Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jtg01q49

CYTOKINE RELEASE SYNDROME IN ONCOLOGIC PATIENTS TREATED WITH CAR-T

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ABSTRACT:
Background: The development and use of immunotherapy, particularly chimeric antigen receptor T cells (CAR-T), has transformed cancer treatment. However, managing related toxicities remains a significant challenge.
Objectives: To provide an overview of cytokine release syndrome (CRS) in cancer patients receiving CAR-T treatment, focusing on its clinical and therapeutic management.
Methods: A literature review was conducted to gather current knowledge and insights on CRS associated with CAR-T therapy. Sources included peer-reviewed journals, clinical studies, and expert reviews.

Results:
- **Prevalence of CRS**: CRS is a common toxicity in CAR-T therapy, with a variable incidence depending on the type of CAR-T product used and patient-specific factors.
- **Clinical Presentation**: CRS can range from mild flu-like symptoms to severe, life-threatening manifestations, including high fever, hypotension, and multi-organ dysfunction.
- **Challenges in Identification**: Differentiating CRS from other conditions such as sepsis is challenging due to overlapping clinical features.
- **Therapeutic Management**: Management strategies include supportive care, corticosteroids, and cytokine inhibitors like tocilizumab. Early recognition and intervention are critical to improve patient outcomes.

Conclusion: Effective management of CRS in CAR-T cell therapy is vital to mitigate its potentially fatal consequences. Continued research and clinical vigilance are essential for improving the safety and efficacy of CAR-T treatments in cancer patients.

KEYWORDS: Chimeric Antigen Receptors; T-cell antigen Receptors; Pharmacological Treatment; Cytokine Release Syndrome.

INTRODUCTION:

The oncology area is in constant scientific evolution, with increasing use of immunotherapy in haematological diseases. However, the clinical application of these therapies highlights the need to evaluate their possible adverse effects, as well as to understand the correct approach and treatment to address them. A systemic inflammatory reaction characterized by a huge production of cytokines and an intensified immunological response is known as cytokine release syndrome (CRS), also referred to as cytokine storm. Numerous things might cause this syndrome, including medications and infections. The most frequent side effect following chimeric antigen receptor T cell (CAR-T) injection is CRS (Mihalyova et al., 2024; Nakamura et al., 2024).

Autologous T cells that have undergone genetic modification to express a T-cell receptor's intracellular domain by fusing it with a B-cell receptor's antigen-binding domain are known as CAR-T cells. As a result, the foundation of this therapy is the harvest of T cells, their genetic modification into CAR-T, and their subsequent infusion into the patient to eradicate tumour cells. Interleukin (IL) 1, IL-2, soluble IL-2R-, interferon- (IFN), IL-6, soluble IL-6R, IL-8, IL-10, the tumour necrosis factor (TNF), and granulocyte and macrophage colony-stimulating factor (GM-CSF) are among the cytokines and chemokines that are produced by activated T cells. Cytokines are also produced by surrounding immune cells, including monocytes, macrophages, and dendritic cells, which add to an overall state of immunological activation (Walton, Frigault, & Maus, 2024; Zheng et al., 2024).

The effectiveness of CAR-T infusion in the management of hematologic malignancies has been shown in multiple clinical studies. Recently, refractory/relapsed (R/R) non-Hodgkin lymphoma (NHL) has been licensed for treatment with two forms of CD19-targeted CAR-T: axicabtagene ciloleucel and tisagenlecleucel; the latter is also approved for R/R acute lymphocytic leucocytosis (ALL). Although CLS is becoming more well-known and more common among patients receiving CAR-T therapy, this symptomatology has already been reported following antibody-based therapies, non-protein anticancer medications (such as oxaliplatin and lenalidomide), and transplant situations (Furqan et al., 2024; Pu et al., 2024).

