CAR-T cell therapies

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Section editor: Fernando Barroso Duarte

Received: Sept. 15, 2025 • **Accepted:** Oct. 18, 2025

ABSTRACT

Chimeric antigen receptor T-cell (CAR-T) therapy has rapidly reshaped the therapeutic landscape for children and adolescents with relapsed or refractory hematologic malignancies. In Brazil, the integration of CAR-T therapy into pediatric oncology practice faces unique logistical, regulatory, and socioeconomic challenges, highlighting the need for structured, context-specific guidance. This national pediatric consensus summarizes current evidence and provides practical recommendations for indications, leukapheresis, washout strategies, bridging therapy, lymphodepletion, infusion procedures, and the management of toxicities, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, coagulopathy, and HLH-like syndromes. Long-term follow-up, immune reconstitution monitoring, vaccination guidance, and survivorship considerations are also addressed. Emerging applications in myeloid malignancies, T-cell neoplasms, and solid tumors—particularly GD2-targeted CAR-T cells for neuroblastoma—are briefly reviewed. By consolidating multidisciplinary expertise from institutions across Brazil, this document sought to support safe, effective, and equitable implementation of CAR-T therapy in the pediatric population and encourages continued development of local manufacturing and academic protocols to expand access to this transformative treatment.

Keywords: Chimeric Antigen Receptors. T-Cell Therapy. Gene Therapy. Hematologic Neoplasm.

INTRODUCTION

Chimeric antigen receptor T-cell (CAR-T) therapy, a groundbreaking regenerative and precision medicine strategy, has transformed the treatment landscape for previously untreatable diseases, particularly in oncology[1]. This therapy is especially impactful for pediatric patients with refractory leukemias and lymphomas, as CAR-T cells can specifically target and eliminate tumor cells, significantly enhancing the prognosis for children and adolescents unresponsive to standard treatments[2].

In Brazil, while the implementation of CAR-T cell therapy faces substantial challenges, its therapeutic potential warrants concerted efforts for integration into the healthcare system. The Brazilian consensus on pediatric cell therapy highlights the importance of a multidisciplinary approach, aiming to create evidence-based guidelines for CAR-T cells that consider the country's unique epidemiological, clinical, and socioeconomic context[3]. Engaging hematologists, pediatric oncologists, immunologists, bioethicists, and health policymakers is essential for ensuring that diverse expertise contributes to the effective rollout of CAR-T cell therapy in Brazil.

INDICATIONS

The only commercially available CAR-T for pediatric leukemia, Tisagenlecleucel, is considered standard therapy, with at least 50% event-free survival in primary refractory acute lymphoblastic leukemia (ALL), relapses resistant to two lines of therapy, beyond second relapse[4] and relapses post-hematopoietic cell transplantation (HCT). In patients excluded from the original Eliana trial, real-world data[5] have shown promising event-free survival as children < 3 years old (69%), patients treated in first refractory relapse (49%), with active extramedullary disease, including the central nervous system (34%), blinatumomab non-responders (24%), and relapses less than six months post-HCT (18.4%). A high disease burden is associated with inferior outcomes (31% event-free survival) and higher treatment-related cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS). KMT2A rearrangement, despite excellent 67% relapse-free survival, has an increased chance of lineage switch. Children with Down syndrome also have 38% disease-free survival[6]. Therefore, in clinical practice, no patient population should be excluded from CAR-T cell therapy if they have an indication based on their disease status.

WASHOUT AND LEUKAPHERESIS

A washout period of therapies before leukapheresis is important for preserving the number and function of T cells. Generally, the interval is at least five half-lives of the drugs, but lymphotoxicity of the treatment is also considered (Table 1)[7].

Table 1. Recommended washout period*.

