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CITOKINE RELEASE SYNDROME MANAGEMENT IN ADULTS AND PEDIATRIC PATIENTS

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ABSTRACT

Chimeric Antigen Receptor (CAR) T cell therapy has demonstrated efficacy in B cell malignances. However, the treatment is not harmless and, in some patients, can lead to a fatal endpoint. For this reason, the knowledge and the early recognition and management of the side effects related to CAR-T cell therapy for the multidisciplinary team is essential. In this article, we have summarized the current recommendations for identification, gradation and management of cytokine release syndrome related to CAR-T cell therapy.

Keywords: cytokine release syndrome. CRS. CAR T complications. Anti IL 6. Tocilizumab. Toxicity.

INTRODUCTION

Treatment with CD19 or CD22-targeted chimeric antigen receptor-engineered T (CD19/CD22 CAR-T) has demonstrated efficacy in B cell malignances, especially in acute lymphoblastic leukemia (ALL) and non-Hodgkin Lymphoma. Currently, tisagenleclucel is approved by ANVISA in Brazil for relapsed and/or refractory pediatric B-ALL up to the age of 25 years and for non-Hodgkin lymphomas.

CRS represents a potentially serious complication of CART therapy. It is a cytokine-mediated systemic inflammatory response that occurs after CAR T cell infusion when cytokines (interleukin 6 (IL-6), interferon gamma (IFNg) and tumor necrosis factor (TNF)) are released by activated T cells or other immune cells, such as monocytes/macrophages[1]. Clinical presentation is variable and depends on the CAR T product and patient characteristics, such as underlying disease and tumor burden. The peak incidence is between 2 and 7 days after infusion up to 3 weeks (median 1 to 3 days)[2]. The incidence varies from 57 to 93% of adult patients receiving cell therapy[3] and up to 77% of children, as reported in the phase 2 clinical trial, ELIANA[4].

Symptoms related to CAR-T-cell-induced CRS may include fever, tachycardia, hypoxia, nausea, headache, skin rash, hypotension requiring administration of vasopressors or not, acute respiratory failure, coagulopathy secondary to disseminated intravascular coagulation and/or multiple organs disfunction / failure[5].

Although the toxicities are mostly reversible with appropriate supportive care and specific treatment, some cases can be fatal. Early recognition of these toxicities and prompt intervention reduces related morbidity and mortality.

To achieve this goal, it is mandatory training healthcare professionals involved in these patients clinical care. The education of patients and their caregivers is also extremely important.

OBJECTIVES

Provide comprehensive direction for the diagnosis, classification, and management of cytokine release syndrome (CLS) related to CAR-T cell treatment in adult and pediatric patients.

PROCEDURE DESCRIPTION

As described above, CRS has a wide variety of signs and symptoms. After its diagnosis, CRS must be classified according to its severity.

GENERAL RECOMMENDATIONS:

The classification proposed by the Consensus of the American Society for Cell Transplantation and Therapy (ASTCT)[5] is the most used and is also recommended by the Brazilian Society for Cell Therapy and Bone Marrow Transplantation (SBTMO). This classification considers only three vital signs (temperature, blood pressure and oxygen saturation), which facilitates their grading (Table 1). Organ toxicities associated to CRS can be categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0[6] and will not influence its classification.

CRS assessment should be performed at least every 12 hours, or more often if the patient clinical status change.

The Intensive Care Unit (ICU) team will consult theses patients as needed. Indications for ICU transfer are: grade 2 CRS not responsive to intravenous (i.v.) fluid bolus, decreased urine output, or other patient-specific clinical factors and grade 3 or 4 CRS.

As many symptoms of CRS can mimic other medical conditions such as sepsis, infection, or adrenal insufficiency, it is very important that a thorough workup is performed to rule them out.

Laboratory tests suggestion: complete blood count, liver profile, renal function, sodium, potassium, magnesium, phosphorus daily. Consider monitoring C-reactive protein (CRP) and ferritin levels daily during the phase when CRS is likely to occur (first 10 days) and continuing monitoring until CRS resolves.

Coagulation profile (APTT, PT, fibrinogen) at least twice a week or more often if clinically indicated.

Consider cytokines dosage panel (such as IL-6) only if indicated for some specific monitoring (e.g., if the patient is not responding to interventions). It is not routinely recommended.

Avoid granulocyte colony-stimulating factor (filgrastim) in the first few weeks after infusion during the period when CRS may occur.

Do not administer corticosteroids unless approved by the hematologist.

If the patient has grade I CRS, levetiracetam 500mg orally 12/12h or 10mg/kg 12/12h for children should be started as prophylaxis.

