

# Immune-Related Adverse Event: Cytokine Release Syndrome

Cytokine Release Syndrome (CRS)

CRS has been defined as a systemic inflammatory state that occurs due to robust and widespread immune activation induced by a cell-mediated immune response. The National Cancer Institute defines CRS as a condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T cells, caused by a large, rapid release of cytokines into the blood from immune cells<sup>1</sup>

### Mild

Fever(≥38°C), with or without constitutional symptoms.
Constitutional symptoms include nausea, fatigue, headache, myalgias, malaise

#### Investigations

Bloods: Immunotherapy Panel including FBC, U&E, LFTS (inc ALT), Clotting, CRP, Cortisol, Cytokine Panel\*

Septic Screen including cultures and a VBG for pH and lactate

ECG CXR

#### Management

Hold immunological treatment if ongoing

Symptomatic management: Paracetamol (1g (unless <50kg then 15mg/kg)

Paracetamol IV QDS)

Antihistamine therapy
(10mg Chlorpheniramine IV)

If evidence of wheezing trial of 2.5mg PRN Nebulised Salbutamol

If becomes
Hypotensive
(SBP<100mg)
move to Moderate
pathway

#### **Moderate**

Fever (≥38°C)
AND/OR
Hypotension (SBP<100mmHg)
responding to fluids.
Hypoxia requiring oxygen therapy
responding to ,40% FiO
AND/ OR
Grade 2 Organ toxicity

#### Investigations

Bloods: Immunotherapy Panel including FBC, U&E, LFTS (inc ALT), Clotting, CRP, Cortisol, Cytokine Panel\*

Septic Screen including cultures and a VBG for pH and lactate

ECG CXR

### Management

Symptomatic management as for mild

IV fluid resuscitation with N.Saline in the first instance (500-1000mL Stat then r/v)

Move to Level 2 (Step-Up bed) for continuous monitoring

Input/Output monitoring

O2 therapy to maintain SaO2 >95%
Inform SpR and Consultant On-Call and the patient's named consultant

If hypotension fails to respond to treatment or remains hypoxic on 40% FiO2 move to Severe/Life Threatening pathway

- Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Theraputics and Clinicak Risk Mamagement. 2019. 15:323-335
   Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*.
- 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
   Shimabukuro-Vornhagen et al. Journal for ImmunoTherapy of Cancer (2018) 6:56 https://doi.org/10.1186/s40425-018-0343-9.
- \*\* Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), GI (nausea, vomiting, diarrhea), hepatic (increased serum ALT, AST, or bilirubin levels), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatological (rash), and coagulopathy (disseminated intravascular coagulation)<sup>2</sup>
  \*\*\*Off licence use in UK, Licenced in USA by FDA

## Severe or Lifethreatening

Hypotension (SBP <90mm Hg) not responding to fluids
Hypoxia not responding to Oxygen therapy (40% FiO2)
Dizziness/Collapse
Hypovolemic shock
Nausea/ Vomiting
Confusion/ delirium
Coma,
Pre-renal/renal failure
And/OR
Grade ≥3 organ toxicity\*\*

Investigations

As for moderate CRS

Management
As for moderate
ADD

2mg/kg/day IV Methylprednisolone<sup>2</sup>

High flow O2 therapy if required Consider escalation to level 3 (ITU) Level care

Subsequent Management

Reassess for improvement If not improvement within 1-2 hours then:

Transfer to ITU

Consideration of circulatory support (vasopressors/Inotropes)

Consider increasing Methylprednisolone to 1g IV Daily

Consider trial of Tocilizumab\*\*\* (anti-IL-6) therapy in addition to IV methylprednisolone

Tocilizumab 8 mg/kg (maximum 800 mg/dose, 12mg/kg if <30kg) infused over an hour<sup>2,3</sup>. IV q8h up to 4 doses (max 800 mg/dose)

Verion: 1.0 Ref: GAMACYTOK Review: September 2022