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INDICATION AND SELECTION OF PEDIATRIC PATIENTS FOR GENETICALLY MODIFIED T CELLS – FOR THE SBTMO TECHNICAL MANUAL OF CELLULAR THERAPY

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ABSTRACT

The use of CAR-T cells will completely change the treatment of many hematological diseases, including relapsed pediatric B-lineage acute lymphoblastic leukemia. This article is part of the Brazilian Society of Bone Marrow Transplantation (SBTMO)'s "Technical manual of cellular therapy" to guide physicians to select patients and indicate the use of the CAR-T cells in pediatric patients with acute lymphoblastic leukemia. Other aspects of CAR-T cell therapy and management of important toxicities are included on other articles of this volume.

Keywords: chimeric antigen receptor; acute lymphoblastic leukemia; pediatric; hematopoietic stem cell transplantation

OBJECTIVE

To assist pediatricians, hematologists and/or oncologists in the selection of patients for early and assertive referral to CAR-T cell therapy to achieve the best results with treatment.

INTRODUCTION

• CAR-T cells are the patients' own T lymphocytes genetically modified in the laboratory to express receptors that recognize the targets of interest, present in the tumor we want to treat.

• A fragment of DNA that encodes these receptors is artificially constructed in the laboratory; it produces a receptor with high affinity to the antigens that are present in the target cells and, at the same time, provides "co-stimulation," for lymphocyte activation.

• The most widely used receptor for the treatment of B lineage acute lymphoblastic leukemia (B-ALL) was designed to recognize the **CD19** antigen on lymphoblasts.

• The most frequently used co-stimulatory molecules are CD28 and 4-1BB.

• As these molecules are constructed, *i.e*, they do not exist in nature, they are called "**chimeric**."

• The patient's leukocytes are collected by leukapheresis, cryopreserved, sent to reference laboratories. Then, the T lymphocytes are separated from the total leukocytes (*buffy coat*).

• The DNA encoding the receptor of interest and the co-stimulatory molecules is introduced into the lymphocyte nucleus and incorporate into the DNA; from the nucleus, it orders the production of the chimeric receptor. For this genetic incorporation ("**transduction**"), it is usually used a retrovirus ("**viral vector**") artificially bound to DNA, which was built to encode the chimeric receptor and co-stimulator molecules. This retrovirus "infects" the T lymphocytes that have already been separated from the patient's blood.

• The T lymphocytes, after the incorporation of the artificial DNA into their genetic material, produces the chimeric receptor. The receptor migrates to the membrane of the mature lymphocyte and there remains ready to recognize the enemy's CD19.

• The T lymphocytes resulting from this process are called **T** lymphocytes *with* ***chimeric antigen receptors*** (**CAR-T**).

• CAR-Ts are led to multiply in the laboratory to the desired amount to treat the patient (they undergo "**expansion**").

• The cells are then frozen again ("**cryopreserved**") and sent to the patient's treatment center, remaining ready to be subsequently thawed and infused into the patient's bloodstream.

• As this therapy uses genetically modified lymphocytes, it is considered a type of **Gene Therapy**.

• Patients should be treated in highly trained and certified **transplant centers** for the management of toxicities associated with cell therapy.

• The time required between the end of other therapies and leukapheresis performed for the collection of lymphocytes that will be treated in the laboratory is called "***wash out***" and it is quite variable, depending on the potential for destruction of normal T lymphocytes of each type of therapy.

• Therapy administered to the patient after the initial leukapheresis is performed, and before the time of receiving the CAR-T cells, it is called "**bridging therapy**." The objective of the bridging therapy is to keep the patient as healthy as possible, with minimal toxicities *and* tumor load control, without necessarily aiming for remission of the disease.

• Normal lymphocytes of the patient should be destroyed with chemotherapy prior to infusion of CAR-T lymphocytes for them not to offer competition. This **lymphodepletion** chemotherapy recommended for children with B-ALL is performed with fludarabine and cyclophosphamide.

• CAR-T cells are usually sent frozen to the treatment center and thawed at the bedside at the time they will be infused through the catheter, without any manipulation, only introducing saline into the bag at the end of the infusion to ensure that the bag is washed, and the entire product is infused.

• After the cells are injected into the patient's bloodstream, it is essential that they multiply again (undergo "**clonal expansion**") and remain for long periods in the patient (have "**persistence**").

