DOI: 10.46765/2675-374X.2022V3N2P181

FOLLOW–UP BEYOND 1 MONTH AFTER AUTOLOGOUS CAR T CELL THERAPY

Andreza Alice Feitosa Ribeiro[1]

1 Hospital Israelita Albert Einstein

Corresponding author: Andreza Alice Feitosa Ribeiro (andreza.ribeiro@einstein.br)

Received: 27 Oct 2022 • Revised: 07 Nov 2022 • Accepted: 13 Nov 2022.

ABSTRACTS

The incidence of medium-term and long-term adverse events are critical factors determining the utility of CAR T-cell therapy and research of risk factors and timeline of late effects will be critical for optimal survivorship care. The most commonly reported toxicities during long-term follow-up after anti-CD19 CAR T-cell therapy are decreased blood B-cell counts, hypogammaglobulinemia, prolonged cytopenias and infections. Common determinants of late toxicities are age, underlying tumor type, previous therapy and CAR construct. Here we will provide some recommendations for patient monitoring during medium-term and long-term follow-up and management of the late adverse effects.

OBJECTIVES

- Describe the clinical, laboratory and radiological follow-up after CAR Cell Treatment.
- Standardize and optimize medical care with screening and therapeutic and preventive interventions of the main complications related to CAR T cell treatment.
- Monitor immune reconstitution during the follow-up and follow-up period.
- Monitor the persistence and expansion of CAR T Cells.

INTRODUCTION

Long-term follow-up of patients who have received treatment with CAR T cells involves collaboration between the hematology team that referred the patient and the cell therapy multi-disciplinary team. Therefore, the center that referred the patient must receive specific instructions and contact information so that the necessary support can be maintained after the patient returns. After CAR T cell therapy, the patient will require close monitoring to deal with possible late complications of therapy: prolonged cytopenias; late neurological toxicity such as tremors, memory changes, increased risk of infection, etc.

Cytopenias

Haematological toxicity has a cumulative 1-year incidence of 58% post-CD19-CAR-T, is often prolonged and can follow an biphasic temporal course. The first phase is attributed to the lymphodepletion regimens, bridging therapy before CAR-T infusion, severe CRS, etc.

An analysis of hematological reconstitution in CAR T-treated patients published in 2020 showed that blood count normalization occurs in only about 15% of patients after 3 months and about 60% after 9 months of CAR T cell infusion. In ZUMA-1, about 17% remained with grade 3 or greater cytopenias after 3 months of infusion[1]. About 30% of patients may have late, beyond D+30, severe neutropenia, and

20% late thrombocytopenia. In addition, up to 20% of patients have neutropenia lasting, longer than 90 days. The pathogenesis of the prolonged cytopenia is not yet well understood, but is likely contributed to by multiple factors, such as the occurrence of a more severe cytokine release syndrome, large tumor mass and low marrow reserve. Furthermore, the cytokine profile in these patients with prolonged cytopenia, revealed elevations in serum levels of IFNγ, IL-6 and IL-8 in patterns similar to those seen in acquired bone marrow failure states. Cytopenias after CAR T anti-BCMA, are intense after lymphodepletion: 97% grade 3 or greater, and tend to recover within 1 month. Rejeski and in a multicenter, retrospective analysis of 258 patients, found a positive correlation between baseline thrombocytopenia and hyperferritinemia and day+60 cytopenia. They developed a score: CAR-HEMATOTOX, which included hemoglobin, platelet count, absolute neutrophil count and baseline inflammatory markers: C-reactive protein, and ferritin. This score can predict the incidence of severe neutropenia more, or less than 14 days.

B-cell aplasia and hypogammaglobulinemia

In a long-term follow-up study of CD19-directed CAR T therapy in relapsed/refractory (R/R) B cell NHL or CLL, 67% of patients had hypogammaglobulinemia beyond 90 days and can persist for months or even years[2]. Updated results of the ZUMA-1 trial, which tested axi-cell in R/R aggressive B cell NHL, show that 31% of patients received intravenous immunoglobulin (IVIG), Generally, polyclonal CD19+ B cells recover in 50% of cases in remission around 6 to 12 months after infusion and can mean an increased chance of relapse. On the other hand, persistence of CAR T cells can result in profound hypogammaglobulinemia or agammaglobulinemia.