Table 1: Overview of Cytokine Release Syndrome (CRS) and CAR-T Therapy

Aspect	Description	References
Definition	Systemic inflammatory reaction characterized by massive cytokine production and intensified immune response	Mihalyova et al., 2024; Nakamura et al., 2024
Causes	Medications, infections, and CAR-T therapy	Mihalyova et al., 2024; Nakamura et al., 2024
Cytokines and Chemokines Involved	IL-1, IL-2, soluble IL-2R-, IFN, IL-6, soluble IL-6R, IL-8, IL-10, TNF, GM-CSF	Walton, Frigault, & Maus, 2024; Zheng et al., 2024
Sources of Cytokines	Activated T cells, monocytes, macrophages, dendritic cells	Walton, Frigault, & Maus, 2024; Zheng et al., 2024
CAR-T Cells	Autologous T cells are genetically modified to express a T-cell receptor's intracellular domain fused with a B-cell receptor's antigen-binding domain.	Walton, Frigault, & Maus, 2024; Zheng et al., 2024

Table 2: Clinical Application and Effectiveness of CAR-T Therapy

Aspect	Description	References
Therapeutic Target	Hematologic malignancies, specifically R/R non-Hodgkin lymphoma (NHL) and R/R acute lymphocytic	Furqan et al., 2024; Pu et al., 2024

	leukemia (ALL)	
Approved CAR-T Products	Axicabtagene ciloleucel and tisagenlecleucel	Furqan et al., 2024; Pu et al., 2024
Other Associated Therapies	Antibody-based therapies, non-protein anticancer medications (e.g., oxaliplatin, lenalidomide), transplants	Furqan et al., 2024; Pu et al., 2024
Pre-clinical Investigations	Chimeric natural killer antigen receptors cell therapy, blinatumomab	Lin et al., 2024

Table 3: Clinical and Therapeutic Management of CRS

Aspect	Description	References
Importance of Management	Crucial to evaluate and address possible adverse effects of CAR-T therapy	Mihalyova et al., 2024; Nakamura et al., 2024
Clinical Presentation	Varies from mild flu-like symptoms to severe, life-threatening conditions	Walton, Frigault, & Maus, 2024; Zheng et al., 2024
Therapeutic Strategies	Supportive care, corticosteroids, cytokine inhibitors (e.g., tocilizumab)	Walton, Frigault, & Maus, 2024; Zheng et al., 2024
Importance of Early Intervention	Early recognition and intervention improve patient outcomes.	Walton, Frigault, & Maus, 2024; Zheng et al., 2024

Stem cells from haploidentical donors. Pre-clinical investigations also reveal that it has been observed in patients receiving chimeric natural killer antigen receptors cell therapy and blinatumomab. The purpose of this review is to describe CRS in cancer patients receiving CAR-T therapy, with an emphasis on the syndrome's clinical and therapeutic management (Lin et al., 2024).

EPIDEMIOLOGY AND RISK FACTORS:

The specific therapy being administered will determine the occurrence of CRS in people with cancer receiving immunotherapy. The risks related to CAR-T therapy have been adequately documented in multiple research investigations. Several clinical trials, including adult and pediatric patients receiving CAR-T therapy for haematological malignancies, have shown a varying prevalence of the syndrome, with any-grade CRS varying from 35% to 100% and severe CRS from 1% to 28%.

It is believed that children are more vulnerable than adults. Early post-infusion CRS onset is suggestive of an increased risk of severe CRS, particularly if it happens during the first 72 hours. Additionally, there is a correlation between disease burden and the "first dose effect," or the emergence of more serious adverse effects following the initial CAR-T infusion, and both are indicators of severe CRS (Hoyt, Ye, & Dasgupta, 2024; Ko et al., 2024).

A higher incidence of this phenomenon has been described in ALL patients with a high disease burden, as well as after high-dose CAR-T administrations. A higher incidence of CRS has been observed in patients with ALL compared to those with NHL and chronic lymphocytic leukaemia (CLL), as well as in patients after lymphodepletion with cyclophosphamide or fludarabine before CAR-T infusion.

In addition, pre-existing inflammatory status (elevated ferritin) and underlying endothelial activation (thrombocytopenia) appear to be predictors of higher degrees of CFS. Factors such as the structure of the chimeric antigen receptor, as well as the CAR-T target antigen, require further studies to clarify their role in toxicity (Galani, Gupta, Waheed, Sennhauser, & Abdou, 2024; Yang et al., 2024).

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS:

CRS is explained by numerous immune dysregulation phenomena, being associated with a wide spectrum of manifestations, some of which are fatal. This syndrome can culminate in organ failure if

adequate treatment is not instituted. Although the CAR-T infusion lasts between half an hour and an hour, the onset and duration of CRS can vary. Symptoms generally appear in the first two weeks after infusion, with a median onset of 3 days and a median resolution time of 8 days.

