Adult Management of Cytokine Release Syndrome (CRS) from CAR-T Therapy

BACKGROUND

Immunotherapies in cancer care are becoming more widely available. As these therapies are being used more commonly, clinicians must be aware of their unique toxicities and the optimal strategies that are recommended for the management of these toxicities.

Cytokine release syndrome (CRS) has been observed with several different immunotherapies, including monoclonal antibodies, bi-specific antibodies, T-cell checkpoint inhibitors, and novel T-cell therapies. It is characterized by widespread activation and proliferation of lymphocytes leading to an abundant release of inflammatory cytokines well above physiologic levels. This cytokine storm can manifest in many ways from constitutional symptoms to cardiovascular and neurologic compromise. Management of this cytokine release storm involves both supportive care, and if clinically warranted, immunosuppression that blunts the aggressive cytokine response. However, administration of immunosuppressive therapies may also counter the desired immune response against targeted tumor cells. Thus, it is important that clinicians be prudent and reserve certain immunosuppressive strategies for the most appropriate clinical scenario. Thus, an algorithm that defines different grades of CRS and the corresponding therapy is necessary to guide clinicians in the delivery of appropriate care.

SIGNS/SYMPTOMS & CLINICAL GRADING

Severity of cytokine release syndrome is variable and may be influenced by tumor burden at the time of treatment with the immune-directed therapy or other pre-existing comorbidities. Clinical grading is important for appropriate management. Organ systems affected by CRS and their corresponding signs and symptoms are listed below in Table 1 and criteria for clinical grading[1] are outlined below in Table 2.

TABLE 1. Signs and Symptoms of CRS and Neurotoxicity

Organ system	Signs/Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, headache, myalgias/arthralgias, nausea/vomiting
Dermatologic	Rash
Gastrointestinal	Nausea/vomiting/diarrhea
Respiratory	Tachypnea, hypoxemia (potentially requiring supplemental oxygen/ventilation)
Cardiovascular	Tachycardia, hypotension
Coagulation	Disseminated intravascular coagulation (DIC) characterized by elevated D-dimer, hypofibrinogenemia, bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Altered mental status, confusion, delirium, aphasia, hallucinations, tremor, seizures, ataxia

MANAGEMENT OF CRS

Management of CRS involves both supportive measures and pharmacologic therapies that inhibit immune activation and amplification. Supportive measures are directed at managing constitutional symptoms and achieving and maintaining hemodynamic stability. Immune targeted therapies are directed at the cytokines released in the pathobiology of the syndrome. Cytokines identified to play a role in CRS

include, but are likely not limited to, TNFα, IFNy, IL-1β, IL-2, IL-5, IL-6, IL-8, and IL-10. Therapies utilized in CRS exhibit either a non-specific inhibition of immune amplification or a more targeted inhibition of a particular cytokine. These therapies are outlined below, and treatment guidelines are shown in Table 2.

Tocilizumab
Tocilizumab is a humanized monoclonal IL-6 receptor antibody that inhibits IL-6 from binding to both cell-associated and soluble IL-6 receptors. IL-6 is a cytokine that has been implicated in the pathogenesis of CRS and presents a pharmacologic target for management. Thus, treatment strategies for CRS have focused on inhibiting IL-6 signaling. Tocilizumab can be administered for the treatment of CRS, resulting in a rapid reversal of symptoms.
Dosing:

- 8 mg/kg IV over 1 hour for one dose (Max individual dose: 800 mg). May repeat another 8 mg/kg dose in 8 hours if there is a lack of clinical response to the initial dose (maximum of 3 additional doses after the initial dose with at least an 8-hour interval between consecutive doses).
- **NOTE: Two doses of tocilizumab should be available on site for immediate use for each patient treated with CAR-T cells. These doses must be available prior to cell infusion and up to 6 weeks following cell infusion.**

Corticosteroids
Steroids may be utilized in the setting of severe CRS with or without neurologic symptoms along with targeted cytokine therapies (i.e. tocilizumab) or as monotherapy for patients with isolated neurologic toxicities without systemic CRS (refer to Guidelines for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome). Steroids exhibit a non-specific immune inhibition. Intravenous dexamethasone is the preferred steroid to be initiated if steroids are warranted due to neurological symptoms given improved CNS penetration. Methylprednisolone can be used as an alternative. With appropriate response, steroids can be tapered rapidly over a few days. See Table 2 for dosing guidelines.