Due to immunological immaturity, immunoglobulin replacement is routine in paediatric CAR-T cell patients to obtain a serum level > 400 mg/dL regardless the clinical picture[3]. In adults, some specific anti-pathogen antibodies may remain, due to CD19 negative plasma cells, and in this population, the Immunoglobulin replacement can be titrated by the incidence of breakthrough infection.

Immune Reconstitution

Several studies with anti-Cd19 CAR T show that CD8+ counts recover quickly, while CD4+ T cells may persist low, with a count less than 200 cells/µL in about 33% in those who remained on remission 1 year after treatment.

Cardiovascular toxicity

Cardiovascular events are common in adult patients after CAR-T, with a correlation between the occurrence of CRS >2, elevated troponin and a longer time between the onset of CRS and the administration of tocilizumab[4].

Secundary Malignancies

Most patients treated with CAR T cells have received several previous oncological treatment lines, and therefore are more susceptible to secondary neoplasms, mainly myelodysplasia or acute myeloid leukemia. A study with 86 patients by Cordeiro et al (2020)[3] showed that 15% developed secondary neoplasms. This percentage rose to 29% in the population that achieved prolonged complete remission. It is noteworthy that 62% of these patients had already undergone hematopoietic stem cell transplantation.

The follow-up after infusion of CAR T cells should also include analysis of persistence and expansion of CAR T cells, either by direct methods, such as flow cytometry or PCR, or by indirect methods, such as recovery of lymphopenia after infusion of CAR cells T. The ELIANA study (CAR T cells for ALL) showed that recovery of B lymphocyte count: >1%/total leukocytes or >3% of lymphocytes before the 6th month was related with lower relapse-free survival.

PROCEDURE

In the pre-treat possibility of evaluation by specialists from other areas, such as: psychology, neurology, infectology and specific exams (depending on the underlying disease), during the follow-up period after hospital discharge.

The frequency of evaluations will vary according to the status of the underlying disease, associated complications, risk of infections and possible need for transfusion. Some patients with prolonged cytopenia may require the use of growth factors or even spinal cord evaluation.

Up to 30 days from the infusion of CAR T cells, the patient must stay at a place for a maximum of 30-45 minutes from the hospital with a companion who knows how to identify signs of treatment toxicity: CRS (cytokine release syndrome, ICANS (Immune effector cell-associated neurotoxicity Syndrome) . Patient should not drive until 8 weeks after infusion of CAR T cells.

In addition to cytopenias and infections, other late adverse events that should be monitored after CAR

T treatment: immune events (pneumonitis, dermatitis); neurological, psychiatric, secondary neoplasms. The proposal assessment after CAR T cell therapy should be individualized for each patient, according to the disease of: CLL, ALL or non-Hodgkin's lymphoma; and patient characteristics: co-morbidities, toxicities, infectious history and risk, etc.

Management Recommendations

- Cytopenias

Granulocyte growth factor (G-CSF) has been used for the treatment of neutropenia, however, to avoid interaction with the risk of peak CRS and CAR T cell expansion, its use is avoided until 14 days after cell infusion. T CAR. Up to 28 days after infusion of CAR T Cells, bone marrow evaluation is not indicated, only follow-up with blood count is sufficient. Clinically, stable patients can be discharged from the hospital, even with cytopenia, using antimicrobial and antifungal prophylaxis.

If cytopenias persist after 28 days, a myelogram and/or bone marrow biopsy are indicated, as well as investigation of infection by viral pathogens[5]. In cytopenias grade 3: anemia: 10-8.0/dL; neutropenia: 500-1000/mm3; thrombocytopenia: 25.000-50,000 per mm3, the use of G-CSF should be considered, as well as the use of corticosteroids. In grade 4 cytopenias: neutropenia less than 500/mm3 and thrombocytopenia < 25,000/mm3, high-dose corticosteroids and the use of granulocytic growth factor may be considered, besides Blood product transfusion and prophylactic antibacterial and antifungal agents in patients with prolonged neutropenia.