For this reason, the European Medicines Agency (EMA) recommends daily monitoring of patients during the first ten days after infusion, as well as their stay in the vicinity (up to 2 hours of travel) of a qualified centre for at least four weeks. After infusion (Pratta et al., 2024; Slade et al., 2024). The most common clinical manifestations are described in Fig. 1. Fever is often the first symptom to appear, and it is common for values above 40ºC to be reached.

In addition, patients may also, in cardiovascular terms, have tachycardia associated with fever. In the most severe cases, hypotension, arrhythmias and a decrease in left ventricular ejection fraction (LVEF) may occur. Cases of cardiorespiratory arrest seven days after infusion have been described in patients with LVEF <25%, undergoing treatment for ALL, as well as atrial fibrillation and asymptomatic QT prolongation. Respiratory symptoms are common in these patients and may progress to severe acute respiratory syndrome (SARS) with dyspnea, hypoxemia, pulmonary oedema, and bilateral opacifications on chest X-ray (Liu, 2024; Ntwali, Gilliaux, & Honoré, 2024).

Depending on the severity, invasive and noninvasive mechanical ventilation (MV) may be necessary. However, the initiation of invasive mechanical ventilation is mostly related to the inability to protect the airway, which is secondary to concomitant neurotoxicity. In fact, due to hypoperfusion, acute kidney injury may occur, most of which is reversible. Fluid and electrolyte disturbances, such as hyponatremia, hypokalemia, and hypophosphatemia, may also occur. Hepatomegaly and gastrointestinal tract manifestations, such as diarrhoea and vomiting, are likely to occur (Javaid et al., 2024). Cytopenias are widespread in haematological terms and put these people at risk for opportunistic infections.

The confluence of thrombocytopenia, coagulopathy, and systemic inflammation increases the risk of spontaneous bleeding. Anasarca and Takotsubo cardiomyopathy may develop in extreme situations. The underlying cause affects and varies the laboratory results. Ferritin and C-reactive protein levels, two indicators of increased inflammation, are frequently observed. The latter is connected to how serious the illness is. As was previously noted, cytopenias are recurrent and linked to the cytokine-mediated mechanism of myelosuppression; anaemia (grades 3-5), thrombocytopenia, leukopenia, neutropenia, and lymphopenia have all been documented cases (Mammadzadeh et al., 2024; Santurio, Barros, Glauche, & Fassoni, 2024).

Disseminated intravascular coagulation is a common outcome of elevated D-dimers and coagulation abnormalities, which are characterized by delayed prothrombin time, increased partly active thromboplastin time, and hypo fibrinogen. Furthermore, there is also a regular elevation of serum inflammatory cytokines, including soluble IL-2R, IL-6, IL-10, and IFN-γ (or CXCL9 and CXCL10, chemokines generated by IFN-γ). Additional analytical alterations could include elevated transaminase and creatinine kinase levels, hyperbilirubinemia, hypertriglyceridemia, and hypogammaglobulinemia (Goldsmith et al., 2024; Tanaka et al., 2024).