6 months	12 weeks	8 weeks	4 weeks	14 days
ATG	Bendamustin	Clofarabine Anthracyclines	DLI	Cytarabine > 100 mg/m2 anthracyclines cyclophosphamide methotrexate ≥ 25 mg/m2 Graft-versus-host disease therapies
Alemtuzumab	Fludarabin Allogeneic stem cell transplant		Peg-pararinase	Long-acting growth factors Imatinib Dasatinib Ponatinib Blinatumomab Cyclophosphamide Vincristine
7 days		**5 days**	**3 days**	**1 day**
Vincristine 6-mercaptopurine 6-thioguanine methotrexate (≤ 25 mg/m2) cytarabine (≤ 100 mg/m2), asparaginase (non-PEGylated)		Short-acting growth factors	Short-acting	Intrathecal Cytarabine
		Nilotinib	Cytotoxic drugs Antiproliferative drugs (for example, hydroxyurea) Tyrosine kinase inhibitor	

*Physiological replacement doses of steroids are allowed—no washout required: up to 12 mg/m²/day hydrocortisone or equivalent in pediatric patients, up to 40 mg/day hydrocortisone or equivalent in adult patients. Topical or inhaled steroids for localized treatment of graft-*versus*-host disease are allowed—no washout required. Source: EBMT/EHA CAR-T Cell Handbook (2022)[9].

It is recommended that leukapheresis be performed as soon as the patient meets the indication for CAR-T therapy—if possible, prior to chemotherapy.

Vascular access must be evaluated. Most pediatric patients require a central venous catheter. High blast counts in peripheral blood and low ALC (< 100/ µL) and T-cell counts are associated with lower collection yield but are not prohibitive. The required target in the product varies according to the manufacturer[7]. Tailor apheresis parameters to the patient's condition. Tailor apheresis parameters to suit the manufacturer's needs and requirements[8].

BRIDGING THERAPY

Bridging therapy refers to administering chemotherapy to maintain disease control between lymphocyte collection, lymphodepletion, and the infusion of the CAR T-cell product. It should ideally not induce significant complications, such as infections, bleeding, or organ dysfunction, that might interfere with the planned lymphodepleting therapy and CAR-T cell infusion.

Effective communication between the CAR-T therapy teams, and the referral centers is essential for successful planning and execution.

Table 2 summarizes possible bridging therapies tailored to these factors[9].

Table 2. Bridging therapy options*+.

Disease characteristics	Bridging therapy options	Notes
Smoldering disease (minimal or no progression)	Observation (no active treatment)	Suitable for patients with stable, low-burden disease
Low disease burden and/or slowly progressing acute lymphoblastic leukemia	• Weekly vincristine (VCR) with oral 6 MP and methotrexate (MTX). • Weekly VCR plus dexamethasone (DEX) 6 mg/ m2 two days/week.	Aimed at maintaining disease control with minimal toxicity
Moderate disease burden and/or progressing acute lymphoblastic leukemia	Consolidation « IB » (6 MP, cytarabine, cyclophosphamide). • Weekly VCR plus DEX, bortezomib, asparaginase	Designed to reduce tumor burden in patients with active disease progression
High disease burden, aggressive disease, or extramedullary disease	High-dose cytarabine, VP16-cyclophosphamide, hyper-CVAD. (cyclophosphamide, VCR, doxorubicin, DEX). • High dose MTX if central nervous system is involved. - VP16 (etoposide) combined with cyclophosphamide.	Intensive regimens aimed at significant tumor reduction; central nervous system-directed therapy for central nervous system disease.

*The selection of bridging therapy should be individualized based on patient-specific factors, prior treatment responses, and institutional protocols. Close monitoring during bridging therapy is essential to manage potential toxicities and ensure timely progression to CAR-T cell infusion; +immunotherapy is carefully used as bridging therapy and is not recommended when it has the same target as the cell therapy. Source: EBMT/EHA CAR-T Cell Handbook[9].

LYMPHODEPLETION IN ALL FOR CAR-T CELL THERAPY

Lymphodepletion is a critical component of the preparative regimen before CAR-T cell infusion in pediatric patients with ALL[1,10]. Table 3 shows the most used regimen.

Table 3. Lymphodepletion.

Chemotherapeutic agents	Doses	Days
Cyclophosphamide	500 mg/m^2 for two days	-5 and -4
Fludarabine	30 mg/m^2 for five days	-5 to -1

Source: EBMT/EHA CAR-T Cell Handbook[9].

INFUSION

Proper preparation prior to CAR-T infusion is essential to maximize treatment efficacy and minimize potential complications[11]. We summarize some orientations in Table 4.

Table 4. Clinical care and recommendations for CAR-T infusion*.

