14	33.4	<.0001
GATA67C/T	40	22.9	19	45.2	
GATA67C/C	7	4.0	9	21.4	
FY*B(-67T>C) alelle					
Present	47	26.9	28	66.6	<.0001
Absent	128	73.1	14	33.4	

*Self-declared race according to Brazilian Institute of Geography and Statistics (IBGE) classification: white (n=175), black (n=20), brown (n=20), yellow (n=1), indigenous (n=1). For these analyses patients self-declared black, brown, yellow or indigenous were grouped as "non-white".

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CORRESPONDENCE

THE ROLE OF A HEMATOLOGY OUTPATIENT CLINIC IN IMPROVING ACCESS TO BONE MARROW TRANSPLANTATION IN LOW-MIDDLE-INCOME COUNTRIES

Fernando Barroso Duarte[1], Yhasmine Delles Oliveira Garcia[2], Rafaela Cristiny Remigio Pitombeira[3], Missielle Duarte Cordeiro Barroso[3], Rafael da Nobrega de Alencar[3], Jose Wilson Linhares Junior[3], Lucas Freire Castelo[3], Beatriz Stela Gomes de Souza Pitombeira Araújo[3], João Paulo de Vasconcelos Leitão[3], Lívia Andrade Gurgel[3], Karine Sampaio Nunes Barroso[3], Beatrice Araujo Durate[4], Maria da Silva Pitombeira[3]

1- Head of the Hematology and Bone Marrow Transplant Service at Walter Cantídio University of UFC.

2 - Biomedical scientist. Federal University of Ceará, Fortaleza.

3 - Hematology and Hemotherapy Service at Walter Cantídio University Hospital.

4 - Physician student. Christus University Center. Fortaleza, Ceará.

Corresponding author: Fernando Barroso Duarte (E-mail: nutriquimio@uol.com.br)

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ABSTRACT

Discussing eligibility early in Bone Marrow Transplantation (BMT) reduces waiting time, donor search, and speeds up pre-transplant care access. The study describes optimizing access to BMT through an outpatient clinic for pre-transplant patient evaluation. Retrospective study, from 2021- 2023 at Walter Cantídio University Hospital. Data analyzed in SPSS shows 226 transplants out of 3646 consultations. The clinic referred 45 patients, contributing 19.1%, 11.7%, and 22.1% of transplants in 2021, 2022, and 2023, respectively, compared to <5% in previous years. This increase highlights the importance of expedited access to pre-transplant care, resulting in a greater number of patients eligible for transplantation.

Keywords: Bone marrow transplantation. Ambulatory Care.

INTRODUCTION

A very important aspect in carrying out a Bone Marrow Transplant (BMT) is the initial patient (?) assessment by a hematologist. In some pathologies, this discussion (the determination?) of eligibility must be considered during the first consultations and must be discussed with the patient and their family members[1]. This consideration is crucial for reducing waiting times, searching for the ideal donor and arriving at the pre-transplant clinic. Aware of this issue, we decided to create a hematological outpatient clinic with a focus on comprehensive assessment prior to referral for pre-BMT care.

MATERIAL AND METHODS

This is a retrospective, observational study of hematology patients from the outpatient hematology service of Walter Cantídio University Hospital (HUWC). Clinical and hematological evaluations were conducted before referral to the pre-HSCT outpatient clinic, conducted from January 2021 to December 2023.

In addition to the comorbidity index (HCT CI)[2,3], we are also broad geriatric assessment criteria[4,5] and, in some cases, the Next Generation Sequencing (NGS) as additional data for clinical decision-making. HDI

(Human Development Index) data for the municipalities of Ceará were obtained from the website of the Brazilian Institute of Geography and Statistics (IBGE)6. The distribution frequency was analyzed using the GraphPadPrism version 9.0 program. We consider $p< 0.05$ significant.

RESULTS

Since 2008, the HUWC BMT service has performed 808 transplants. From January 2021 to December 2023, the outpatient clinic conducted 3646 medical consultations for the HUWC BMT service. These consultations covered patients with various diagnostic possibilities including acute myeloid and lymphoid leukemias, lymphoproliferative diseases, plasma cell dyscrasias, and bone marrow failures, myelodysplasias, as well as new patients without defined diagnoses, and those coming from the HUWC hematology ward requiring chemotherapy monitoring. In total, 226 transplants were performed over the analyzed three-year period.