Hypogammaglobulinemia

Patients with serum IgG levels <400 mg/dL prophylactic replacement should be considered and when the patient has recurrent infections replacement is indicated.

Replacement: IVIG or s.c. formulation, dosing every 3-4 weeks at 400-600 mg/kg body weight to maintain an IgG through level of >400 mg/dL and continuing until B cell recovery with spontaneous.

Monitoring Recommendations:

From hospital discharge to D+100

- Weekly visits until D+60, which can be fortnightly after D+60.

- Weekl y exams up to D+60, which can be biweekly: Blood count, reticulocytes, biochemistry, DHL, Liver Profile, Blood glucose, C-reactive protein, Creatinine, urea, fibrinogen.

- Quantitative CMV blood PCR in cases of cytopenias, fever or other clinical indication in patients previously submitted to HSCT. PCR for EBV or adenovirus only on clinical suspicion.

- Tests requested monthly: ferritin, Immunoglobulins (IgA, IgM, IgG); peripheral blood immunophenotype: CD3/CD4/CD8/CD16/CD19/CD56.

- Assessment for persistence of CAR T. From D+100 a D+365

- Monthly visits up to D+180, which can be every 2 months after D+180.

- Exams requested monthly: Blood count, reticulocytes, biochemistry, DHL, AST, ALT, bilirubin, Blood glucose, C-reactive protein, Creatinine, Urea, fibrinogen, ferritin.

- Monthly visits up to D+180, which can be every 2 months after D+180.

- Every 2 months up to D+180: Quantitative immunoglobulins or serum protein electrophoresis and peripheral blood immunofenotyping: CD3/CD4/CD8 /CD16/CD19/CD56. After the 6th month, exams can be done every 3 months.

Monitoring the loss of B cell aplasia is useful to assess the risk of CD19+ disease relapse, definitions vary, but an increase of 50% of CD19 cells or 3% of the B cell population can mean recovery. The loss of B cell aplasia before 6 months of infusion is associated with an increased risk of relapse.

- Other tests according to age and patient: Iron Profile, Hormone Profile (TSH, T4, FSH, LH, estradiol, progesterone, ACTH, cortisol, total and free testosterone, PTH, GH, IGF-1, Prolactin). Lipid profile, Bone assessment, Autoantibody profile (ANA, ENA, Rheumatoid factor, ANCA, anti-TPO, anti-Thyroglobulin) in cases with suspected autoimmunity diseases.

- Transthoracic echocardiogram and high-resolution chest CT (depending on age, symptoms and previous treatments).

In case of persistent grade 3 or 4 cytopenias, bone marrow aspiration or biopsy should be performed to assess cellularity and rule out hematophagocytosis, myelodysplasia, or leukemia recurrence.

After 1 year: Visits at least every 3 to 6 months. - Start screening for secondary neoplasms after 1 year

(D+365) and according to general age recommendations (total/free PSA, Mammography, Pap smear, Colonoscopy and Endoscopy).

Training and updates should be defined by institution decision. As CAR T cells is a therapy with increasing and continuous advances, we suggest training and annual assessment of the competence of teams annually.

REFERENCES

1. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv. 2020;4(15):3776-3787.
2. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol Blood Marrow Transplant. 2020;26(1):26-33.
3. Hill JA, Giralt S, Torgerson TR, et al. CAR-T- and a side order of IgG, to go? - Immunoglobulin replacement in patients receiving CAR-Tcell therapy. Blood Rev. 2019;38:100596.
4. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular Events among Adults Treated With Chimeric Antigen Receptor T-Cells (CAR-T). J Am Coll Cardiol. 2019;74(25):3099–108.
5. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer. 2020;8(2):e001511.