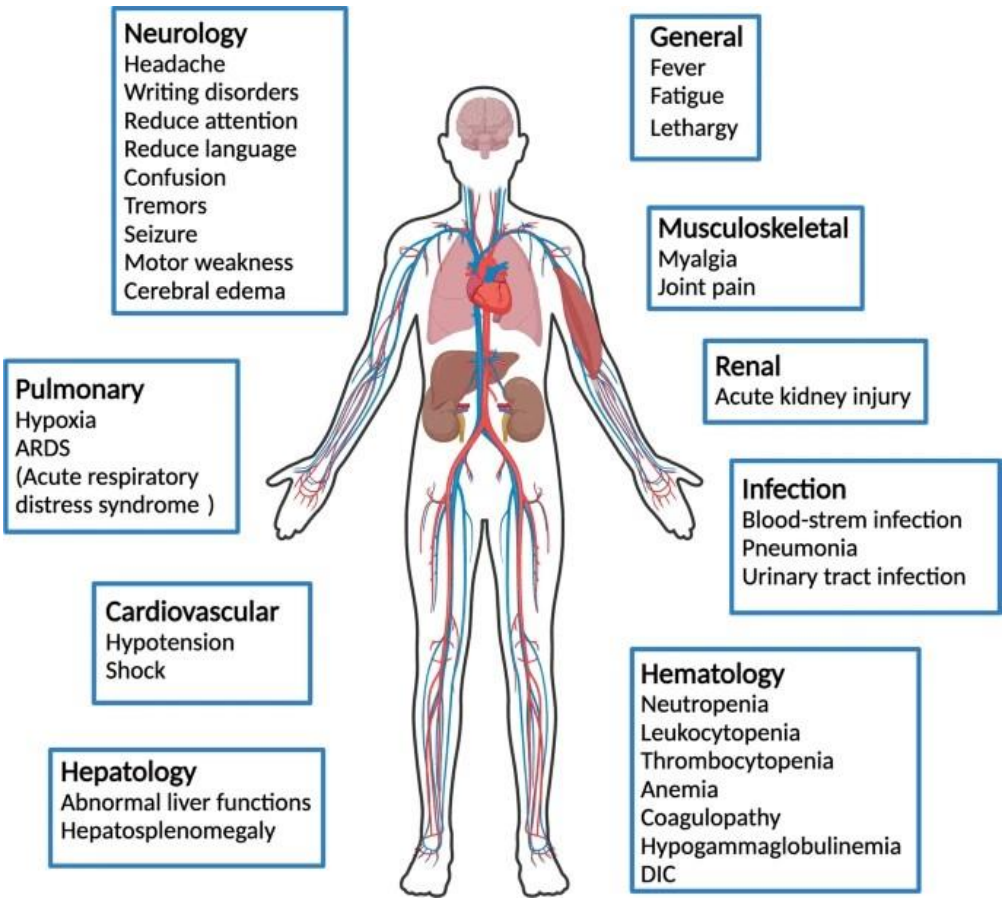

Figure 1: *Most frequent clinical manifestations of CRS and neurological manifestations after CAR-T infusion.*

DIC: *disseminated intravascular coagulation; CK: creatinine kinase; HF: cardiac failure; AKI: acute kidney injury; CRP: cardiorespiratory arrest; TLS: tumour lysis syndrome.*

NEUROTOXICITY:

Neurological manifestations appear to have a distinct pathophysiology from CRS, as neurological phenomena may occur before, after or even in the absence of CRS. The incidence of this toxicity varies and can reach 50%. Neurological manifestations present a broad spectrum, namely hallucinations, headache, aphasia, ataxia, dysmetria, paresis, drowsiness and convulsions. Neurological manifestations present a broad spectrum, namely hallucinations, headache, aphasia, ataxia, dysmetria, paresis, drowsiness and convulsions. In severe cases, progression to encephalopathy may occur. However, further studies are needed to better understand the clinic and pathophysiology of neurotoxicity and its relationship with CFS (Chohan et al., 2024; Patton, Monteith, Heffernan, Herzinger, & Wilson, 2024).

GRADES OF TOXICITY:

The CRS toxicity grading systems have been presented in recent years by several authors and institutions, including the Penn criteria, the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, and the CAR T-Cell Therapy–Associated Toxicity (CARTOX) criteria. The Common Terminology Criteria for Adverse Effects (CTCAE), (version 4, 4.03 and 5.0) = Penn criteria. Nevertheless, there was a requirement for these criteria to be uniform because they varied in some ways. To categorize the levels of CRS toxicity in patients receiving CAR-T therapy, the American Society for Blood and Marrow Transplantation assembled many specialists in this area in June 2018 and released a new system, which is displayed in Table 1 (Soltantabar et al., 2024; Wang et al., 2024).

Table 1: *CRS classification system from the 2018 consensus of the American Society for Blood and Marrow Transplantation.*

1	Fever that is higher than 38°C
2	Higher than 38ºC fever along with hypotension not requiring vasopressor assistance and hypoxia needing a nasal cannula.
3	Fever over 38ºC combined with hypotension requiring one vasopressor and hypoxia requiring a face mask, Venturi mask, or high-output nasal cannula.
4	High temperature (above 38ºC) combined with hypotension (needing more than one vasopressor vasopressin excluded and hypoxia (requiring positive pressure breathing)
5	Death

A classification system for neurotoxicity was created in 2018 through the CARTOX working team. It consists of the ten challenges listed below; one point is given for each job correctly completed: Inquire of the patient about the following: write a sentence (1 point); count backwards from 100 in intervals of 10 (1 point); name three things (maximum of three points); ask about the time of year, the month, city, hospital settings, and President/Prime Minister of the place where they live (total 5 points).