• CAR-T cells are considered "living drugs," as they tend to remain viable in the patient's body for long periods. Because CAR-Ts to treat B-ALL also destroys normal B cells (cause "**B-cell aplasia**"), the patient remains dependent on **immunoglobulin replacement** for infection prevention.

• Adequate levels of immunoglobulins in patients who received anti-CD19 CAR-T or the presence of circulating normal B lymphocytes are indicative of loss of the CAR-T cells, so the options of a new CAR-T infusion, effective in approximately half of patients, or the indication of an allogeneic bone marrow transplantation should be discussed with the team, even before the leukemia relapses.

• The only international centers that offer treatment with (in house) CD19 CAR-T cells for ALL at a fixed price is Barcelona (150,000 Euros for everything in the treatment), according to a personal verbal communication from Dr. Alvaro Urbano-Ispizua *at the European School of Haematology meeting on* CAR-T cells in 2021.

• As the treatment still has a very high cost (often higher than a hematopoietic stem cell transplant), its clinical use outside a research protocol remains restricted to patients who do not have the possibility of curing the disease with other therapeutic strategies.

• To the best of our knowledge, the only **commercially available** therapy worldwide in 2022 for treating children with B-ALL is **Tisagenlecleucel, Kymriah®, Novartis**, which has the CD19 antigen as therapeutic target.

• In **Brazil**, the Tisagenlecleucel, Kymriah® was used as a Class II Advanced Therapy Product for a BELINDA clinical trial sponsored by Novartis Biociencias S.A. for the treatment of adults with relapsed or refractory lymphomas according to Resolution-re No. 1,105 of April 15, 2020.

• The Tisagenlecleucel was submitted to the National Health Surveillance Agency (Anvisa), included in the list of Brazilian Common Denominations of Brazilian Pharmacopoeia, according to RDC No. 480 of March 15, 2021, and it was **approved by Anvisa** in February, 2022 but up to September, 2022, has not been granted a price to be commercialized in the country and, therefore, is not yet available as we write this manual. The prescribing information is already available in Portuguese at the Novartis website

• These commercial CAR-T cells can only be administered in **centers with teams trained and approved by the Novartis laboratory** for the use of CAR-T cells, recognition and treatment of their toxicities, and immediate availability of interleukin-6 inhibitor (IL-6), **Tocilizumab** – Actemra®, Roche.

• There are hundreds of experimental products and protocols abroad for treating children and adults with B-ALL (including the CD22 therapeutic target), T-ALL, acute myeloid leukemia, lymphomas, myeloma, neuroblastoma, brain tumors and various other solid tumors, in addition to HIV/AIDS, but only one trial opened in Brazil for newly diagnosed multiple myeloma "A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by Cilta-cel, a CAR-T Therapy Directed Against BCMA Versus VRd Followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants With Newly Diagnosed Multiple Myeloma for Whom ASCT is Not Planned as Initial Therapy (CARTITUDE-5)" enrolling patients at the Hospital Sao Rafael, Salvador and AC Camargo Cancer Center and Hospital Israelita Albert Einstein in Sao Paulo, Brazil

INDICATIONS OF CAR-T CELL TISAGENLECLEUCEL:

Indications in pediatric B-ALL as of today are restricted to the commercially approved product Tisagenlecleucel, according to the Brazilian prescribing information:

• Children and young adults up to (including) 25 years of age with ALL:

- refractory to therapy *or*
- in second or subsequent relapse *or*
- relapsed after hematopoietic stem cell transplantation.

• Adults with diffuse large cell lymphoma that is refractory of relapsed after two or more lines of therapy.

SELECTION OF PATIENTS WITH B-ALL FOR TISAGENLECLEUCEL:

• Expression of the CD19 in the B-ALL blasts;

• Primary refractoriness *or*

• any relapse after allogeneic hematopoietic stem cell transplantation *or*

• second or further relapse *or*

• patients with relapsed disease ineligible for hematopoietic stem cell transplantation due to comorbidities, impossibility of tolerating a myeloablative conditioning regimen, with not HLA-compatible or partially compatible donor *and*

• possibility to wait for the minimum period without the prohibited medications ("wash-out") *and*

• clinically stable enough to tolerate leukapheresis, a bridging therapy until cells are prepared, lymphodepletion therapy, prolonged aplasia, cytokine release, neurotoxicity and hypogammaglobulinemia.