Anti-cytokine therapy:

In general, first-line therapy for patients diagnosed with CRS is done by IL-6 blockers such as the anti-IL 6 antibody, tocilizumab. Its administration may be considered in patients with CRS grade 1 who persist with fever for 72 hours with no other defined cause or who persist with fever above 39°C for 48 hours, as well as in patients with CRS grade 2. Tocilizumab should be administered for patients with grade 3 and 4 CRS[7,8].

It is important to know that initiating therapy with anti-IL-6 antibodies and/or corticosteroids within 24 hours of the beginning of symptoms was associated with reduced CRS severity without compromising the effect of CAR T cells[9].

The recommended dose for tocilizumab is 8mg/kg for patients weighing over 30kg and 12mg/kg for patients weighing less than 30kg, with a maximum dose of 800mg/dose[10]. The minimum interval between the first dose and subsequent doses is 8 hours, and in practice, a dose of tocilizumab has been given every 24 hours in patients who do not experience progressive clinical deterioration requiring faster intervention.

Although it is established that up to 4 doses of tocilizumab are allowed and possible, it is believed that after two doses the drug has already achieved as much blockade as possible in the T cell receptors.

In rare situations in which the patient does not improve with the proposed measures (estimated at less than 10% of cases), the therapy must be modified[11,12], either by the combination of corticosteroids or by changing the anti-IL-6 antibody (for example, Siltuximab, with a different mechanism of action) or by choosing another target of action such as the interleukin 1 (IL-1) receptor antagonist, Anakinra (not yet approved in our country) or the monoclonal antibody that blocks IL 1 beta (Canakinumab, the only anti IL 1 approved and available in Brazil at this time)[11,12]. More serious situations may require the use

of cyclophosphamide or even anti-immunoglobulin to control the inflammatory condition and must be discussed individually.

CORTICOSTEROIDS

For grade 2 hypotension, methylprednisolone 1mg/Kg in a single dose or dexamethasone 0.5mg/Kg (maximum dose 10mg) also in a single dose should be associated.

For grade 3 hypotension, if the patient is using 1 vasopressor, the use of methylprednisolone 1mg/kg/day divided every 12 hours or dexamethasone 0.5mg/kg per IV dose divided every 6 hours is indicated (maximum dose 10mg). If the patient is using 2 vasopressors, methylprednisolone 2mg/kg/day divided every 12 hours or dexamethasone 1mg/kg per IV dose (maximum dose 20mg) divided every 6 hours.

For grade 2 hypoxia, methylprednisolone 1mg/Kg in a single dose or dexamethasone 0.5mg/Kg (maximum dose 10mg) also in a single dose is associated.

For grade 3 hypoxia, methylprednisolone 1mg/kg/day divided every 12 hours or dexamethasone 0.5mg/kg (maximum dose 10mg) divided every 6 hours is used. If hypoxia does not improve within 24 hours or if pulmonary infiltrates progress rapidly or if the need for oxygen increases rapidly, the corticosteroid dose should be increased to 2mg/kg/day of methylprednisolone divided every 12 hours or of dexamethasone to 1mg /kg per dose divided every 6 hours (maximum dose 20mg).

For grade 4 hypoxia or hypotension, we will use pulse methylprednisolone, 30mg/kg/day for 3 days (maximum 1.000mg/dose).

Once the patient has started corticosteroid use, gradual withdrawal or complete discontinuation is recommended once SRC improves to grade < or = 1.

PEDIATRIC PATIENTS PARTICULARITIES[7]:

Hypotension is defined by age-specific physiological normal ranges for age and/or by comparison with the patient's baseline values. In table 2 we can see the 5% percentile of systolic pressure by age group.

The i.v. fluid bolus should be done with 10ml/kg (maximum of 1000ml) and can be repeated once to maintain the normal blood pressure defined by age. After this attempt, if the child still needs fluid resuscitation, the use of colloids should be considered, especially if the patient has hypoalbuminemia.

The use of colloids in this situation is recommended because i.v. albumin can reduce the duration of vasopressors support and decrease the degrees of respiratory, cardiac and neurological failure. In very critically ill patients, albumin administration is associated with a reduction in endothelial dysfunction during the inflammatory processes similar to those seen after CAR T cell therapy.

In addition, acute fluid overload in patients with capillary leaky (especially infants and children weighing < 20 kg, who may be less able to tolerate substantial volume changes) is a major concern as it may contribute to respiratory failure.

Vasopressors and cytokine blockade should start in the time of hypotension and should not be delayed in favor of more than two consecutive i.v. fluid bolus.

