Management of Cytokine Release Syndrome (CRS) and HLH

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Cytokine Release Syndrome (CRS)

Definition and Occurrence

Cytokine release syndrome (CRS) is caused by a rapid and mild to massive release of cytokines from immune cells involved in immune reactions, particularly after immunotherapy. The frequency and severity of CRS after CAR-T cell therapy varies between products (any grade: 37–93%, G3/4: 1–23%) (Neelapu et al. 2017; Schuster et al. 2019; Abramson et al. 2020).

Diagnosis

Clinical Symptoms, Laboratory Diagnosis, Differential Diagnosis, and Predictive Factors

CRS usually manifests with fever preceding or accompanied by general symptoms, such as malaise, headache, arthralgia, anorexia, rigours, and fatigue, and can rapidly progress to hypoxia, tachypnoea, tachycardia, hypotension, arrhythmia, culminating in shock cardiorespiratory organ dysfunction, and failure.

Although the diagnosis of CRS cannot be established or ruled out by laboratory diagnostics, they can be used to monitor organ dysfunction. CRS symptoms and laboratory findings closely mimic infection; therefore, infectious workup and

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treatment are of primary importance. Other relevant differential diagnoses include tumour lysis and progression of the underlying malignancy.

Prediction of CRS in an individual patient is not yet possible. However, some factors, such as high tumour burden and CAR-T cell dose, seem to be associated with a higher risk of CRS.

Management

Patients receiving CAR-T cells should be monitored continuously or at regular intervals for cardiovascular function and temperature. The first sign of CRS is usually fever. Mild CRS (G1) can be managed conservatively. All higher grades require intensive monitoring and intervention. Early use of tocilizumab and, in some cases, steroids is now recommended (Table 26.1) (Yakoub-Agha et al. 2020).

Table 26.1 Scoring of CRS (adapted from Yakoub-Agha et al. 2020)

CRS Parameter	Grad 1	Grad 2	Grad 3	Grad 4
Fever	Fever $\geq 38^{\circ}\text{C}$ (not attributable to any other cause). In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.			
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow oxygen (delivered at $\leq 6\text{ l/min}$)	Requiring high-flow oxygen (delivered at $> 6\text{ l/min}$)	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Fig. 26.1 Management of CRS—Modified according to EBMT recommendations

Monitoring: Patients with CRS 1 can be monitored on the regular ward or Intermediate Care ward, starting from G2, and admission to an ICU should be considered.

Supportive therapy consists of fluids and antipyretics. The use of vasopressors automatically marks higher grade CRS.

Anti-Cytokines

Tocilizumab is EMA and FDA approved for the treatment of CRS. Prophylactic, preemptive or risk-adapted use may reduce the risk of severe CRS without attenuating antitumour efficacy.

(Locke et al. 2017; Caimi et al. 2020; Gardner et al. 2019; Kadauke et al. 2021). Clinical trial data on the use of siltuximab and anakinra are still lacking.

Steroids

In contrast to initial clinical studies, short courses of steroids do not seem to have detrimental effects on CAR-T cell expansion and survival or clinical outcome.

Antibiotics

Because CRS cannot be decisively differentiated from infection, most centres administer antibiotic treatment in cases of neutropenic fever. However, the use of growth factors during the first few weeks should be restricted. GM-CSF is to be avoided.

sHLH/MAS

Secondary or reactive haemophagocytic lymphohistiocytosis (sHLH) is a life-threatening hyperinflammation syndrome that occurs in the context of allo-HCT, haematological malignancies, infection, and rheumatic or autoimmune disease and is characterized by hyperactive macrophages and lymphocytes, haemophagocytosis, and multiorgan damage (Carter et al. 2019; Neelapu et al. 2018; Sandler et al. 2020). The proposed diagnostic criteria are summarized in Table 26.2. Management of sHLH generally follows similar algorithms as that for severe CRS. In refractory patients, treatment may follow the management framework proposed by Mehta et al. (2020), with a key role for anakinra.

Table 26.2 Diagnostic criteria for HLH (adapted from Neelapu et al. 2018)

Diagnostik criteria for CAR-T cell mediated sHLA/MAS (Neelapu et al., 2018)		Adult HScore (Fardet et al., 2014): Respective scores are in brackets Produces a probability outcome; scores >169 are 93% sensitive and 86% specific for HLH
Clinical	Clinical	
Grade ≥3 pulmonary oedema*	Fever	<38.4 (0); 38.4–39.4 (33); >39.4 (49)
	Hepatomegaly /	Neither (0); either hepatomegaly or splenomegaly (23); both (38)
	Immunosuppression	No (0); yes (18)
Laboratory	Laboratory	
Peak ferritin 10,000ng/ml during CRS and any 2 of the following	Ferritin, ng/mL	<2000 (0); 2000–6000 (35); >6000 (50)
Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels*	Cytopenias >2 lineages	One lineage (0), two lineages (24), or three lineages (34)
Grade ≥3 oliguria or increase in serum creatinine levels*	Hypertriglyceridaemia, mmol	<1.5 (0); 1.5–4 (44); >4 (64)
Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry	Haemophagocytosis	No (0), yes (35)
*According to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0	Liver function tests, IU/L	AST<30 (0); >30 (19)
	Hypofibrinogenaemia, g/L	>2.5 (0); <2.5 (30)

Key Points

- Cytokine release syndrome is a frequent complication. However, severe CRS is rare if management is proactive.
- sHLH/MAS is a rare but severe complication that requires prompt recognition and intervention.

References

- Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839–52.
- Caimi PF, Sharma A, Rojas P, et al. CAR-T therapy for lymphoma with prophylactic tocilizumab: decreased rates of severe cytokine release syndrome without excessive neurologic toxicity. *Blood*. 2020;136:30–1. <https://ash.confex.com/ash/2020/webprogram/Paper143114.html>
- Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)*. 2019;58(1):5–17.
- Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR-T cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood*. 2019;134(24):2149–58.
- Kadauke S, Myers RM, Li Y, et al. Risk-adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. *J Clin Oncol*. 2021;39(8):920–30.

- Locke FL, Neelapu SS, Bartlett NL, et al. Preliminary results of prophylactic Tocilizumab after axicabtagene ciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). *Blood*. 2017;130(Supplement 1):1547.
- Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol*. 2020;2(6):e358–67.
- Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR-T cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531–44.
- Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47–62.
- Sandler RD, Carter S, Kaur H, Francis S, Tattersall RS, Snowden JA. Haemophagocytic lymphohistiocytosis (HLH) following allogeneic haematopoietic stem cell transplantation (HSCT)-time to reappraise with modern diagnostic and treatment strategies? *Bone Marrow Transplant*. 2020;55(2):307–16.
- Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45–56.
- Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the joint accreditation committee of ISCT and EBMT (JACIE). *Haematologica*. 2020;105(2):297–316.

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