Cytokine Release Syndrome in the Pediatric Population and Implications for Intensive Care Management

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KEYWORDS

• CAR-T • Cytokine release syndrome (CRS) • Pediatric intensive care

KEY POINTS

- Immune effector cell therapies have led to significantly improved survival in relapsed, refractory leukemias and lymphomas and have increased cancer survival rates in pediatric patients.
- Cytokine release syndrome (CRS) represents an immune hypersensitivity syndrome that can lead to profound multiorgan system failure and death.
- A universal grading system for CRS allows clinicians to accurately diagnose and initiate treatment regimens.

INTRODUCTION

Although leukemia remains the most common pediatric cancer, improvements in treatment have led to improved survival. For pediatric patients with acute lymphoblastic leukemia (ALL), survival rates approach 90%. However, survival rates for patients who have a relapse are significantly lower, with 5-year overall survival rates ranging from 19% to 52%, depending on ALL type.[1,2] A variety of new treatment modalities are available, among them new treatments in immunotherapy, using the body's own immune system to target malignant cells.[3,4] Tisagenlecleucel, the first chimeric antigen receptor (CAR) T cell to be approved by the Food and Drug Administration (FDA), demonstrated 90% remission in relapsed and refractory ALL. Recent studies show long-term disease-free survival in pediatric patients treated with CAR T cells as high as 60% at a median of 4.8 years out.[3,5] Although CAR T cell therapy has yet to be FDA approved in other pediatric cancers, treatment of B-cell non-

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Hodgkin lymphoma, mantle cell lymphoma, follicular lymphoma, and multiple myeloma are approved in ages 18 years and older and clinical trials are ongoing for other pediatric cancers.[6,7] Although these agents have the potential to revolutionize therapeutic options, they also come with their own set of toxicities, which in the most extreme form can lead to life threatening multiorgan system failure.[3,4,8] In this review article, we focus on the diagnosis and management of cytokine release syndrome (CRS).

Chimeric Antigen Receptor T-cells and Development of Cytokine Release Syndrome

Before understanding the pathophysiology behind CRS, an understanding of the therapy inciting it is necessary. CAR T cells represent one of several types of adoptive cell transfer, an immunotherapeutic approach whereby a patient's own cells are collected and used to target cancer cells. Following a blood draw, T cells are separated out and genetically engineered to produce receptors on their surface called CARs. This allows the T cells to recognize and attach to antigens on cancer cells. Once engineered to express the antigen-specific CAR, the T cells are expanded into the hundreds of millions. Patients undergo lymphodepletion and are then infused with the engineered CAR T cells.[9] There are currently 6 FDA-approved CAR T cells, all of which target either CD-19 or B-cell maturation antigen. Of these, only tisagenlecleucel, which targets CD-19, is FDA-approved in children.[9,10]

Once infused, CAR T cells recognize the antigen, resulting in CAR T proliferation, cytokine release, and immune cell activation.[11,12] Following activation, the CAR T cells produce interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and granulocyte-macrophage colony-stimulating factor, which further activate monocyte and macrophages to secrete interleukin (IL)-1, IL-6, and inducible nitric oxide synthase.[12–14] It is this immune response that enables the patient's own immune system to fight against their cancer. However, when the above response is exaggerated, these immune effector cells are hyperactivated by excessive release of inflammatory mediators. This overactivation of this immune response leads to CRS.

Although recognized early as a side effect of CAR T therapy, it was not until 2018 when the American Society for Transplantation and Cell Therapy (ASTCT) convened an expert panel, that a uniform definition and grading system was created for CRS. Widely accepted, the ASTCT criteria define CRS as a "supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."[15]

Although most well recognized in CAR T therapy, it is important to note that CRS has also been described in the treatment with blinatumomab, a bispecific T cell engaging antibody, and following haploidentical hematopoietic stem cell transplant.[16,17]

Epidemiology and Predictors of Disease Severity

CRS exists along a spectrum of diseases with similar symptomology to macrophage activation syndrome and hemophagocytic lymphohistiocytosis (HLH).[18] The clinical syndrome of CRS can range from mild flulike symptoms to multisystem organ failure and death, and awareness and early recognition are key to management.[14,19] The incidence of CRS following CAR T cell therapy for relapsed/refractory ALL has been reported as high as 100% for all grades of CRS but falls slightly less than 70% for grades 3 or 4 CRS.[20] In children and young adults, CRS symptoms usually occur between 0 and 10 days after CAR T cell infusion, with a mean onset of 4 days for mild/moderate and 1 day for severe CRS.[20]