This makes it possible to evaluate improvements in speech, writing, and focus. When patients are admitted to the hospital following CAR-T therapy, it is advised that this evaluation be carried out every eight hours. A total score of 10 corresponds to a patient with normal cognitive function. When a total score is less than 10, some degree of neurotoxicity is considered. Based on the total score or, if the patient is obtuse, the inability to perform tasks, neurological toxicity is classified into four different grades (Table 2) (Ferreri & Bhutani, 2024; Tang, Li, & Wang, 2024).

DIFFERENTIAL DIAGNOSIS:

CRS is a systemic inflammatory syndrome and, as such, presents varied and nonspecific clinical manifestations, which may overlap with other inflammatory diseases. It is, therefore, imperative to consider other differential diagnoses to guide appropriate treatment. Tumour lysis syndrome (TLS) is an oncological emergency that is regularly encountered in patients with haematological malignancies, particularly NHL and acute leukaemias (Camilli et al., 2024).

Table 2: *Neurotoxicity classification system developed by the CARTOX group.*

GRADES	**LEVEL OF TOXICITY**
Grade 1:	Not very poisonous
Grade 2:	Toxicity is moderate
Grade 3:	Extremely poisonous
Grade 4:	Critically ill patients unable to carry out duties

This syndrome occurs due to the release of tumour cell contents into the bloodstream, either spontaneously or after treatment, which can lead to fever and renal and cardiovascular dysfunction. Therefore, it is understandable that, clinically, it is difficult to distinguish SLT from SLC. However, some analytical findings, such as hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, indicate a higher probability of TLS. Sepsis is currently defined as a multiorgan dysfunction caused by an inadequate host response to an infection. In turn, septic shock corresponds to a subtype of sepsis with a particular effect on the circulatory, cellular and metabolic systems (Biery, Turicek, Diorio, Schroeder, & Shah, 2024; Brudno & Kochenderfer, 2024). Despite having a distinct pathophysiology, CRS and sepsis are often associated with hypotension and fever, which makes them clinically and analytically indistinguishable. Infections are one of the main risks for patients with cancer undergoing immunosuppressive treatment. Clinically, it is difficult to

distinguish CRS from an infectious process. Indeed, when CRS is diagnosed, the immunosuppressive treatment administered may mask the presence of an infection. Therefore, a detailed clinical, analytical and imaging evaluation is essential.

The presence of a typical clinical infection, associated with an increase in procalcitonin and the identification of an infectious focus on radiological/microbiological examinations increases the probability that it is an infectious process (Bogacz et al., 2024; Salvino et al., 2024). The CARTOX working group developed a neurotoxicity classification system in 2018.

It is made up of the ten tasks listed below, with one point awarded for each task finished correctly. Ask the patient the following questions: Describe three things (maximum of three points); compose a sentence (1 point); count backwards from 100 in intervals of 10 (1 point); inquire about the month, the year, the city, the hospital settings, and the President or Prime Minister of the region in where they dwell (total 5 points).

This facilitates the assessment of gains in concentration, writing, and speech. It is recommended that patients receiving CAR-T therapy be evaluated every eight hours when they get admitted to the hospital (Chang & Kim, 2024; Irizarry Gatell, Huang, & Puglianini, 2024).

The pathophysiology of CRS and HLH/SAM is similar, with excessive immunological activation. These patients generally present with refractory fevers, hepatosplenomegaly, liver dysfunction, coagulopathy and a marked increase in ferritin. Finally, hypersensitivity reactions related to excessive T-cell stimulation can mimic the symptoms of CRS.

Fever and multiorgan dysfunction may occur, which are difficult to distinguish from CRS. However, only a few cases of hypersensitivity reactions after CAR-T infusion have been described in the literature (An et al., 2024).

THERAPEUTIC APPROACH:

Given the diagnosis of CRS, hemodynamic stabilization of the patient becomes essential. One of the challenges in the management and therapeutic approach is to attenuate the effect of the inflammatory cascade without reducing the antitumor effect of CAR-T therapy. The monitoring and therapeutic strategy of CRS is directed according to the classification level. The approach must involve a multidisciplinary team and may require referral to an Intensive Care Unit.

