Management of Cytokine Release Syndrome (CRS) from Cellular 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. One toxicity in particular associated with these immunotherapies is cytokine release syndrome (CRS). This life-threatening toxicity, if not managed both appropriately and in a timely manner, can lead to multi-organ failure and death.

Cytokine release syndrome 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 are outlined below in Table 2.

TABLE 1. Signs and Symptoms of CRS

Organ system	Signs/Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, 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

CRS Grading/Severity
The outlined clinical grading criteria is designed to guide clinicians in the management of CRS. Many of the signs and symptoms associated with CRS can also be attributable to other common complications of cancer therapy such as neutropenic fever, other infectious complications, and tumor lysis syndrome. Thus, in applying the criteria below, clinicians should exercise appropriate clinical judgement in each patient-specific scenario in an effort to distinguish true CRS from other cancer treatment-related toxicities. This will ensure appropriate delivery of care and avoidance of therapies that may otherwise not be indicated.

TABLE 2. CRS Grading

Grade 1 – Mild (Symptomatic Management)
Symptoms largely limited to constitutional symptoms listed above (Table 1) Only requires symptomatic management
Grade 2 – Moderate (Moderate Intervention)
Hypotension responsive to fluids or single, low dose vasopressor Oxygen requirement <40% Grade 2 organ toxicity
Grade 3 – Severe (Aggressive Intervention)
Hypotension requiring high dose or >1 vasopressor Oxygen requirement ≥40% Grade 3 organ toxicity Grade 4 transaminitis
Grade 4 – Life-threatening (Life-sustaining intervention)
Ventilator support required Grade 4 organ toxicity

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.

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 in Grade 2-4 CRS, resulting in a rapid reversal of symptoms. If there is a lack of clinical improvement, a second dose can be repeated.
Dosing:

- < 30 kg: 12 mg/kg IV over 1 hour for one dose. May repeat another 12 mg/kg dose in 8 hours if there is a lack of clinical response to the initial dose. May repeat up to 3 additional doses after the initial dose (with at least an 8 hour interval between consecutive doses).
- ≥ 30 kg: 8 mg/kg IV over 1 hour for one dose (Max 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. May repeat up to 3 additional doses after the initial dose (with at least an 8 hour interval between consecutive doses).

Corticosteroids

Steroids may be utilized in the setting of severe CRS with neurologic symptoms along with targeted cytokine therapies (i.e. tocilizumab) or as monotherapy for patients with isolated neurologic toxicities without systemic CRS. 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. Dosing is as follows.

- Dexamethasone;
  - Adult: 4-10 mg (max single dose 10 mg) IV q 6 hours
  - Pediatrics: 0.1 mg/kg (max single dose 10 mg) IV q 6 hours
- Methylprednisolone
  - Adults: 1-2 mg/kg/day IV
  - Pediatrics: 1-2 mg/kg/day IV; max daily dose 125 mg

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

Important Considerations

The following adult and pediatric treatment algorithms serve 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.

Initiation of tocilizumab and/or steroids for CRS from CAR-T therapy must be approved by one of the following attendings:

- **Paul Armistead**
- **James Coghill**
- **Matthew Foster**
- **Natalie Grover**
- **George Hucks**
- **Katarzyna Jamieson**
- **Kimberly Kasow**
- **Marcie Riches**
- **Jonathan Serody**
- **Thomas Shea**
- **Patrick Thompson**
- **Sascha Tuchman**
- **Benjamin Vincent**
- **Michael Winstead**
- **William Wood**

Adult CRS Treatment Algorithm

Signs/Symptoms	Management
Grade 1 CRS	
- Fever (≥ 38.0^0 C) - +/- additional constitutional symptoms (rigors, malaise, fatigue, anorexia, myalgias/arthralgias, nausea/vomiting) - **Renal:** Scr >ULN – 1.5 x ULN and/or Scr 1.5 – 2.0 x above baseline and/or Scr increase > 0.3 mg/dL from baseline - **Hepatic:** AST/ALT > ULN – 2.5 x ULN T.bili > ULN – 1.5 x ULN	- Complete infectious workup (Cultures, Chest XR/CT, etc.) - Daily weights; accurate I/Os - Vital signs q30 mins. until symptom resolution - **Initiate empiric antibiotics** - **Supportive measures:** acetaminophen prn fevers; ondansetron or prochlorperazine prn nausea/vomiting; meperidine/morphine prn rigors
Grade 2 CRS	
- **CV:** Hypotension (SBP <90 mmHg or ≥ 20% decrease in baseline SBP or DBP) +/-	- Continue monitoring and supportive measures outlined under Grade 1 CRS