Observations:

- Age **below 3 years *does not*** contraindicate therapy

- The presence of **Down's Syndrome *does not contraindicate*** therapy

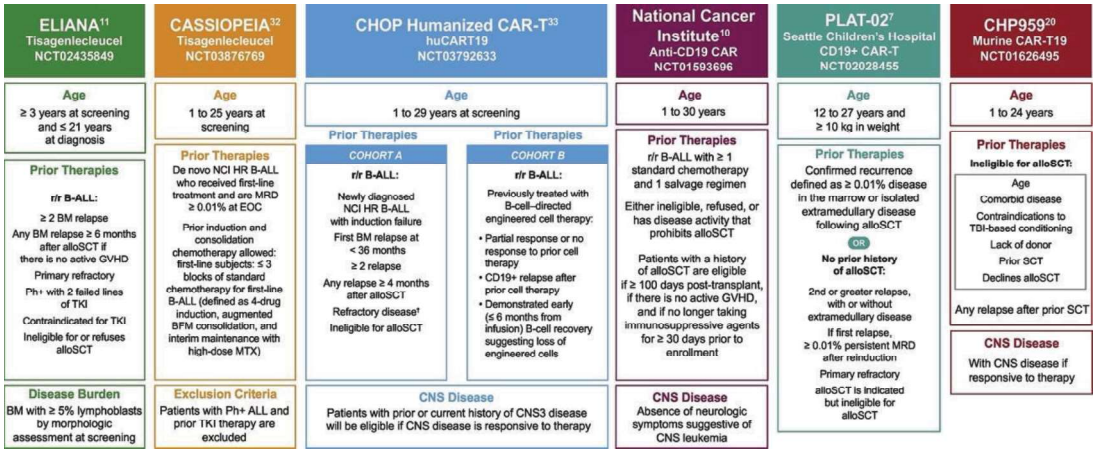
- The various **adverse genetic risk factors *do not*** contraindicate therapy

- The presence of **extra-medullary disease *does not*** modify the indication of therapy. It is clear CAR-T cells can enter the central nervous system and spinal fluid, but their ability to reach other immunoprivileged sites, such as testicles, optic nerve or eye globe, is still less clear.

- The disease being in **activity** or in **remission** at the time of infusion ***does not*** modify the patient's eligibility, although the results of the therapy are superior when patients have chemossensitive disease and achieve remission with the bridging therapy.

- The use of **blinatumomab** before CAR-T cell therapy ***does not*** contraindicate its use. Patients who respond to blinatumomabe generally also respond to CAR-T. However, if a negative CD19 clone emerges, the CAR-T will be totally inactive. The use of pre-CAR-T **inotuzumab** is not considered ideal due to the potential to decrease the chance of response to CAR-T, but it is not a contraindication.

FIGURE 1: Clinical eligibility for children when included in research protocols[11]



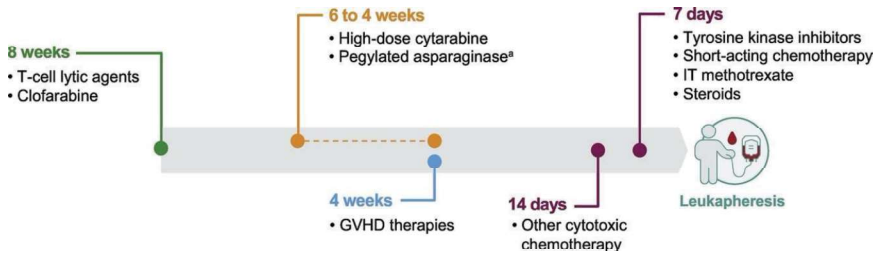
Patient eligibility to perform leukapheresis for T-cell collection and CAR-T cell manufacturing**:**

Absolute **lymphocyte count of >500/µL** (although some studies require ≥100/µL) ***or*** peripheral blood CD3 count of >150/µL

Age below 3 years and weight ***does not*** contraindicate leukoapheresis but indicates that it must be performed in a pediatric centers experienced with leukapheresis in these patients.