The Hematology Outpatient Clinic referred a total of 45 patients to the hematopoietic stem cell transplantation (HSCT) pre-transplant outpatient clinic. Of these, 41 (91.1%) underwent transplantation at the HUWC, while 4 (8.8%) patients did not undergo transplantation due to disease progression, becoming ineligible. In 2021, 13 transplants were performed, corresponding to 19.1% of the 68 performed in the current year. In 2022, due to the COVID-19 pandemic and the lack of chemotherapy drugs to perform transplants, 8 transplants were performed, representing 11.7% of the total of 68 transplants performed. In 2023, 20 transplants were performed, representing 22.1% of the 90 procedures carried out that year(Table 1). Before the implementation of this hematological outpatient clinic, the percentage of all transplants originating from this clinic was less than 5%.

Of the patients undergoing transplantation, 57.50% were male, and the average age was 43.12 ± 14.44 years. 27.5% received autologous transplantation, and 75.5% received allogeneic transplantation. Of these, 22.5% were from related , 25% were from unrelated , and 25% were from haploidentical donors.

The patients came from different municipalities in the state of Ceará, with the majority coming from Fortaleza (52.50%), which had the highest HDI (0.754). We observed that the lowest HDI was recorded in Mombaça (0.604), located 306 km from the hematology service. The average HDI of the patients' cities was 0.7098 ± 0.523, and the average distance from the hematology service was 124.4 km ± 94.05 km. (Table 2).

It is relevant to highlight that the outpatient waiting list consists of 160 patients in the pre-transplant period, and due to the limited number of beds, some patients are unable to undergo transplantation within the ideal timeframe. We observed that around 20% of the patients we saw pre-term were considered ineligible. In our sample, 38.4% of patients with lymphoproliferative disease were ineligible patients due to advanced and chemoresistant disease, which increases the difficulty of accessing adequate treatment as an initial approach without complete remission, making transplantation an unfeasible alternative. This reality is also observed in patients with bone marrow aplasia who, after multiple transfusions, find themselves alloimmunized, with platelet refractoriness and often unable to proceed with transplantation. With the changes in the processes, we observed an increase in the rates of patients eligible for BMT.

DISCUSSION

Given these preliminary data from the last three years, we can observe that changing processes and greater knowledge of the strategic role of BMT can be very useful tools in the attempt to shorten the path between the hematology outpatient clinic and the pre-BMT outpatient clinic. This interaction can be very beneficial in shortening the time between diagnosis and BMT, which for some pathologies such as acute leukemias, myelodysplasias and bone marrow failures, it is crucial in the final outcome[5,7].

Greater awareness has emerged that age alone is not the sole defining factor for eligibility[8,9]. Instead, it is an additional aspect that must be considered together with comorbidities[7] and cognition[10]. This shift has changed the life stories of many previously ineligible patients.

Access to transplantation, as well as its results, depends on socioeconomic factors that may vary between and within countries[11]. Studies in developing countries with high ethnic and demographic diversity have demonstrated an association between socioeconomic level and access to transplantation and mortality after transplantation. The HDI assesses longevity, knowledge, and standard of living, an HDI (<0.500) is considered a low development status, an HDI between (0.500 to 0.799) is considered intermediate and an HDI (>0.800) is considered high[12]. In this study, we observed that the majority of patients who had access to HSCT at our service had an intermediate HDI. In the European multicenter study, high HDI was associated with greater relapse-free survival and reduced risk of relapse[11].

We must also consider the decision to contraindicate the HSCT procedure, which can make the path of palliative medicine a wise alternative. This approach may bring more peace, comfort and dignity to the patient and their family, particularly when all parties converge on the same decision[4].

It is important to highlight the growth and importance of this action in our service. We currently have five assistant medical doctors on the team, and a multidisciplinary team that contributes significantly, strengthening our initial efforts.

Aware of the relevance and advances achieved through this initiative, we chose to share our experiences, with the purpose of highlighting that changing processes, especially in a public university service in a region with significant financial restrictions like ours, could serve as support to other centers in our country and in nations classified as low and middle income (LMIC).

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Competing Interests
The authors declare no competing interests.

TABLE 1: Patients from the pre-BMT outpatient clinic who underwent bone marrow transplantation between 2021 and 2023.

YEARS	NUMBER OF TRANSPLANTS PERFORMED PER YEAR	NUMBER OF PATIENTS REFERRED FOR PRE-BMT (%)
2021	68	13 (19,1%)
2022	68	8 (11,7%)
2023	90	20 (22,2%)
Total	226	41 (18,1%)

Note: BMT: Bone Marrow Transplantation; (%) = Percentage

TABLE 2: Origin, HDI and travel distance of patients treated at the outpatient clinic who were referred to pre-term care.