Several studies have been conducted to create recommendations regarding the management and treatment of CRS. In 2019, Brudno and Kochnderfer proposed a new therapeutic approach based on specific criteria of hemodynamic stability and organ dysfunction target (Zakhour et al., 2024).

Fig. 2 illustrates a possible approach algorithm adapted from this same proposal. Patients with low-grade CRS are indicated for symptomatic treatment with antipyretics, antihistamines, and fluid therapy.

Additional complementary diagnostic means should be used to exclude the broad spectrum of differential diagnoses. When an infectious process cannot be excluded with a high degree of certainty, initiation of empirical antibiotic therapy is recommended. The most severe forms of CRS, generally characterized by the need for vasopressor support, are life-threatening situations that require a rapid approach and targeted treatment (Perna et al., 2024).

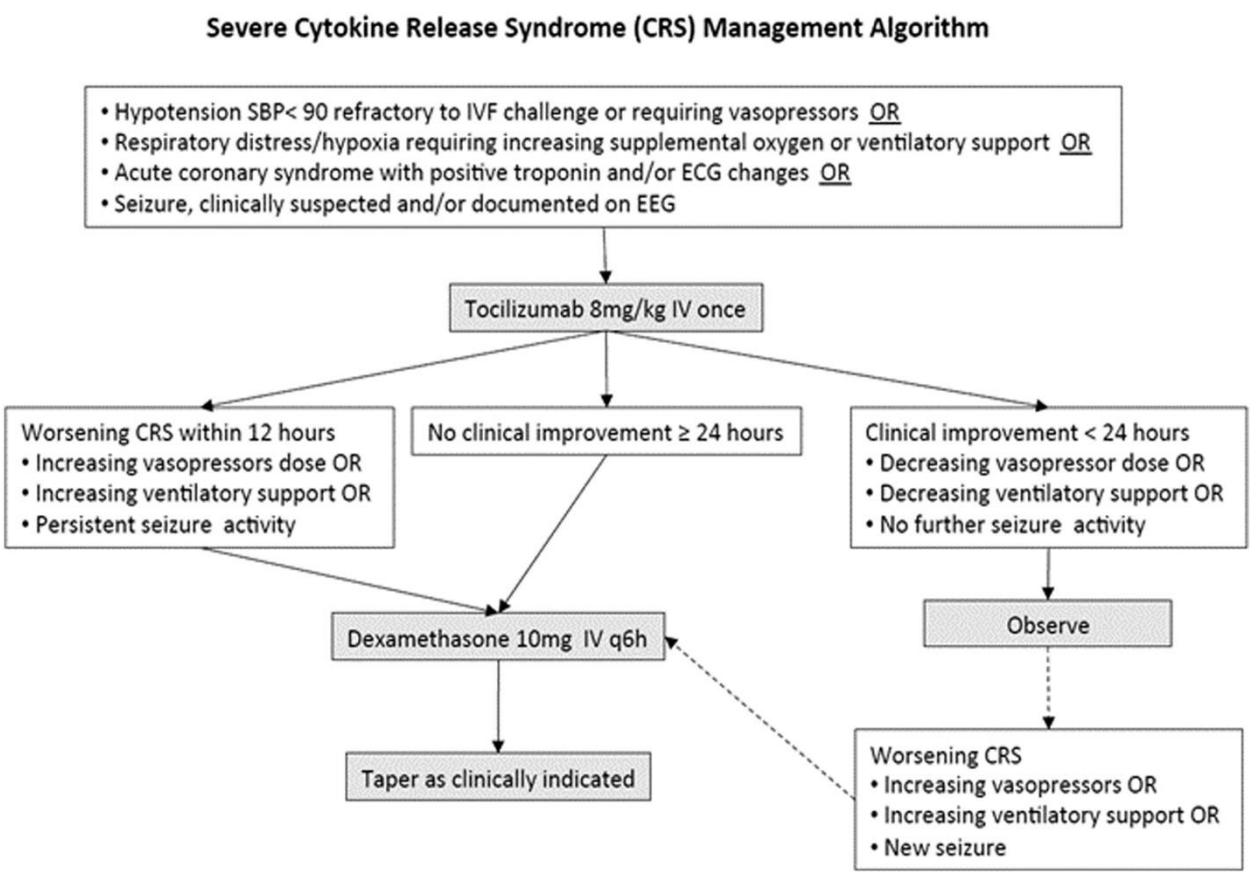

Figure 2: *Algorithm for the approach to CRS toxicity and neurotoxicity after CAR-T infusion*

According to some authors, intravenous immunoglobulin (Ig) G administration is recommended when the IgG value is less than 400 mg/dL. Given its good penetration across the blood-brain barrier, systemic corticosteroid therapy represents the first line of therapy in patients with isolated neurotoxicity, as can be seen in Fig. 2 (Müller, 2024).