As previously mentioned, patients with CRS have elevated plasma level IFN-γ, IL-6, IL-10, IL-2, and TNF-α as well as C-reactive protein (CRP) and ferritin.[12] Elevated CRP levels have been shown to correlate with disease severity, although no specific thresholds for prediction of disease severity have been reproducibly established.[16,19] Similarly, no other biomarker or combination of biomarkers has been found to predict disease severity because most peak after patients become acutely ill.[18,21] The timing and magnitude of immune cell activation seems to coincide with maximal in vivo T cell expansion and correlate with disease burden and therefore likely high levels of T cell activation.[15] Higher dose level of CAR T cells also correlates with risk of developing CRS.[22]

Diagnosis

Presenting symptoms of CRS are relatively nonspecific and may impact every organ system (**Table 1**). Fever greater than 38°C is a requirement for diagnosis.[15] Patients may present with rigors, malaise, fatigue, myalgias, nausea vomiting, and headache. Respiratory involvement may present as tachypnea and hypoxemia progressing to acute hypoxemic respiratory failure. Patients may have cardiac insufficiency with tachycardia, arrhythmia, or progression to shock. Other signs of end-organ dysfunction may include renal dysfunction and azotemia, hepatic dysfunction with transaminitis and hyperbilirubinemia, and frank disseminated intravascular coagulation (DIC).

Grading is broken into 4 categories based on the ASTCT criteria and are outlined in **Table 2**. For these symptoms to be included in the grading scheme, they cannot be attributed to other causes. All grades involve fever greater than 38°C (unless patients have received antipyretic or anticytokine therapy, in which case fever is not required for diagnosis). From there, grading severity increases based on severity of respiratory and cardiovascular dysfunction.[15] Notably, there are no laboratory criteria for the diagnosis of CRS.

As symptoms of CRS are relatively nonspecific to CRS, caution should be taken to exclude other causes, particularly sepsis. Sepsis may occur concurrently with CRS or even be mistaken for CRS.

Clinical Management

Critical to proper management of CRS is awareness of its prevalence, high degree of clinical suspicion, and cardiopulmonary monitoring. The expert consensus document

Table 1
Signs and symptoms of CRS

Organ System	Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, myalgias
Neurologic	Headache, mental status changes, confusion, delirium, hallucinations, tremor, altered gait, seizures
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, cardiomyopathy
Respiratory	Tachypnea, hypoxemia, pulmonary edema, pneumonitis, ARDS*
Gastrointestinal	Nausea, vomiting, diarrhea, ascites
Renal	Acute kidney injury, renal failure
Hepatic	Hepatomegaly, transaminitis, hyperbilirubinemia, cholestasis, liver failure
Skin	Rash, edema
Coagulation	Elevated D-dimer, hypofibrinogenemia, bleeding
Rheumatologic	Vasculitis, arthralgias

* Acute Respiratory Distress Syndrome

Table 2
Grading and management of CRS

Grade 1 CRS	Grade 2 CRS	Grade 3 CRS	Grade 4 CRS
Signs and symptoms			
• Temperature ≥38°C[a] • No hypotension • No hypoxia	• Temperature ≥38°C[a] with • Not requiring vasopressors and/or[b] • Requiring low-flow nasal cannula[c] or blow by	• Temperature ≥38°C[a] with • Requiring a vasopressor with or without vasopressin and/or[b] • Requiring high-flow nasal casual[c], facemask, nonrebreather mask or Venturi mask	• Temperature ≥38°C[a] with • Requiring multiple vasopressors (excluding vasopressin) and/or[b] • Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)
Management			
• Acetaminophen, as needed, for fever • Evaluate for infectious causes • Consider broad-spectrum antibiotics and filgrastim (if patient is neutropenic) • Assess for adequate hydration • Consider anti-IL-6 therapy for persistent or refractory fever[d] • Supportive care	• Manage according to recommendations for grade 1 CRS (if applicable) • IV fluid bolus as needed to maintain normotension for age • For hypotension refractory to fluid bolouses or hypoxia, consider anti-IL-6 therapy with i.v. tocilizumab (12 mg/kg for patients weighing <30 kg or 8 mg/kg for those weighing ≥30 kg, to a maximum of 800 mg per dose) repeat dose every 8 h for up to 3 doses within 24 h (but titrate frequency according to response) • If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors,	• Manage according to recommendations for grades 1 and 2 CRS • Transfer patient to PICU and obtain echocardiogram, if not performed already • Administer i.v.dexamethasone 0.5 mg/kg (maximum 10 mg per dose) every 6 h; can increase dose to maximum of 20 mg every 6 h if patient is refractory to lower dose (alternatively methylprednisolone 1–2 mg/kg/d divided every 6–12 h can be used)[f]	• Administer i.v. fluids, anti-IL-6 therapy, corticosteroids, and vasopressors and perform hemodynamic monitoring as described for grades 1, 2, or 3 CRS • If low doses of corticosteroids do not lead to clinical improvement, consider high-dose methylprednisolone (1g daily for 3 d followed by rapid taper on the basis of clinical response)

	transfer patient to PICU, and obtain echocardiogram • For patients at high risk or severe CRS[e], if hypotension persists after anti-IL-6 therapy, or there are signs of hypoperfusion or rapid deterioration, use stress-dose hydrocortisone (12.5–25 mg/m^2/d divided every 6 h; i.v. dexamethasone 0.5 mg/kg(maximum 10 mg per dose) every 6 h; or methylprednisolone 1–2 mg/kg/d divided every 6–12 h)	

