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

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ABSTRACT

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

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

INTRODUCTION

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

The treatment using genetically modified cells have potential risks for late effects for recipients manufacturing process may lead to the development of subsequent malignancies, including insertional mutagenesis or through the presence of replication competent retrovirus or lentivirus¹. Brazil's National Health Surveillance Agency (Anvisa) has adopted the requirement from other national regulatory health authorities in requiring that recipients of these therapies to be followed for 15 years for assessment of

safety outcomes, including the development of subsequent neoplasms.

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

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

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

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

OBJECTIVE

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

METHODS

Data Sources

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

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

Selection

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

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

Definitions and Outcomes

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

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

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

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

Statistical analysis

Descriptive statistics was used for categorical data, with the number of cases and percentage. Graphics were

generated by PBI and exported to Microsoft PowerPoint for publication. Overall survival was estimated by the Kaplan Meier method, survival analyses were 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 Hamerschlag).

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

RESULTS

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

CONCLUSION

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

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

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- Dr. Nelson Hamerschlak, Dr. Vergilio Antonio Rensi Colturato and Dr. Fernando Barroso Duarte have been influential advocates for the progress of HCT and CAR-T cell in Brazil, having catalyzed significant advances in the field since 2016.
- Dr. Marcelo Pasquini facilitates direct collaboration with the CIBMTR, ensuring that the latest research updates and best practices are disseminated within the community.
- Monique Ammi has played an active role facilitating the affiliation of Brazilian centers and has been pivotal in educating and supporting data managers involved in HCT and CAR-T cell initiatives.
- The multidisciplinary CAR-T cell teams across the country, through their dedicated efforts, directly contribute to the ongoing development and success of this specialized field of medicine.
- Finally, the invaluable contribution of patients who have undergone CAR-T cell cannot be overstated, as their willingness to share data and participate in scientific research is critical to advancing knowledge and improving outcomes in this important area of healthcare.

TABLE 1. CAR-T cell centers]

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

TABLE 2. Brazilian academic CAR-T cells initiatives

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

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

Source: Information kindly provided by Dr. Nelson Hamerschlak.