Procedure	Details
Premedication	Administer antihistamine (diphenhydramine) 30–60 minutes before infusion
Corticosteroid use	Avoid prior or immediate use post-infusion
Cell infusion	The cells are delivered intravenously at a 10–20-mL/min infusion rate (gravity flow) without prewarming through a peripheral or central catheter. A non-leukodepletion in-line filter is used
Post-infusion monitoring	Assess vital signs every 15 min in the first hour, every hour for 2 hours, and then at least every 4 hours, more frequently in unstable patients or those with suspected cytokine release syndrome. Monitor fluid balance, oxygen requirements, and signs of capillary leak or organ dysfunction. Use ICE score or equivalent twice daily; increase the frequency if neurotoxicity is suspected. Neurology evaluation daily whenever immune effector cell-associated neurotoxicity syndrome (ICANS) is suspected or diagnosed. Conduct daily labs (complete blood count, renal and hepatic function, and others according to clinical status).
Multidisciplinary team	Involve trained multidisciplinary, intensive care unit, neurology, infectious disease, and oncology teams with experience in CAR-T-related toxicities. Must be prepared for cytokine release syndrome and ICANS management.
Post-discharge care	Provide patient information materials on warning signs and ensure the patient stays within 60 minutes of the infusion center until day 30. Provide reference center letters to continue the clinical follow up. Remain available for discussions and specific orientations

*Admission for at least 14 days after infusion is recommended by clinical trials due to the risk of acute complications. Source: EBMT/EHA CAR-T Cell Handbook and ASTCT / CARTOX Guidelines[9].

EARLY AND LATE TOXICITIES OF CAR-T CELLS

Managing inflammatory toxicities associated with CAR-T cell therapy is crucial for ensuring its safe and effective use, thereby enabling its broader application as a key therapeutic approach.

CRS is a common inflammatory complication following CAR-T cell therapy, characterized by an excessive release of pro-inflammatory cytokines in response to the activation of modified T lymphocytes. The parameters for diagnoses are temperature, blood pressure, and pulse oximetry[12].

ICANS is a neuropsychiatric condition that can occur with immunotherapies, particularly CAR-T cell therapy, and is characterized by symptoms like confusion, headache, and attention deficit[12].

Both CRS and ICANS are classified according to their severity from grade 1 (mild) to grade 4 (severe), and the treatment, guided considering the severity, includes tocilizumab, steroids, and anakinra. It is mandatory for each patient who will receive the CAR-T infusion to have two doses of tocilizumab ready to be used at his/her admission.

Since 2019, the American Society for Transplantation and Cellular Therapy has implemented a grading system for immune effector cell (IEC) toxicity that incorporates key elements from the widely recognized IEC Therapy Toxicity Assessment and Management guidelines. We recommend utilizing the CARTOX App[13] for the diagnosis and management of CAR-T toxicities. Additionally, a Portuguese version is available at CATLOG Terapia Celular[14].

Macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) is a life-threatening toxicity characterized by hyperinflammation and manifesting as persistent fevers, splenomegaly, end-organ damage, cytopenias, coagulopathy, and hypofibrinogenemia. It demands early recognition and prompt treatment to better prognosis[12].

Coagulopathy is observed in multiple clinical trials using CD19 CAR-T cells, particularly in patients with more severe CRS/ICANS (*e.g.*, grade ≥ 3)[15–17]. Hypofibrinogenemia is, to date, the most clinically significant laboratory

abnormality in CRS-associated coagulopathy and is associated with increased incidence of bleeding, requiring close monitoring and replacement[15–17]. It can manifest in the context of severe CRS with HLH-like manifestations. The onset and duration of coagulopathy are less well defined and vary greatly among trials.

Determinants of post-treatment immune reconstitution are multifactorial, including effects of lymphodepleting chemotherapy and on-target off-tumor toxicities. The duration of B-cell aplasia is extremely variable, at times lasting months and years, and has been identified as a surrogate for CAR T-cell persistence[18].

Intravenous immunoglobulin has been administered as routine in children at a dose of 400 mg/kg. We suggest checking IgG level and supplement as needed every three or four weeks to maintain a level of IgG ≥ 400 mg/dL[19].

There is a potential benefit to pursuing post-CAR vaccination for a subgroup of patients, overall responses are inferior to immunocompetent patients. In certain situations, vaccines may be contraindicated. For inactivated vaccines, they should be avoided if supplemental immunoglobulin was administered within the past two months. For attenuated vaccines, they are contraindicated if the CD4+ count is below 200 cells/mm^3 or if the patient has undergone CAR-T cell therapy within the last year. Vaccination can be resumed six months after CAR-T cell therapy. SARS-CoV-2 and influenza vaccines can be administered three months after treatment, regardless of B-cell status[18].