Early recognition of CRS and appropriate intervention are essential to avoid life-threatening complications of this toxicity. CRS should be suspected if any of the above listed signs and symptoms are present within the first 3 wk after CAR T cell therapy. CRS grading should be performed at least twice a day and when a change in the patient's clinical status occurs.

[a] Fever is defined as temperature 38°C or greater not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at 6 L/min or greater. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at greater than 6 L/min.

[d] For example, persistent fever lasting more than 3 d or fever with a temperature of 39°C or greater for 10 h that is unresponsive to acetaminophen.

[e] Patients with early onset of CRS signs and symptoms (within 3 d of cell infusion), bulky disease, and comorbidities are at high risk of developing severe CRS.

[f] Simultaneous administration of corticosteroids and anti-IL-6 therapy or waiting to see if the patient responds to anti-IL-6 monotherapy before administering corticosteroids are both reasonable approaches (strategy used might vary depending on the CAR T cell products and/or risk factors).

Adapted from 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. https://doi.org/10.1038/s41571-018-0075-2.

for management of pediatric patients receiving CAR T therapy recommends strong consideration of inpatient monitoring for a minimum of 3 to 7 days, as well as reassessment of CRS grading at a minimum of every 12 hour and more frequently with any change. Postinfusion, the guidelines recommend a minimum of daily monitoring of CBC, hepatic function, CRP, ferritin, and evaluation for both DIC and tumor-lysis syndrome as CRS can result in both of these conditions.[23] Low threshold for admission to the pediatric intensive care unit (PICU) is reasonable, given up to 50% of CRS patients require critical care services. The most common indications for admission to the PICU are hemodynamic instability, respiratory insufficiency, and neurologic deterioration.[12,24]

Once the diagnosis of CRS is made, treatment focuses on mitigating the exaggerated immune response, both through broad strategies of immunosuppression, as well as focused therapies targeting specific cytokines.[19] This immunosuppression, however, may also negatively affect the efficacy of the originally intended treatment. The goal, therefore, is to balance administration of immunosuppressive therapy to adequately control the CRS but not completely extinguish the intended therapeutic effect of the immunotherapy.[18] The development of the CRS severity stratification system has helped to optimize this balance.

Initial evaluation of a patient with suspected CRS must include consideration of other diagnoses, followed by appropriate evaluation and diagnosis. Most notably, given that fever is a hallmark CRS symptom, infectious causes must be especially considered in this vulnerable population. It is recommended that blood cultures be drawn in all patients and empiric antibiotics initiated. This is particularly important in neutropenic patients.[12,23]

Once a diagnosis of CRS is established, the mainstays of management include supportive care with goal of symptom relief, as well as immune suppression.

In general, fever and malaise associated with CRS should be managed with standard antipyretic therapies. As previously mentioned, all patients should undergo a thorough infectious evaluation and receive broad spectrum antibiotics. Close attention should be given to hydration status, avoiding fluid overload. Cardiovascular involvement may manifest as tachycardia, arrhythmias, or shock, which may be vasodilatory, cardiogenic, or mixed vasodilatory and cardiogenic shock. As such, frequent hemodynamic assessments, including serial blood pressure measurements, facilitate early recognition of cardiovascular involvement. Predictors of development of hypotension requiring vasopressor support include those with leukemic blast count greater than 25% pretreatment, or preexisting cardiac dysfunction.[24] This is especially important to note given a significant percentage of the patients receiving these therapies are already at increased risk for cardiac dysfunction due to exposure to cardiotoxic medications such as anthracyclines, and/or radiation exposure as part of their prior treatment regimen.[24] For patients with suspected adrenal insufficiency, stress dose hydrocortisone should be administered.

Involvement of the respiratory system may lead to respiratory insufficiency, ranging from mild hypoxia to severe pediatric acute respiratory distress syndrome (PARDS).[25] The cause of respiratory failure in CRS is largely believed to be a result of pulmonary edema from capillary leak.[26] Respiratory support should be escalated as needed, and managed according to PARDS guidelines.[12,27]

Providers should also be aware of potential involvement of gastrointestinal and renal systems, and liver and renal function should be monitored. Fluid overload and/or renal insufficiency may require dialysis.