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

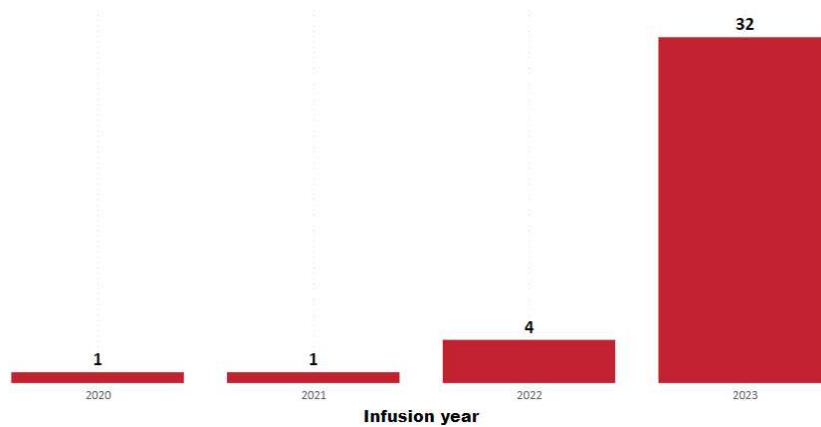


FIGURE 2. Distribution of CAR-T cell recipients by age

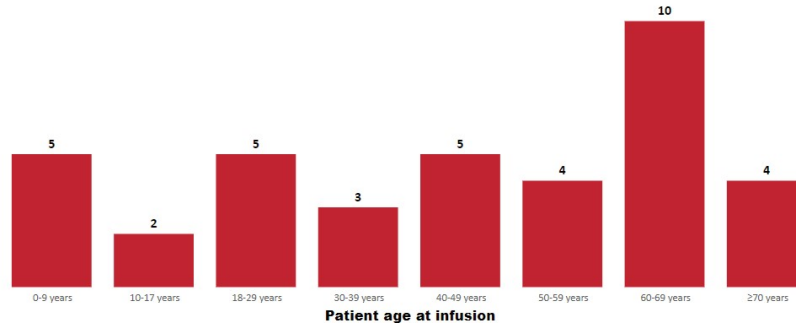


FIGURE 3. CAR-T cell indications

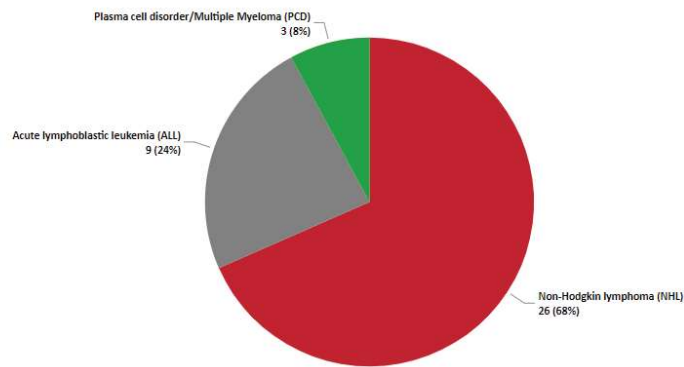


FIGURE 4. CAR-T cell indications by commercial and non-commercial product

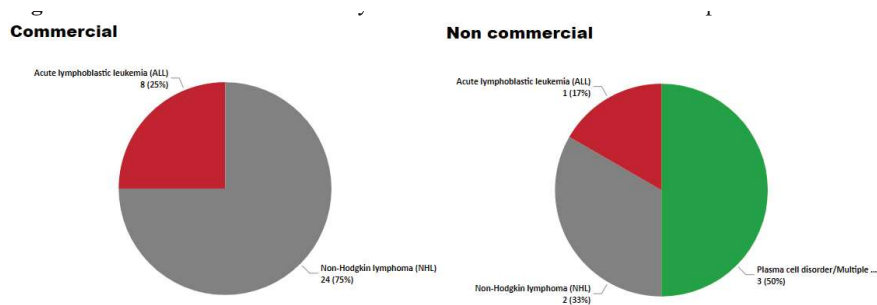


FIGURE 5. Use of Car T infusions with prior HCT for diseases

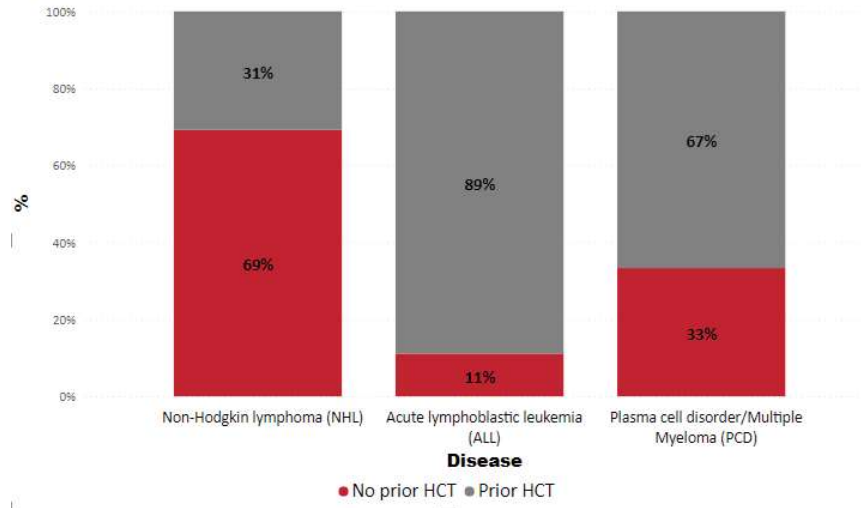


FIGURE 6. Overall Survival Non-Hodgkin lymphoma. The survival estimates at 150 days were 73% (95% CI, 57-95).

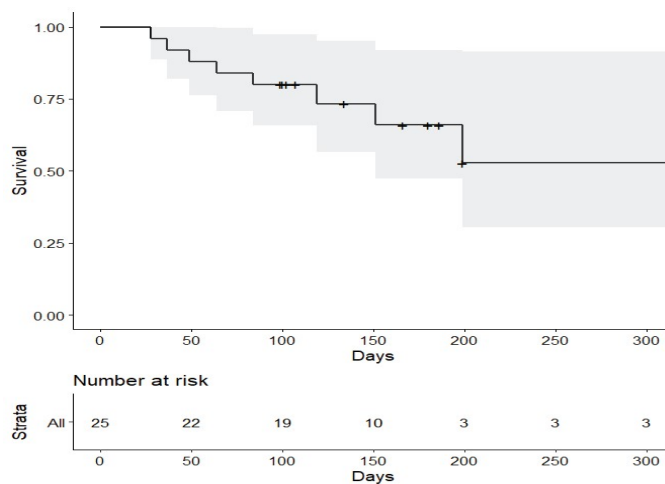


FIGURE 7. Overall Survival Acute leukemia. The survival estimates at 150 days were 60% (95% CI, 33-100).

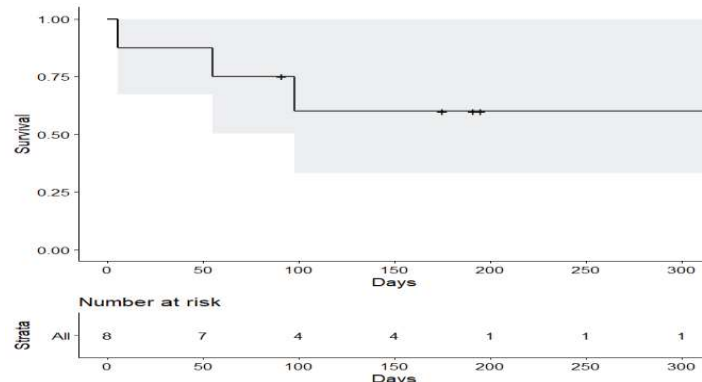
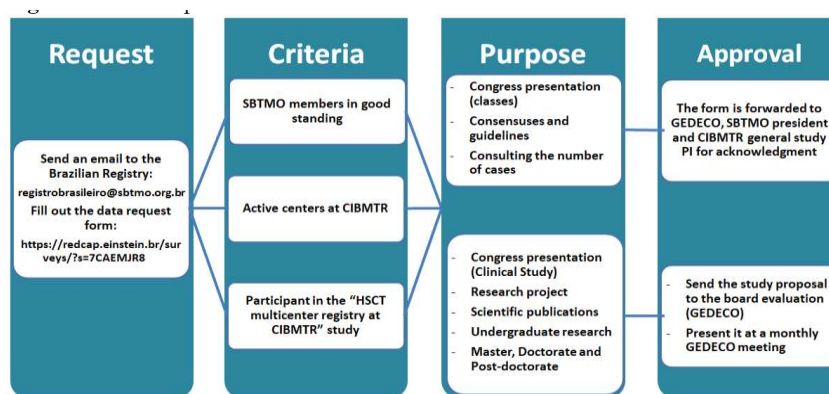


FIGURE 8. Data request flow



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