CITIES	NUMBER OF PATIENTS	HDI	DISTANCE (km)
Fortaleza	21	0,754	10
Itapipoca	2	0,64	146
Russas	2	0,674	168
Horizonte	1	0,679	46,5
Itaitinga	1	0,68	33,3
Limoeiro do Norte	1	0,682	198
Trairi	1	0,632	124
Redenção	1	0,651	62
Ibicuitinga	1	0,642	195
Eusebio	1	0,701	25
Independência	1	0,632	303
Mombaça	1	0,604	306
Sobral	1	0,714	240
Canindé	1	0,612	116
Maracanaú	1	0,736	19,6
São Gonçalo do Amarante	1	0,665	62,8
Palmácia	1	0,65	67,7
Mulungu	1	0,65	116

Note: HDI=Human development index; Km=kilometers.

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CORRESPONDENCE

DENGUE TRANSMISSION BY GRAFT OR BLOOD TRANSFUSION IN HCT RECIPIENTS

Clarisse Martins Machado[1]
Marcia Garnica Maiolino[2]
Jessica Fernandes Ramos[3]
Fabianne Carlesse[4]
Ana Verena de Almeida Mendes[5]

1 - Laboratório de Virologia, Instituto de Medicina Tropical da faculdade de Medicina da USP, Brazil
2 - Universidade Federal do Rio de Janeiro
3 - Hospital Sírio Libanês
4 - Universidade Federal de São Paulo
5 - Hospital São Rafael, Universidade Baiana, Brazil

Corresponding author: Clarisse Martins Machado (E-mail: clarimm@usp.br)

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Dear Sir,

Dengue is an arbovirus caused by a small RNA virus (DENV) belonging to the genus Flavivirus, family Flaviviridae, mainly transmitted by mosquitoes of the genus *Aedes*. However, dengue can also be transmitted by blood transfusion, blood components, or by the graft in solid organ (SOT) and hematopoietic cell transplantation (HCT).

Concern about non-vector transmission of dengue started in 2002, when the first cases of transfusion-transmitted (TT) dengue were reported in Hong Kong[1,2].

The current dengue epidemic in Brazil shows figures never before documented. By the end of March 2024, more than 2,300,000 probable cases of dengue had been registered, almost five times more than the number of cases reported during the entire year of 2023[3].

It is well known that dengue may present with a large percentage of asymptomatic cases (around 50%). Given the high activity of the current epidemic, HCT centers are rightly concerned about the likelihood of graft- or TT dengue, and the need for universal screening of donors.

Data from studies carried out in Brazil and around the world can help us evaluate the problem, answering the questions that naturally arise in the current situation:

1. What is the chance of an asymptomatic blood or hematopoietic cell donor having dengue viremia at the time of donation?

In blood donors from endemic countries, studies have documented viremia rates ranging from 0.04% to 0.8% during epidemics[4,5].

There are no studies on the rate of dengue viremia in HCT donors. However, it is reasonable to assume that such rates are similar to those for blood bank donors during epidemics.

2. Do all viremic donors transmit dengue to recipients?

No. A study carried out in Brazil by Sabino et al. demonstrated that approximately 1/3 of blood donations with positive PCR transmitted dengue during the DENV-4 epidemic in Brazil in 2012. The rate of TT dengue in that study was 37%. However, there was no difference in clinical symptoms or overall survival in recipients who received RNA-positive or RNA-negative transfusions. The lack of clinical impact of TT dengue observed in this study supported

the decision not to introduce dengue screening in blood banks in the country[5].

During epidemics, vector-borne dengue is by far the most common way to contract dengue. According to some authors, the lower infection rate observed after exposure to a human-derived parenteral inoculum compared to a mosquito-derived cutaneous inoculum can be explained by differences in glycosylation patterns of the virus replicating in mosquitoes or humans, and/or to the injection of mosquito saliva, which triggers local inflammation and other potentiating factors that can increase local viral replication and systemic infection[6,7].

Regarding HCT recipients, in a prospective cohort study carried out at the HCT Program of Hospital das Clínicas at USP, the authors observed that 5.3% of the 93 recipients had a serological diagnosis of dengue during follow-up (one by IgM detection and four by IgG seroconversion). None of the blood components infused into these patients showed a positive PCR for dengue. Therefore, no cases of TT dengue were recorded, and dengue cases were acquired through vector bites[8].

3) Are there cases of graft-transmitted dengue reported in HCT recipients?