TOCILIZUMAB:

Rheumatological illnesses are treated with tocilizumab, a humanized monoclonal antibody that acts as an antagonist of the IL-6 receptor. The FDA and EMA have currently approved it for the management of significant CRS in adults as well as children two years of age and older.

Typically, a dose of 8 mg/kg is administered; however, a dose of 12 mg/kg is advised for patients who weigh less than 30 kg. Its nonlinear pharmacokinetic profile demonstrates a biphasic release in the bloodstream (Justiz-Vaillant, Soodeen, Gopaul, Arozarena-Fundora, & Akpaka, 2024).Up to three more doses may be given, separated by at least eight hours, if the first dose does not result in a clinical improvement.

Over 800 mg of dosage per infusion is not advised. A greater likelihood of cytopenias and infections has been reported among individuals with rheumatoid arthritis, along with a potential rise in the frequency and extent of neurological damage associated with these therapies, even though this medication is not believed to impact the growth and long-term effectiveness of CAR-T treatment (Qureshi, Altaf, Jamil, & Siddique).

ALTERNATIVES TO TOCILIZUMAB:

Several studies are underway to evaluate the efficacy of new therapies. Corticosteroid therapy may play an important role in the treatment of CRS. Drugs such as siltuximab, anakinra, and suicide genes are also being considered as possible treatment options (Stankiewicz et al.).

CORTICOSTEROID THERAPY:

Despite the current use of systemic corticosteroid therapy to control CRS, evidence suggests that its administration may reduce the antitumor efficacy and persistence of CAR-T. Therefore, its use is reserved for CRS refractory to tocilizumab or concomitantly in the most severe cases. On the other hand, in patients with isolated neurotoxicity, this should be the first line of therapy. In this scenario, intravenous dexamethasone 10 mg with a 6-hour interval is recommended (Luo et al., 2024).

SILTUXIMAB:
The FDA and EMA have not yet approved the IL-6 antagonist siltuximab for the treatment of CRS; it is only recommended for people with multicentric Castleman illness who are not infected with the human immunodeficiency virus or the human herpes virus type 8.30. Since it has a stronger affinity for IL-6, some writers contend that it should be used in every case of CRS that is resistant to tocilizumab. Given that the siltuximab-IL-6 complex is unable to pass the blood-brain barrier, it may play a significant part in the management of CAR-T-induced neurotoxicity. However, more research is required to assess and approve its application in CRS (Colomes, Ellouze, Fontaine, Thieblemont, & Peyrony, 2024).

ANAKINRA:
This medication is an antagonist of the human IL-1 receptor and was derived from Escherichia coli using recombinant DNA technology. Its therapeutic use for the relief of rheumatoid arthritis that does not respond well to methotrexate alone Still's a disease, and autoinflammatory periodic fever syndromes, including cryopyrin-associated syndromes (CAPS) and family-related Mediterranean fever, has been approved by the European Medicines Agency (EMA). This drug may play a significant role in the management of CFS, as it is believed that the pathophysiology of the condition and the neurotoxicity associated with CAR-T involves the production of IL-1 by macrophages. However, more research is required to fully comprehend this therapy (León-Román et al., 2024).

SUICIDE GENE:
In situations of refractory toxicity, it may be necessary to use suicide genes. These correspond to genetically modified elements that are incorporated into cells and, after the administration of an activating agent (pro-drug), selectively destroy these cells. In the case of CAR-T, a mechanism currently under investigation is that of caspase 9 (iCasp9)/AP1903. This consists of the insertion of iCas9 into the CAR-T. In the presence of refractory toxicity, the prodrug AP1903 can be administered intravenously, which activates the cascade of cellular apoptosis. In this way, the CAR-T cells are eliminated, as well as the toxicity associated with them (Kagoya, 2024).