Patients should be monitored for the long-term effects of CAR-T therapy, as suggested in Table 5. Special attention is needed to infections, predominantly bacterial and of the upper respiratory tract, psychiatric disorders, and autoimmune and endocrinological issues[19]. Neurological effects can occur in approximately 10% (neuropathy and cerebrovascular events).

Table 5. Follow-up post-CAR-T cell therapy recommendations.

Period	Frequency	Assessments
Day 28–1 year	Monthly	- Complete blood count, biochemistry panel, viral infection screening (peripheral blood, polymerase chain reaction, nasopharyngeal aspirate) as clinically indicated; - Quantitative immunoglobulins; - Peripheral blood immunophenotyping (CD3/4/8/16/56/19a/CD20) monthly for the first six months, then every three months; - CAR-T cell monitoring when available; - Endocrine function and other age-appropriate late effects testing annually or as clinically indicated.
1–2 years	Every six months	- Complete blood count; - Biochemistry panel; - Viral infection screening as needed; - Quantitative immunoglobulins; - Peripheral blood immunophenotyping as needed; - CAR-T cell monitoring when available; - Endocrine function and other age-appropriate late effects testing annually or as clinically indicated.
2–15 years	Annually	- Complete blood count; - Biochemistry panel; - Viral infection screening as needed; - Quantitative immunoglobulins; - Peripheral blood immunophenotyping as needed; - CAR-T cell monitoring wen available; - Endocrine function and other age-appropriate late effects testing annually or as clinically indicated.

Source: EBMT/EHA CAR-T Cell Handbook and ASTCT / CARTOX Guidelines[9].

CAR-T IN OTHER HEMATOLOGICAL MALIGNANCIES

CAR-T cell therapy for T-cell malignancies faces challenges like fratricide, in which target antigens on both malignant and normal T cells cause immunodeficiency and prolonged T-cell aplasia. CD30 is a promising target in phases I/II studies for T-cell malignancies and Hodgkin's lymphoma, but no formal recommendations exist yet[20]. In myeloid malignancies, the absence of ideal target antigens that do not affect normal hematopoietic cells presents a major hurdle, risking myelotoxicity. Strategies like dual CAR targeting and allogeneic CAR-T cells are being explored, but no consensus recommendations are available[21].

CAR-T IN SOLID TUMORS

CAR-T cell therapy is under active investigation for various solid tumors, but significant breakthroughs must be achieved yet. Challenges such as tumor heterogeneity, the immunosuppressive tumor microenvironment, and limited T-cell infiltration hinder its efficacy in solid cancers[22,23].

CAR-T cells targeting disialoganglioside GD2, an antigen commonly expressed on the surface of neuroblastoma cells, have shown promising results in treating neuroblastoma, particularly in relapsed or refractory high-risk cases[24]. Clinical studies have demonstrated their safety and feasibility, with some trials reporting significant sustained clinical responses. For example, a third-generation GD2 CAR-T construct showed encouraging results, with three-year event-free survival and overall survival rates of 36 and 60%, respectively. This study reported clinical responses in 21 out of 27 patients, including complete responses and partial responses[25]. In another study, a second-generation GD2 CAR-T construct demonstrated transient responses in three out of six patients receiving higher doses[26].

Despite these successes, challenges remain. While CAR-T cells represent a promising innovation for neuroblastoma treatment, their effectiveness varies depending on the construct, preparative regimens, and patient-specific factors. Further research and clinical trials are needed to refine these therapies and expand their use in frontline treatments[23].

CONCLUSION

This national consensus reflects the collective expertise of working in pediatric hematology, oncology, transplantation, and cellular therapy. It aims to guide clinical practice, ensuring safety, efficacy, and equitable access to this innovative treatment. Ongoing research, long-term follow-up, and the development of local production and academic protocols are essential to consolidate CAR-T cell therapy in our setting.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Zanette A. **Conception and design:** Borges NMTF. **Technical procedures:** Sousa AM. **Statistics analysis:** Kuwahara C. **Manuscript writing:** Zanette A, Sousa AM, Kuwahara C, Caleffi M, Borges NMTF, Seber A and Garcia JL.

FUNDING

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

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