In addition to supportive care, specific treatment of CRS involves the use of anti-IL6 therapies and corticosteroids. Tocilizumab, a monoclonal antibody that works by

blocking the IL-6 receptor, was approved by the FDA for treatment of CRS in 2018.[27] Timing of use depends largely on the severity of CRS as discussed below. Fortunately, although remarkably effective at treating CRS, tocilizumab has not been shown to have an impact on long-term efficacy of CAR T cells.[16]

For most cases of Grade 1 and 2 CRS, the use of anti-IL-6 therapy and/or corticosteroids are not usually recommended, unless other comorbidities are present, or symptoms persist for 3 or more days (see **Table 2**). For grade 3 or 4 CRS, treatment generally begins with tocilizumab at a dose of 8 mg/kg, up to 3 doses. If CRS persists, corticosteroids may be added, typically as dexamethasone 0.5 mg/kg (up to 10 mg) every 6 hours or methylprednisolone 1 to 2 mg/kg/d divided every 6 hours for continued symptoms. In patients with grade 4 CRS who are unresponsive to prescribed therapies, consideration may be given to high dose methylprednisolone followed by a rapid taper once clinical improvement is achieved.[23] For patients unresponsive to management with tocilizumab and corticosteroids, the addition of other anticytokine agents may be considered, such as siltuximab, anakinra, ruxolitinib, or cyclophosphamide. For patients refractory to all of the above therapies, an alternate diagnosis, such as HLH, should be reconsidered.[23]

Complications and Immune Effector Cell-Associated Neurotoxicity Syndrome

Immune effector cell-associated neurotoxicity syndrome (ICANS) refers to a neurotoxicity syndrome that develops following the administration of CAR T cell therapy. Although it is related to CRS, the term ICANS refers to a separate, independent disease process. It is fairly common and can be seen in 25% to 44% of treated patients.[2] ICANS typically presents in patients who have had precedent CRS, usually within the first 7 to 10 days following administration of CAR T cell therapy. Common symptoms include confusion, language disturbance, and altered mental status. More severe presentations may include the development of seizures or coma and have been described in 10% to 20% of patients with ICANS. On the most severe end of the spectrum, patients can develop rapidly progressive cerebral edema, which may result in death. Associated risk factors for the development of severe ICANS include high tumor burden, severe CRS, neurologic comorbidities, high CAR T cell doses, and high peak levels of CAR T cell expansion. The presence of active or previously treated CNS disease has not been shown to be associated with the development of severe ICANS.[2]

All patients who received CAR T cell therapies should be monitored closely for the development of neurologic symptoms with validated screening tools.[24] The ASTCT guidelines recommend using the Immune Effector-Cell Encephalopathy score for children aged greater than 12 years, and the Cornell Assessment of Pediatric Delirium for those aged less than 12 years.[11,25] Patients with a positive screen should be considered for the diagnosis of ICANS.

There are no consensus guidelines on the treatment of ICANS. There have been descriptions of grading systems similar to that used with CRS, where ICANS severity is graded on a scale from 1 to 4. First-line therapy for all patients includes supportive care. The need for CNS imaging with CT scan or MRI should be considered, as well as EEG monitoring for seizure development and consideration of the use of prophylactic antiepileptic therapies. Tocilizumab does not cross the blood–brain barrier and is therefore not a therapeutic option in the treatment of ICANS. Patients may be treated with corticosteroids such as dexamethasone. The use of the IL-1 receptor antagonist anakinra is an active area of research at this time.

Typically, patients will have resolution of ICANS symptoms within 28 days of CAR T cell therapy. Long-term neurocognitive outcomes in patients who have received CAR T cell therapy remains an active area of study.

SUMMARY

The development of immune effector cell therapies has led to tremendous strides in the treatment of refractory pediatric ALL. CAR T cells have helped turn relapsed, refractory ALL from an entity with high mortality to one where many patients go on to long-term survival. CRS represents a potentially life-threatening complication of CAR T therapy. Providers caring for patients receiving CAR T cells should maintain a high index of suspicion as prompt recognition and intervention is critical to reduce morbidity and mortality.

CLINICS CARE POINTS

- Our understanding of cytokine release syndrome and its management continue to evolve as this remains an active area of research.
- A diagnosis of cytokine release syndrome should be strongly considered in any patient who develops a fever following treatment with CAR T cells.
- Management of cytokine release syndrome depends on disease severity, and ranges from supportive care to use of corticosteroids and anti-IL6 therapies.

CONFLICTS OF INTEREST

None.

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