T R E A T M E N T A L G O R I T H M

Important Considerations:

The following adult treatment algorithm was developed based on the package inserts for the currently FDA approved CAR T cell products and published consensus guidelines from several clinical oncology and cancer immunology organizations.[2-4] It serves as a framework for the management of patients with CRS and is not meant to replace physician discretion. Given that each patient will require thorough clinical evaluation for proper management, an attending physician should be notified at the first signs/symptoms suggestive of CRS and should be involved in each therapeutic decision made throughout the progression of care. This includes supportive and pharmacologic interventions, as well as escalation of care from the floor to ICU-level care.

The majority of clinical evidence for the early use of corticosteroids is derived from data in the adult CD19+ CAR population for lymphoma patients. Caution should be exercised in early use of corticosteroids in adult ALL patients on CD19+ CAR therapy as the effects on CAR-T efficacy and persistence is unknown at this time.

Initiation of tocilizumab and/or steroids for CRS from CAR-T therapy must be approved by a cell therapy physician who has undergone REMS training.

Adult CRS Treatment Algorithm

Grade	Tocilizumab	Corticosteroids
Grade 1 Fever (≥ 38.0^0 C) No hypotension No hypoxia	I f fever persists > 24h consider tocilizumab 8 mg/kg IV over 1 hour x 1 dose (Max individual dose: 800 mg); may repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose If fever persists > 72h administer tocilizumab 8 mg/kg IV over 1 hour x 1 dose (Max individual dose: 800 mg); may repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose	Not indicated
Grade 2 Fever (≥ 38.0^0 C) Hypotension not requiring vasopressors Hypoxia requiring low-flow nasal cannula (≤6 L/minute) or blow-by N.B: Fever is not a necessary criterion for CRS grading after antipyretics or tocilizumab have been administered	Tocilizumab 8 mg/kg IV over 1 hour x 1 dose (Max individual dose: 800 mg); may repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose	I If patient has any high-risk features as outlined below, consider dexamethasone 4 mg IV BID. Continue dexamethasone until resolution to Grade 1 <u>High-risk features:</u> - Age ≥ 60 yrs. - 2 or more comorbidities that are cardiac, hepatic, pulmonary, or renal - Significant tumor burden - Early onset CRS (within 24 hours of CAR-T infusion) If CRS has not improved to Grade 1 after 24 hours, consider dexamethasone 10 mg IV q6h

Grade	Tocilizumab	Corticosteroids
Grade 3 Fever (≥ 38.0^0 C) Hypotension requiring a vasopressor with or without vasopressin Hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, nonrebreather mask, or Venturi mask	Tocilizumab as outlined in Grade 2 CRS	Administer dexamethasone 10 mg IV every 6 hours. Continue dexamethasone until resolution to Grade 1
Grade 4 Fever (≥ 38.0^0 C) Hypotension requiring multiple vasopressors (excluding vasopressin) Hypoxia requiring positive pressure (e.g.: CPAP, BiPAP, intubation and mechanical ventilation)	Tocilizumab as outlined in Grade 2 CRS	Administer dexamethasone 20 mg IV every 6 hours. Continue until resolution to Grade 1 If there is no improvement after 24 hours, administer Methylprednisolone: 500 mg IV q12h for 3 days 250 mg IV q12h for 2 days 125 mg IV q12h for 2 days 60 mg IV q12h for 2 days

References

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4. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol 2021;39(35):3978-3992. DOI: 10.1200/JCO.21.01992.