# Toxicities of CAR T-Cell Therapy: Cytokine Release Syndrome

The introduction of chimeric antigen receptor (CAR) T-cell therapy is changing the treatment landscape for patients with acute lymphoblastic leukemia and non-Hodgkin's lymphoma with additional studies in solid tumors and other hematologic malignancies underway. Cytokine release syndrome (CRS) is an increasingly recognized complication of chimeric antigen receptor CAR T-cell therapy. When severe, CRS can be life-threatening and up to 50% of patients may require ICU admission.

## Pathophysiology

CRS is an inflammatory response that correlates with CAR T- cell activity and immune system activation.

- Activated T cells release interferon gamma which results in the activation of macrophages and an inflammatory cascade with high levels of cytokines including IL-6, IL-10, interferon-gamma, and tumor necrosis factor-alpha.
- Although CRS represents CAR T cell activation, the severity of CRS and clinical response to treatment do not always correlate.

## Risk Factors

Risk factors for severe CRS include the following:

- High disease burden
- Dose of CAR-T cells infused
- Pre-treatment thrombocytopenia
- Specific signalling pathway targeted
- Type of pre-treatment chemotherapy regimen

CRS most commonly develops in the first week after CAR T-cell infusion, but delayed presentations are also described.

## Clinical Presentation and Grading

**Grade 1**
- Temperature ≥38°C
- No hypotension
- No hypoxia

**Grade 2**
- Temperature ≥38°C
- Hypotension does not require vasopressors
- Requiring low flow oxygen by nasal prongs

**Grade 3**
- Temperature ≥38°C
- Requiring one vasopressor +/- vasopressin
- Requiring facemask, Venturi mask, non-rebreather, or high flow nasal cannula

**Grade 4**
- Temperature ≥38°C
- Requiring multiple vasopressors +/- vasopressin
- Requiring positive pressure ventilation

D.W. Lee et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

**Clinical Features:**

- Initially: Fever, malaise, headache, fatigue, myalgias, and rash.
- When severe may cause vascular leak, distributive shock, ARDS, multi-organ failure, and DIC.
- Immune effector cell-associated neurotoxicity (iCANS) which presents with neurocognitive changes may occur simultaneously. Close monitoring is required to avoid missing this diagnosis.

**Bloodwork abnormalities include:**

- Elevated creatinine, AST/ALT
- Elevated INR, low fibrinogen
- Elevated ESR/CRP
- Cytopenias

**Other diagnoses that may co-exist or mimic CRS:**

- Sepsis
- Hemophagocytic lymphohistiocytosis
- Tumor lysis syndrome

## Management

**1** **Initial Assessment**:

- CRS is potentially reversible → ICU team should be involved early, and patients should be offered ICU admission and full supportive measures.
- Have a low threshold to empirically treat for infection (difficult to distinguish from sepsis).
- As there is also a risk of iCANS, avoid sedatives to facilitate accurate neurologic assessments. .

**2** **First Line Therapy**:

- Grade 3 or 4 CRS: Administer tocilizumab, a monoclonal antibody against the IL-6 receptor.
- Grade 2 CRS: Consider tocilizumab based on local protocols.
- If no improvement, repeat doses of tocilizumab can be given.

**3** **CRS Refractory to Tocilizumab:**

- Steroids are indicated in refractory CRS
- Historically, controversial due to concerns that steroids may reduce the anti-tumor effect of the CAR-T cells. However, given the potential life-threatening nature of severe CRS, it is recommended if Grade 3 or 4 CRS does not resolve with tocilizumab.

**4** **CRS Refractory to Tocilizumab and Steroids:**

- Adjuncts that can be considered include the IL-6 monoclonal antibody siltuximab and the IL-1 antagonist anakinra.
- Decisions to escalate to these therapies should be determined at an institutional level and should be made in conjunction with the Oncology team.

COIN