

# Cytokine Release Syndrome - CRS General Review

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**Abstract:** Cytokine release syndrome-CRS is a systemic inflammatory response can progress to life threatening, resulting from generalized immune activation observed on day 2-7 after CAR-T cell infusion. The typical clinical mild symptoms presentations of CRS associated with flu-like symptoms, presented with high body fever as the first clinical symptom of CRS, including fatigue, headache, rash, arthralgia, and myalgia's. The pathophysiology of CRS remains not understandable yet. What is known it is results from release massive of cytokines. CAR-T therapy considered as risk factor for sever CRS. Aggressive treatment should be given, including intensive monitoring. The typical symptomatic treatment of patients with severe CRS include tocilizumab, corticosteroids, vasoactive agents, organ protection treatment, antibiotics to prevent infections in neutropenic patients, transfusion support, volume resuscitation, and mechanical ventilation. The challenge knows is to understand the pathophysiology of CRS, this understanding can lead us to better control and minimizing the CRS symptoms.

**Keywords:** cytokine release syndrome, CAR-T, inflammatory response, immune activation, tocilizumab, corticosteroids

## 1. Introduction

Cytokine release syndrome-CRS is a systemic inflammatory response can progress to life threatening, resulting from generalized immune activation observed on day 2-7 after CAR-T cell infusion. [1] [2]

The typical clinical mild symptoms presentations of CRS associated with flu-like symptoms, presented with high body fever as the first clinical symptom of CRS, including fatigue, headache, rash, arthralgia, and myalgia's. However, it is depending on the severity of the inflammatory, some patients experience a severe case, characterized by hypotension, organ dysfunction, hypoxia, tachypnea, dyspnea, vascular leakage, renal failure, cardiac dysfunction, peripheral and pulmonary edema. Some patients develop neurotoxicity. The neurologic symptoms presented also as mild-sever symptoms like disorientation, confusion, headaches, hallucination, aphasia, hemiparesis, seizures. [1] [4] [5]

### Pathophysiology

The pathophysiology of CRS remains not understandable yet. What is known it is results from release massive of cytokines including C-reactive protein (CRP), ferritin, interferon alpha, and interleukin-6 (IL-6). The massive release of cytokines related to the activation between the malignant cells and the immunotherapy treatment such as CAR-T. [3]

### Risk factors

CAR-T therapy considered as risk factor for sever CRS, and it is depending on the dose of the cells of the CAR-T, high doses of CAR-T can predict severity of CRS. Another risk factors such as high disease burden, lymph depletion of high conditioning treatment, sever thrombocytopenia, and high baseline serum ferritin. [6] [7]

### Grading

Defining the grading in CRS is useful to decide the treatment. The grading depends on the characteristic clinical presentations.

**Grade 1:** mild reaction not life-threatening: general symptoms requiring symptomatic therapy: fever, malaise, nausea headache, and myalgia's.

**Grade 2:** moderate reaction, symptoms requiring moderate intervention: blood oxygen requirement <40%, hypotension responsive to fluids or low dose vasopressors.

**Grade 3:** sever reaction, symptoms requiring aggressive intervention, blood oxygen requirement >40%, hypotension responsive to high dose vasopressors.

**Grade 4:** life-threatening symptoms, very sever hypotension, requirements for ventilator support [3] [8]

### Treatment

Aggressive treatment should be given, including intensive monitoring. The typical symptomatic treatment of patients with severe CRS include tocilizumab, corticosteroids, vasoactive agents, organ protection treatment, antibiotics to prevent infections in neutropenic patients, transfusion support, volume resuscitation, and mechanical ventilation. [9]

### Tocilizumab

Tocilizumab is humanized IL-6 receptor antagonist which functions by inhibiting IL-6 signaling on immune cells. It's prevents IL-6 from binding to cell-associated membrane-bound and soluble IL-6 receptor, leading to decrease in IL-6 signaling and reducing immune activation and inflammation. [7] [9]

Tocilizumab is now recommended as a first-line treatment of CRS, was approved by the FDA for treatment of severe or life-threatening CAR-T cell induced CRS in adults and pediatric patients > 2 years old. Tocilizumab reduce fevers

and CRS symptoms without effecting CAR-T levels in serum or bone marrow. [7] [9] [10]

### Corticosteroids

Systemic corticosteroids are effective treatment in CRS, since it's considered in an effective anti-inflammatory. The corticosteroid uses in early stage of the CRS. Using corticosteroids dose not effect CAR-T outcomes. [7] [9] [10]

## 2. Summary

CRS is a life-threatening leading to dramatic clinical responses after CAR-T treatment. The pathophysiology of CRS incompletely understood. Anti-IL-6 receptors such like tocilizumab and corticosteroids, considered as first-line treatment and provide excellent results without effecting the CAR-T treatment. The challenges know is to understand the pathophysiology of CRS, this understanding can lead us to better control and minimizing the CRS symptoms.

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