asymptomatic tachycardia - **Pulmonary:** Decreased O2 saturation (≤88%) - **Renal:** Scr ≥ 1.5 – 3.0 x ULN and/or Scr 2.0 – 3.0 x above baseline - **Hepatic:** AST/ALT > 2.5 – 5.0 x ULN and/or T. Bili > 1.5 – 3.0 x ULN	- **Supplemental O2 up to 40% to saturation ≥93%** - **Fluid bolus: 1000 mL IV over 1-2 hours;** - **Low dose vasopressor (Table 3) if unresponsive to fluid bolus** - **Tocilizumab 8 mg/kg IV over 1 hour x 1 dose (Max dose: 800 mg); may repeat in 8 hours if no improvement from initial dose**
Grade 3 CRS	
- **CV:** Hypotension (SBP <90 mmHg or ≥ 20% decrease in baseline SBP or DBP) unresponsive to fluids and low dose vasopressors given for grade 2 CRS (Table 3) +/- symptomatic tachycardia - **Pulmonary:** Decreased O2 saturation (≤88%) requiring >40% to achieve saturation ≥93% - **Neuro:** Neurologic symptoms (confusion, AMS, seizure) - **Renal:** Scr > 3.0 – 6.0 x ULN and/or Scr > 3.0 x above baseline or > 4.0 - **Hepatic:** AST/ALT > 5.0 – 20.0 x ULN and/or T. Bili > 3.0 -10.0 x ULN	- Continue monitoring and supportive measures outlined under Grade 1 and 2 CRS - **Increase supplemental O2 to achieve saturation ≥93%** - **High dose or multiple vasopressors (Table 3)** - **Tocilizumab as outlined in Grade 2 CRS** - **Dexamethasone 10 mg IV q6h if neurologic symptoms present**
Grade 4 CRS	
- **CV:** Persistent hemodynamic instability (hypotension and tachycardia refractory to aggressive fluids and pressor support) - **Pulmonary:** Hypoxic respiratory failure: O2 saturation ≥93% not able to be achieved with supplemental O2 (nasal cannula, non-rebreather) - **Neuro:** Neurologic symptoms (confusion, AMS, seizures) - **Renal:** Scr > 6.0 x ULN - **Hepatic:** AST/ALT > 20.0 x ULN and/or T. Bili > 10.0 x ULN	- Continue monitoring and supportive measures outlined in Grade 1, 2, and 3 CRS - Continue/initiate vasopressors, tocilizumab, and dexamethasone as outlined in Grade 3 CRS - **Ventilatory support** - **Dialysis if indicated (CVVHD or HD)**

TABLE 3. High dose vasopressors in adult patients

Vasopressor	Dose (high dose)*
Norepinephrine	≥ 20 mcg/min monotherapy
Dopamine	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine	≥ 10 mcg/min
Vasopressin + additional vasopressor	Vasopressin + norepinephrine equivalent of ≥ 10 mcg/min

*vasopressors at doses lower than those outlined are considered low dose vasopressors