Wait for proper *wash-out time* (Figure 2)

FIGURE 2: Waiting time (wash out) until the patient is released for the collection of autologous lymphocytes by leukapheresis[11]



Center eligibility to use Kymriah in the United States (still unclear in Brazil)**:**

To receive authorization for the use of Kymriah hospitals must have:

Risk Evaluation and Mitigation Strategies **(REMS)** program approved by Novartis with a trained and authorized representative to:

• Carry out the certification process and supervise the implementation and compliance of the REMS Program in the hospital;

• **Train and evaluate** the knowledge of **all relevant employees** involved in the **prescription, dispensation, or administration** of Kymriah;

• Establish processes and procedures for:

- ensure that **new employees** involved in the prescription, dispensation, or administration of Kymriah are trained and complete the Knowledge Assessment.

- check for at least **two doses of tocilizumab** available at the site for each patient and are ready for immediate administration (within 2 hours).

- provide patients with the **Patient Card**.

Before the first infusion the center shall:

- Check for at least **two doses of tocilizumab** available on site for each patient and that they will be ready for **immediate administration (within 2**

hours) through the processes and procedures established in the Service's REMS Program

Before the patient is discharged the center shall:

- Provide **Pocket Card** to the patient (according to your REMS program)
- To maintain certification to dispense, if there is change in authorized representative:
- Have the new authorized representative enrolled in the REMS Program.

To maintain certification to dispense Kymriah, if the center has not dispensed at least once a year from the date of certification in the REMS Program:

- Train all relevant employees involved in the prescription, dispensing or administration of Kymriah according to the REMS Program
- Assess the knowledge of the relevant team involved in the prescription, dispensing or administration

At all times the center shall:

- **Report any adverse events** suggestive of cytokine release syndrome or neurological toxicities to the REMS Program.
- **Keep personnel training records**.
- **Keep records that all processes and procedures are in place and being followed**.
- **Comply with audits** conducted by Novartis or a third party working on behalf of Novartis to ensure that all processes and procedures are in place and are being followed.

Recommended bridging therapy:[11]

Tumor load	Recommended bridging therapy	Outpatient
Low	Maintenance pulses with vincristine/ corticosteroids Targeted drugs, for example, tyrosine kinase inhibitors Maintenance oral mercaptopurine and methotrexate Immunotherapy (?)	Yes
Slow progression	Capizzi style Methotrexate in (with or without PEG asparaginase) Low doses of Cytarabine (300 mg/m^2) and etoposide (150 mg/m^2) every 2–3 weeks Maintenance rotating drug pairs (St. Jude) Immunotherapy (?)	Yes
Rapid progression	Etoposide (100 mg/m^2/day) and cyclophosphamide (440 mg/m^2/day) for 3–5 days FLAG High-dose Cytarabine (3 g/m^2 every 12 h × 4 doses) D1,D2	No
Extra-medullary disease	Radiotherapy can be performed	Yes

Recommended lymphodepleting therapy:

- **Fludarabine** (30 mg/m^2 intravenously daily for 4 days) and **cyclophosphamide** (500 mg/m^2 daily for 2 days, starting with the first dose of fludarabine).
- If the patient has previously had a grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrated a chemo refractoriness to a cyclophosphamide-containing regimen administered just before the lymphodepletion chemotherapy, the following regimen may be used: Cytarabine (500 mg/m^2 intravenously daily for 2 days) and etopoide (150 mg/m^2 intravenously daily for 3 days, starting with the first dose of cytarabine).

Critical points:

- Avoid the patient's elective exposure to anti-CD19 immunotherapy (BiTE - Blinatumomabe - Blincyto®) when the patient is being considered for CAR-T cell therapy to prevent tumor cell escape to anti-CD19 CAR-T.
- Also avoid exposure to anti-CD22 (Inotuzumab) as it decreases response to anti-CD19 CAR-T.
- Check availability of centers offering CAR-T cell therapy.
- Check how the CAR-T cell will be paid.
- Check the availability of a **programmable freezer**, and **nitrogen cryopreservation**.

• **Team training** for all stages of therapy, especially the management of toxicities.

• Immediate availability of **tocilizumab**.

• Availability of **infrastructure** and **intensive care**.

• Availability of **data manager** to report treatment results and patient follow-up for **at least 15 years.**

Risks involved in the process:

• **Frustration** of the family members and physicians due to the inability to offer treatment due to medical, infrastructure or financial reasons.

• Severe **cytokine release syndrome**.

• Severe **neurotoxicity**.

• Prolonged **cytopenias**, and subsequent **infections**.

• Long-term **B lymphocyte aplasia** requiring **immunoglobulin replacement** and increased **susceptibility to viral infections**, already so common in our country.

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