Understanding Cytokine Release Syndrome Associated With Immunotherapies

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Overview of CRS

Cytokine Release Syndrome (CRS) is a systemic inflammatory response defined as an immune disorder caused by the large, rapid release of cytokines from the cells. It is characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia.[1]

CRS is a potentially life-threatening toxicity associated with many immune-based therapies.[2]

It usually develops following high immune activation, resulting in elevated circulating levels of cytokines such as interleukin 6 and interferon γ.[2]

Symptoms associated with CRS include but are not limited to those shown in Table 1.

Patients experiencing CRS may also have overlapping symptoms due to fever, neutropenia, infection, tumor lysis syndrome, or other medical complications.[2]

Optimal management of the unique adverse events associated with immune-based therapies is critical to improve overall patient care.

Table 1. Symptoms That May Be Associated With CRS[2]

Constitutional
- Fever ± rigors
- Anorexia
- Nausea
- Malaise
- Myalgias
- Vomiting
- Fatigue
- Arthralgias
- Headache

Neurologic
- Headache
- Difficulty finding words or frank aphasia
- Dysmetria
- Mental status change
- Hallucinations
- Altered gait
- Confusion
- Tremor
- Seizures
- Delirium

Gastrointestinal
- Nausea
- Vomiting
- Diarrhea

Cardiovascular
- Tachycardia
- Hypotension
- Widened pulse pressure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)

Coagulation
- Elevated D-dimer
- Hypofibrinogenemia ± bleeding

Renal
- Azotemia

Hepatic
- Transaminitis
- Hyperbilirubinemia

Respiratory
- Tachypnea
- Hypoxemia

Skin
- Rash

Grading and Severity of CRS

The NCI CTCAE are often used to classify the grade and severity of CRS (Table 2).[1] These criteria were used to define CRS in the blinatumomab clinical trials.[3] Other grading systems have been developed that may be used to characterize the severity of CRS associated with chimeric antigen receptor T-cell therapy.[2,4-6]

Comparison of CRS Grading Systems

Lee et al	The grading system by Lee et al classifies patients requiring high-dose vasopressors and ventilators into grades 3 and 4, respectively.[2,4]
Teachey et al	Patients with grade 3-5 events on the Lee et al grading system are considered equivalent to patients with grade 4-5 events on the Teachey et al grading system (adapted from Porter et al).[2,4,5]
Davila et al	Davila et al define severe CRS by the length of days with fever, maximum fold change in either 1 or 2 cytokines and clinical signs of toxicity.[4,6]

Although the NCI CTCAE is one of the most commonly used CRS grading systems, various CRS grading approaches are used in clinical trials depending on specific factors. A better understanding of the differences in grading and classification will improve the interpretation of the currently available data on CRS associated with immunotherapies.

Table 2. CRS Grading Systems

NCI CTCAE[1]	Lee et al[2]	Teachey et al (adapted from Porter et al)[4,5]
Grade 1 Fever with or without constitutional symptoms	**Grade 1** Symptoms (e.g., fevers, nausea, fatigue, headache, myalgias, malaise) are not life-threatening and require symptomatic treatment only	**Grade 1** Mild reaction treated with supportive care only
Grade 2 Hypotension responding to fluids; hypoxia responding to < 40% O_2	**Grade 2** Symptoms require and respond to moderate intervention Oxygen requirement < 40%, or hypotension responsive to fluids, or low dose of 1 vasopressor, or grade 2 organ toxicity	**Grade 2** Moderate reaction requiring intravenous therapies or parenteral nutrition Mild signs of organ dysfunction (creatinine ≤ grade 2 or LFTs ≤ grade 3) related to CRS
Grade 3 Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	**Grade 3** Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40%, or hypotension requiring high-dose or multiple vasopressors, or grade 3 organ toxicity, or grade 4 transaminitis	**Grade 3** More severe reactions. Moderate signs of organ dysfunction (grade 3 creatinine or grade 4 LFTs) related to CRS Hypotension treated with intravenous fluids or low-dose vasoactive medications Hypoxemia requiring oxygenation, CPAP, or BiPAP
Grade 4 Life-threatening consequences; urgent intervention indicated	**Grade 4** Life-threatening symptoms Requirement for ventilator support, or grade 4 organ toxicity (excluding transaminitis)	**Grade 4** Life-threatening complications, including hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation
Grade 5 Death	**Grade 5** Death	**Grade 5** Death

Severe CRS: diagnostic criteria per Davila et al[6]

- Fever for ≥ 3 consecutive days
- Maximum fold change of ≥ 75 in two cytokines or ≥ 250 in one cytokine
- At least one clinical sign of toxicity, such as hypotension (requiring ≥ 1 intravenous vasoactive pressor), *or*
- Hypoxia (PO_2 < 90%), *or*
- Neurologic disorders (including mental status changes, obtundation, and seizures)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; LFT, liver function test; NCI, National Cancer Institute; PO_2, partial pressure of oxygen.

References 1. National Cancer Institute. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed November 5, 2018. **2.** Lee DW, et al. *Blood*. 2014;124:188-195. **3.** Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847. **4.** Teachey DT, et al. *Cancer Discov*. 2016;6:664-679; supplementary material. **5.** Porter DL, et al. *Sci Transl Med*. 2015;7:303ra139; supplementary material. **6.** Davila ML, et al. *Sci Transl Med*. 2014;6:224ra25.

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