CLINICAL TRIALS IN BEARS:
To assess the state of the art regarding new therapies for CRS after CAR-T infusion, we performed a search on ClinicalTrials.gov (performed on 31/03/2023), using the condition or disease as the condition for cytokine release syndrome and other terms (other terms) each drug evaluated separately (tocilizumab, siltuximab and anakinra). We, therefore, present the clinical trials currently under development in the context of CRS. Only studies targeting the treatment of CAR-T-induced CFS were included. Results are available in Annex 1 (Zhou et al., 2024).

***Annex 1**: Ongoing clinical trials.*

SEARCH	TITLE	PHASE	CURRENT STATE	OBJECTIVE	PRIMARY OUTCOME
Tocilizumab Found 19 Included 2	NCT02906371 The purpose of this pilot trial is to assess two cohorts of tocilizumab	1	Complete	We are assessing the effectiveness of co-administration	CRS grade 4 frequency (per year)

	optimization times in children diagnosed with CD19-expressing relapsed/refractory B-cell ALL (acute lymphoblastic leukaemia) to control CART19-associated cytokine rupture syndrome (CRS).			of tocilizumab in pediatric R/R ALL patients' treatment of CRS following CAR-T therapy.	
	(NCT04082910) Metoprolol for the management of inflammatory rupture syndrome in recipients of chimeric antigen receptor T cell therapy	1/2	Recruiting	To assess the usefulness and effectiveness of the beta-blocker metoprolol in the management of CAR-T therapy-induced CLS, confirm the effectiveness of IL-6 lowering, and ascertain whether metoprolol is a suitable substitute for antibodies such as tocilizumab.	Metoprolol's effectiveness in CRS depending on body temperature (two weeks)
Siltuximab Found 3 Included 1	NCT04975555 To assess the effectiveness of siltuximab in treating cytokine rupture syndrome (CRS) and neurotoxins linked to CART19 Immunologically Effective (ICANS) for chimeric antigenic receptor (CAR-T) T cell therapy in hematologic		Recruiting	Examine how well siltuximab works for treating the severity of CRS and ICANS in patients receiving CAR-T therapy for hematologic disorders.	CRS resolution, measured in terms of symptom severity per day, is 14 days.

	malignancies, a phase II pilot trial has been conducted.				
Anakinra Found 9 Included 3	NCT04359784 Phase 2 pilot research to assess Anakinra's safety and effectiveness in avoiding neurotoxins and CD19-specific CAR-T cell-related cytokine rupture syndrome (CRS) in B-cell lymphoma patients	2	Not recruiting yet	The use of siltuximab is beneficial when using CAR-T therapy to safely treat CRS and ICANS.	severe 90-day CRS severity
	NCT04148430 A phase II study using the IL-1 receptor antagonist Anakinra to alleviate chronic inflammation associated with COVID-19 and prevent severe neurosis and cytokine rupture syndrome among individuals with CD19-specific chimeric antigen receptor (CAR) T cells		Recruiting	Anakinra's effectiveness in treating and preventing cough in patients who have had CAR-T therapy is being assessed.	Rate of severe neurotoxic in individuals receiving CAR-T treatment (4 weeks) percentage of patients who have survived 28 days without dying or requiring artificial ventilation
	NCT04150913: Anakinra: A Phase 2 Research to Prevent CAR-T Cell-Mediated Neurotosis	2	Recruiting	Anakinra and axicabtagene ciloleucel together are being evaluated for their potential to treat neurotosis, chronic bronchitis, and CRS deficiency in patients with R/R NHL.	High rate of neurotoxins (30 days)

CONCLUSION:

The advancement of knowledge in the field of immunotherapy, i.e. through CAR-T infusion, makes it increasingly clear that there is a need to understand the possible adverse effects associated with these therapies. CRS is the most common adverse effect of CAR-T therapy and requires a high index of suspicion for its diagnosis. As it is a potentially fatal situation, it is essential to educate clinicians on this issue, as well as on its management and therapeutic approach. In terms of treatment options, the use of tocilizumab is recommended, and in the most severe cases, systemic corticosteroid therapy can be combined. In the presence of isolated neurotoxicity, systemic corticosteroid therapy is recommended. Further studies on this topic, i.e. large-scale studies, will be needed in the future to clarify and standardize the knowledge regarding CRS after CAR-T infusion.

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