DOI: 10.46765/2675-374X.2020v2n1p55-62

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

Cinthya Corrêa da Silva[1], Leonardo Javier Arcuri[1], Anderson João Simione[2], Heliz Regina Alves das Neves[3], Bruna Letícia da Silva Santos Geraldo[4], Afonso C Vigorito[5], Vaneuza Araújo Moreira Funke[3], Marcos Paulo Colella[5], Andreza Alice Feitosa Ribeiro[1], Vanderson Geraldo Rocha[6], Iracema Esteves[1], Carmem Bonfim[3], Victor Zecchin[7], Fernando Duarte[8], Roberto Luiz da Silva[4], Cintia Monteiro[7], Germison Silva Lopes[8], Larissa Guzelotto[5], Samir Nabhan[3], Vergílio A.R. Colturato[2], Nelson Hamerschlak[1]

1Hospital Israelita Albert Einstein, São Paulo, 2 Hospital Amaral Carvalho, Jaú, 3 Hospital de Clínicas – Universidade Federal do Paraná, Curitiba, 4 Bio Sana's, São Paulo, 5 Universidade Estadual de Campinas, Campinas, 6 Hospital das Clinicas da Universidade de São Paulo – São Paulo, 7 Grupo de Apoio ao Adolescente e à Criança com Câncer, São Paulo, 8 Hospital Universitário Walter Cantídio, Ceará

Correspondence to: Cinthya Corrêa da Silva – cinthya.silva@einstein.br

ABSTRACT

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

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

INTRODUCTION

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

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

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

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

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

OBJECTIVE

Primary Objective

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

Secondary objective

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

Methodology

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

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

Results

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

CONCLUSION

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

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

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TABLE 1 - Patients baseline profile

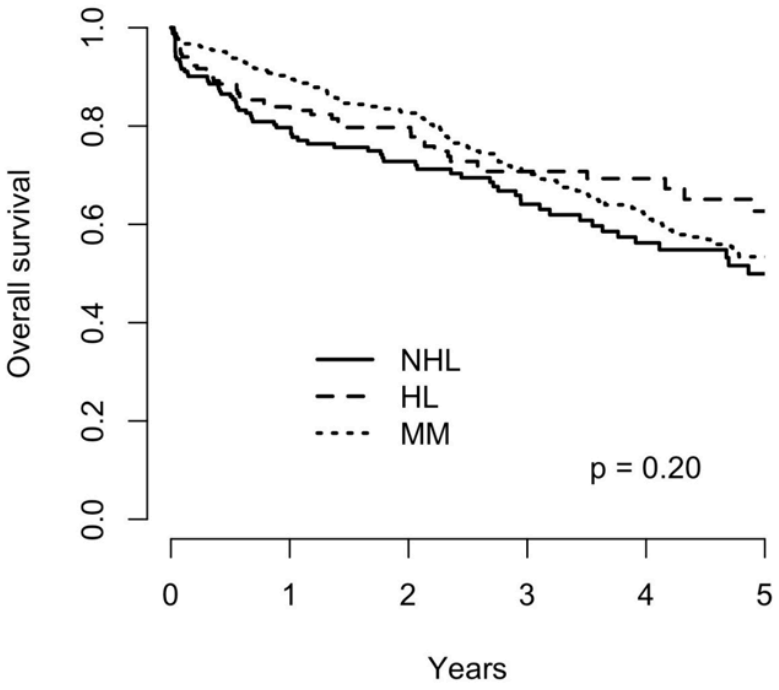
	ALLO	AUTO	TOTAL	P VALUE
Total	2659	1574	4233	
idade				< 0.001
median(IQR)	25 (11,42)	49 (29,58)	34 (15,51)	
Gender				0.627
Male	1571 (59.1)	918 (58.3)	2489 (58.8)	
Female	1088 (40.9)	656 (41.7)	1744 (41.2)	
Primary.Disease				< 0.001
Acute myelogenous leukemia	648 (24.4)	26 (1.7)	674 (15.9)	
Non-Hodgkin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

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

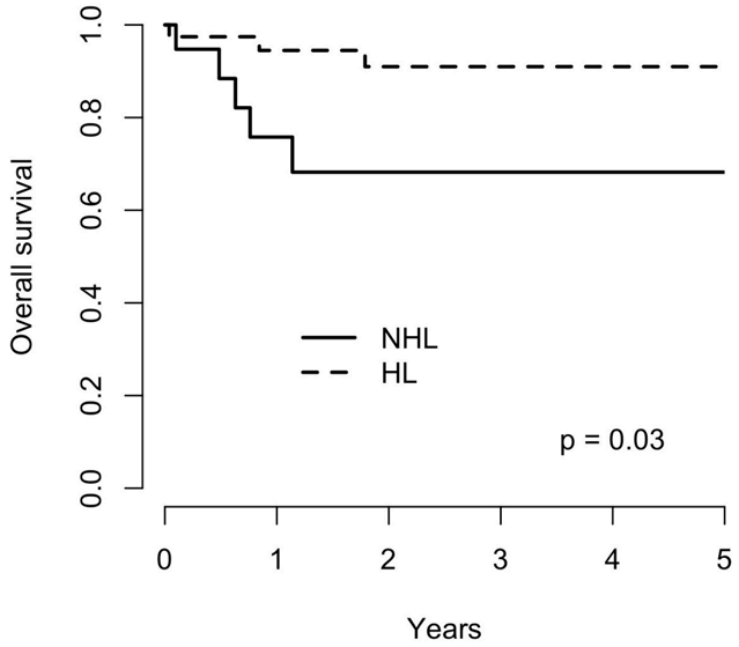
TABLE 2 - Main outcomes

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

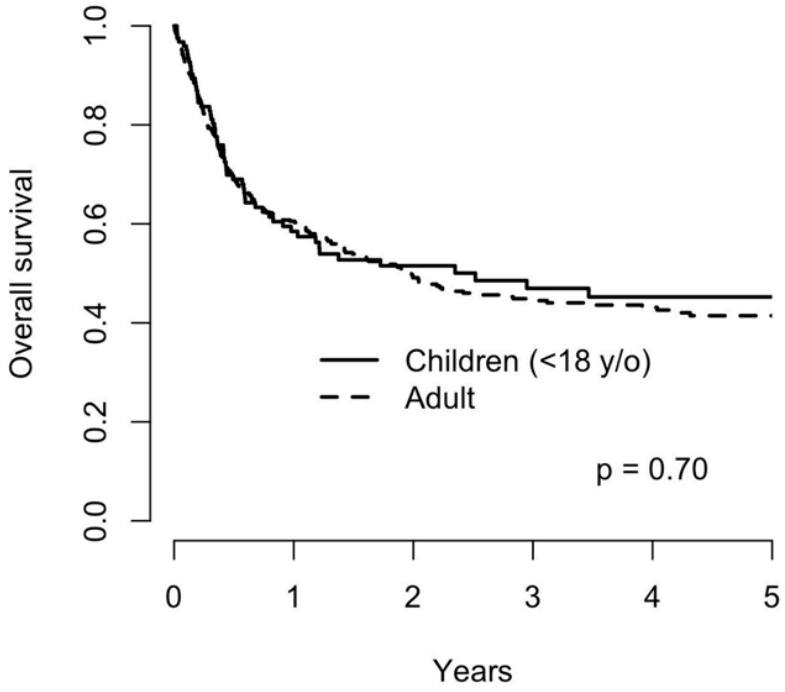
GRAPHIC 1 - Overall survival of adult patients to MM, HL and NHL



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



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



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