Assessment of cardiac function by Doppler echocardiography should be performed in pre cell therapy clinical evaluation to obtain the patient's baseline function. At the time of CRS (from grade 2) it will be very important that the exam be repeated in order to determine which vasopressor will be the most suitable for the child.

In patients with grades 2 to 4 CRS who may have adrenal insufficiency (e.g., patients treated with pediatric ALL protocols), administration of stress-dose hydrocortisone (25mg/m2 6/6h for 24 hours or 100mg/m2) or even Fludrocortisone (0,1mg/dose once a day) may precede initiation of vasopressor therapy and/or cytokine blocking therapy.

In grade 3 CRS, for whom the amount of oxygen at high flow is not sufficient, noninvasive continuous positive pressure ventilation may be a viable option. If indicated, it should be performed in the ICU and not delay intubation.

According to the first classification of CRS proposed by Lee et al[13], if the patient needs high doses of vasopressor, he/she should be classified with CRS grade 4. It's worth mentioning that there is no consensus to define high dose vasopressor in children as there is for adults[13]; thus, this evaluation must be carried out in an individualized and dynamic way by the ICU team who will take care of the patient so that they can promptly inform the hematologist about the progressive increase in dose and/or association of vasopressors for the pediatric patient, because in this context the CRS will be classified in grade 4.

In **Figure 1**, there is a flowchart with the steps to be followed for the pediatric and adult patients experiencing CRS according to their classification.

Critical points and risks of the process
Emergency medical equipment (eg, complete and checked emergency car) must be present throughout the procedure. At least four doses of tocilizumab must be readily available to each patient before initiating lymphodepletive chemotherapy.

Access to corticosteroids should also be easy and quick, but their prescription must always be done by the physician responsible for the patient receiving CAR-T.

Keep ICU and neurology staff trained and aware of patients at risk.

Practice Standard
Not applicable

Training and Competence Assessment Frequency
Annual training for medical and multidisciplinary staff (including ICU and neurology unite), and whenever there is a new member in the team.

Quality Indicators
Incidence of cytokine release syndrome.
Response to treatment.
Mortality.

REFERENCES

1. Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica. 2020;105(2):297-316.
2. Novartis Pharmaceuticals corporation. Kymriah (tisagenlecleucel) [package insert]. U.S. Food and Drug Administration website. Available from: https://www.fda.gov/media/107296/download.
3. Neelapu S, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. Nat Rev Clin Oncol . 2018;15(1):47-62.
4. Maude SH, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-48.
5. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant . 2019;25(4):625-638.
6. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Novembro, 2017. Disponível em https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
7. Ragoonanan D, Khazal JS, Abdel-Azim H, et al. Diagnosis, Grading and management of toxicities from immunotherapies in children, adolescents and young adults with cancer. Nat Rev Clin Oncol. 2021;18(7):435-53.
8. Maude SL, Barrett D, Teachey DT, et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20(2):119-22.
9. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood. 2019;134(24):2149-58.
10. FDA: Highlights of prescribing information for Actemra. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf
11. Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol. 2019;16(1):45-63.
12. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-95. Erratum in: Blood. 2015 Aug 20;126(8):1048. Dosage error in article text. Erratum in: Blood. 2016 Sep 15;128(11):1533.

TABLE 1: **ASTCT Consensus Grading for Cytokine Release Syndrome adapted**[5]

CRS PARAMETERS	GRADE 1	GRADE 2	GRADE 3	GRADE 4
FEVER	Axillary temperature > = 37.8ºC (no other cause) In patients receiving antipyretic and/or anti-cytokine therapy such as tocilizumab or corticosteroids, fever is no longer needed to classify the CRS severity. In this case, the CRS classification will consider hypotension and/or hypoxia. The degree of CRS is determined by the most severe event between hypoxia and hypotension.			
WITH				
HYPOTENSION	Absent	No vasopressor needed	Need 1 vasopressor with or without vasopressin	Need of multiples vasopressors (excluding vasopressin)
AND / OR				
HYPOXIA	Absent	Low-flow O2 supplementation (O2 nasal catheter or blow-by oxygen or venturi mask)	O2 supplementation with high-flow nasal cannula or non-rebreather mask or face mask	O2 Supplementation with Positive Pressure (non-invasive or IOT with mechanical invasive ventilation)

TABLE 2: **Percentile 5% Hypotension by Age**

	Systolic pressure (mmHg)
Age	**Percentile 5%**
0-1 month	< 60
>= 1 month – 1 year	< 70
2 years	< 74
3 years	< 76
4 years	< 78
5 years	< 80
6 years	< 82
7 years	< 84
8 years	< 86
9 years	< 88
> = 10 years	< 90

FIGURE 1: Grading and Management of Cytokine-Released Syndrome5,12