Pediatric CRS Treatment Algorithm

Signs/Symptoms	Management
Grade 1 CRS	
- Fever (≥ 38.0^0 C) - +/- additional constitutional symptoms (rigors, malaise, fatigue, anorexia, myalgias/arthralgias, nausea/vomiting) - **Renal:** Scr >ULN – 1.5 x ULN and/or Scr 1.5 – 2.0 x above baseline and/or Scr increase > 0.3 mg/dL from baseline - **Hepatic:** AST/ALT > ULN – 2.5 x ULN and/or T.bili > ULN – 1.5 x ULN	- Complete infectious workup (Cultures, Chest XR/CT, etc.) - Daily weights; accurate I/Os - Vital signs q30 mins. until symptom resolution - **Initiate empiric antibiotics** - **Supportive measures:** acetaminophen prn fevers; ondansetron or prochlorperazine prn nausea/vomiting; meperidine/morphine prn rigors
Grade 2 CRS	
- **CV:** Hypotension +/- asymptomatic tachycardia (Tables 4 & 5) - **Pulmonary:** Decreased O2 saturation (≤88%) - **Renal:** Scr ≥ 1.5 – 3.0 x ULN and/or Scr 2.0 – 3.0 x above baseline - **Hepatic:** AST/ALT > 2.5 – 5.0 x ULN and/or T. Bili > 1.5 – 3.0 x ULN	- Continue monitoring and supportive measures outlined under Grade 1 CRS - **Supplemental O2 up to 40% to saturation ≥93%** - **Fluid bolus: 20 mL/kg (Max: 1000 mL) IV over 1-2 hours;** - **Low dose vasopressor (Table 6) if unresponsive to fluid bolus** - **Tocilizumab** - **- <30 kg: 12 mg/kg IV over 1 hour x 1 dose; may repeat in 8 hours if no improvement from initial dose** - **- ≥30 kg: 8 mg/kg IV over 1 hour x 1 dose (Max dose: 800 mg); may repeat in 8 hours if no improvement from initial dose**
Grade 3 CRS	
- **CV:** Hypotension unresponsive to fluids and low dose vasopressors given for grade 2 CRS +/- symptomatic tachycardia (Tables 4 and 5) - **Pulmonary:** Decreased O2 saturation (≤88%) requiring >40% to achieve saturation ≥93% - **Neuro:** Neurologic symptoms (confusion, AMS, seizure) - **Renal:** Scr > 3.0 – 6.0 x ULN and/or Scr > 3.0 x above baseline or > 4.0 - **Hepatic:** AST/ALT > 5.0 – 20.0 x ULN and/or T. Bili > 3.0 -10.0 x ULN	- Continue monitoring and supportive measures outlined under Grade 1 and 2 CRS - **Increase supplemental O2 to achieve saturation ≥93%** - **High dose or multiple vasopressors (Table 6)** - Tocilizumab as outlined in Grade 2 CRS - **Dexamethasone 0.1 mg/kg (Max 10 mg) IV q6h if neurologic symptoms present**
Grade 4 CRS	
- **CV:** Persistent hemodynamic instability (hypotension and tachycardia refractory to aggressive fluids and pressor support) - **Pulmonary:** Hypoxic respiratory failure: O2 saturation ≥93% not able to be achieved with supplemental O2 (nasal cannula, non-rebreather) - **Neuro:** Neurologic symptoms (confusion, AMS, seizures) - **Renal:** Scr > 6.0 x ULN	- Continue monitoring and supportive measures outlined in Grade 1, 2, and 3 CRS - Continue/initiate vasopressors, tocilizumab, and dexamethasone as outlined in Grade 3 CRS - **Ventilatory support** - **Dialysis if indicated (CVVHD or HD)**

- **Hepatic:** AST/ALT > 20.0 x ULN and/or T. Bili > 10.0 x ULN	

TABLE 4. Definition of hypotension in pediatric patients

Age	Hypotension (SBP)
0 – 28 days	< 60 mmHg
1 – 12 months	< 70 mmHg
1 – 10 years	< 70 mmHg + (age x 2)
>10 years	< 90 mmHg

TABLE 5. Definition of tachycardia in pediatric patients

Age	Tachycardia (HR at Rest)	Tachycardia (HR while Awake)
0 – 3 months	> 160 BPM	> 205 BPM
3 months – 2 years	> 160 BPM	> 190 BPM
2 – 10 years	> 90 BPM	> 140 BPM
>10 years	> 90 BPM	> 100 BPM

TABLE 6. High dose vasopressors in pediatric patients

Vasopressor	Dose (high dose)*
Norepinephrine	≥ 2 mcg/kg/min
Dopamine	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 5 mcg/kg/min
Epinephrine	≥ 1 mcg/kg/min
Vasopressin	> 100 milliunits/kg/hr

*vasopressors at doses lower than those outlined are considered low dose vasopressors

References

1. Maude SL, Barrett D, Teachey DT, Grupp S. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *J Cancer* 2014;20(2):119-122.
2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124(2):188-195.
3. Frey NV, Levine BL, Lacey SF, et al. Refractory cytokine release syndrome in recipients of chimeric antigen receptor (CAR) T cells. *Blood* 2014;124(21):2296.
4. National Cancer Institute Common Terminology Criteria for Adverse Events v4.03; 2010. Available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (accessed 11/28/2015).
5. Brundo JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* 2016;127(26):3321-3330.