To date, only 2 proven cases of dengue acquired by the graft have been reported in HCT. The first case occurred in a 6-year-old child during an epidemic of DENV 4 in Puerto Rico. The donor developed fever and headache the day following HCT. DENV 4 was retrospectively diagnosed in the donor by IgM detection. The recipient died of severe dengue 11 days after HCT[9].

The other case of DENV 1 was reported in Germany, in a 51-year-old HCT recipient, whose donor reported a recent travel to Sri Lanka, returning 3 days before the start of G-CSF mobilization. In the second day of apheresis, donor platelet count dropped to 47,000/mL and dengue was diagnosed by IgM, NS1 and PCR positive. Due to urgent medical need, HCT proceeded. Venoocclusive disease and dengue were diagnosed 3 days after HCT. Other bacterial and fungal infections followed and the patient died 9 days after transplantation[10].

In both cases, the viruses identified in the donor and recipient were genetically related.

Considering the Brazilian scenario of endemic dengue alternating with periods of epidemic, one would expect more reports of dengue in HCT recipients, if transmission through the graft were frequent and led to exuberant and severe clinical manifestations.

4) Is dengue transmitted by blood or transplant more severe than transmitted by mosquitoes?

Due to the lack of prospective studies on the incidence of dengue in HCT, it is not possible to estimate the real morbidity and mortality of dengue in this population.

The two published cases of graft-transmitted dengue died on d+11 and d+9 after HCT. In the case of the patient from Germany, it was not possible to assess the role of dengue in the patient's death due to concomitant severe venoocclusive disease and other complications[9,10].

Reviewing the literature, it is observed that the mortality rate attributed to dengue is higher in case reports compared to case series, both in SOT and HCT[11-14]. In general, reports of severe cases are published more frequently than those of mild or moderate cases, leading to publication bias and the false impression of high mortality. Indeed, a recent review of endemic and geographically limited infections, including published Brazilian cases of post-HCT dengue, showed that the vast majority of patients showed complete clinical recovery[15].

5) What are the immediate implications of implementing universal donor screening?

Firstly, the logistics of implementing and ensuring access to dengue diagnosis by PCR to all HCT centers. Once the diagnosis has been implemented, it is important that the PCR result is released within a short period of time so that the recipient's treatment is not compromised. It is essential that the result is available before the conditioning regimen begins.

Next, the cost-benefit of such a procedure. Considering the scenario of a viremia rate of 1% in asymptomatic donors, 100 tests would be needed to identify 1 donor with a positive PCR. Donors diagnosed with dengue are deferred from donation and HCT must be postponed.

In view of the above, the Infection Committee of The Brazilian Society for Marrow and Blood Transplantation and Cell therapy (SBTMO) recommends:

1. Guidance for donors and patients who are close to the scheduled date of stem cell (SC) harvesting and preparation for HCT to avoid contact with the vector.

2. Careful investigation of dengue symptoms during pre-transplant assessment. Dengue may initially present as flu-like syndrome.

3. Test all symptomatic donors and recipients, preferably by PCR. Be aware that the sensitivity of NS1

antigen test is lower in first three days of symptoms and in secondary dengue infection[16].

4. PCR is the best test to diagnose dengue in the 1st week of symptoms. In HCT recipients, it is probable that PCR remains positive after the 1st week, due to prolonged viremia observed in this population (13). NS1 is more frequently detected between the 3rd and 5th day of symptoms, and is frequently negative after the 7th day. Serology may be used if PCR or NS1 is not available. IgM generally appears after the 5th day of symptoms[16]. IgG has a limited value in the diagnosis of dengue in endemic countries due to the possibility of previous dengue infection.

5. In the case of a donor with a positive PCR, the period of ineligibility for donation is 30 days for mild cases of dengue, and 180 days if the donor has severe dengue.

6. In the case of a candidate for HCT with a positive PCR, the transplant must be postponed for 30 days after clinical resolution of the disease. Be aware that immunocompromised candidates and HCT recipients may have prolonged viremia[13].

7. Instruct all donors to report fever, malaise, headache or other symptoms that appear in the week following stem cell harvesting. It is important to exclude the possibility that the donor had the SC harvested during the dengue incubation period.

8. During periods of epidemics, it is strongly recommended to include dengue PCR and NS1 test as appropriated, in the investigation of febrile episodes, thrombocytopenia or shock in HCT recipients.

9. The live attenuated dengue vaccine has not been evaluated in immunocompromised patients and is not recommended in HCT recipients. However, close contacts with patients must follow the National Immunization Program (PNI) regarding vaccination against dengue.

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