Diagnosis and treatment of Cytokine Release Syndrome in patients receiving CAR-T therapy

Introduction

Cytokine Release Syndrome (CRS) is a systemic inflammatory response following the infusion of immune effector cells (IEC) or immunotherapy. CRS is the most common complication after immune effector cell therapy (IECT); incidence ranging from 30-100% with a 10-30% risk of grade 3 or 4 CRS. It usually occurs between 1 and 14 days (median 3 days) after the immune effector cell infusion and can last from 1 to 10 days (median 6 days).

Risk factors include tumour burden, the presence of active infection at time of IEC infusion, early onset CRS (within the first 3 days), the dose of infused IECs, the type of IEC construct and the choice of lymphodepleting regimen.
The key clinical signs are fever, hypotension and hypoxia as these are used to grade the severity and patient management.

Whilst there are a number of grading systems for safety this protocol grades all patients according to the EBMT system (shown in Table 1).
CRS grading is determined by the *more severe* event: for example a temperature of 39'C and hypotension requiring vasopressor support is classified as Grade 3.
CRS can mimic other complications which must be considered in parallel:

- Infective causes
- Cardiac causes including arrhythmias and cardiac failure
- Acute Respiratory Distress Syndrome

Management

Early recognition and treatment is essential for patient safety.
All patients should be graded according to the EBMT system (Table 1).

Assessment and grading should be done at least twice per day (8am and 8pm) and whenever a change in the patient's status is observed and recorded on the CRS Assessment Record (Table 2).Specific management steps according to grade are given in Table 3.

Tocilizumab should not be administered more than four times during one episode of CRS. Siltuximab (anti IL-6) or Anakinra (anti IL-1) can be used as second line treatments under Consultant Haematologist direction.

Table 1: EBMT system for grading of Cytokine Release Syndrome

*Not attributable to other causes
NB. Once Tocilizumab has been administered fever is no longer required to grade severity of CRS

CRS Parameter	GRADE 1	GRADE 2	GRADE 3	GRADE 4
FEVER *	**Temperature ≥ 38°C**	**Temperature ≥ 38°C**	**Temperature ≥ 38°C**	**Temperature ≥ 38°C**
WITH EITHER:				
HYPOTENSION * (≤ 90mmHg)	**None**	**Not requiring vasopressor**	**Requiring one vasopressor**	**Requiring multiple vasopressors**
AND / OR				
HYPOXIA * (Saturations <92% on air)	**None**	**Low-flow nasal cannula (≤6l/min)**	**High-flow nasal cannula, facemask, non-rebreather mask or Venturi mask**	**Requiring positive pressure (CPAP, BiPAP, Intubation and Ventilation)**

Table 2: CRS assessment record

	Baseline						
Date							
Time							
Temperature ≥ 38°C							
Hypotension							
Hypoxia							
CRS Grade							

Table 3: Management of CRS according to EBMT Grade

CRS Grade	Treatment
GRADE 1	• Infection screen as per Microbiology Investigations Policy HAEM/CLIN/014 • Commence preemptive broad spectrum antibiotics as per Antimicrobial Treatment Policy HAEM/CLIN/004 • Supportive care including antipyretics and IV fluids • If persistent (lasting >3 days) or refractory fever give tocilizumab (8mg/kg infused over 1 hour, maximum single dose not to exceed 800mg and inform ICU
GRADE 2	• Liaise with ICU and document plan for ongoing management and review. • IV fluid bolus 500-1000ml to maintain SBP > 90mmHg • If persistent fever ≥39°C, hypotension after initial fluid bolus or requiring supplemental oxygen give tocilizumab (8mg/kg infused over 1 hour, maximum single dose 800mg) • In the absence of improvement at **8 hours** repeat tocilizumab (8mg/kg infused over 1 hour, maximum single dose 800mg, maximum 2 further doses) • If hypotension persists after 2 fluid boluses (≥1.5L) and tocilizumab transfer to ICU for closer monitoring and vasopressor consideration • Add 3examethasone 10mg IV 6 hourly if hypotension persists after tocilizumab and fluids, high risk for severe CRS, worsening hypoxia or clinical concern
GRADE 3	• Administer tocilizumab 8mg/kg infused over 1 hour, maximum single dose 800mg) • Transfer to Intensive care (transfer not to delay administration of tocilizumab) • Add dexamethasone 10mg IV 6hourly (1-3 days) • In the absence of improvement at **8 hours** repeat tocilizumab (8mg/kg infused over 1 hour, maximum single dose 800mg, **maximum 4 doses**) and increase 3examethasone dose to 20mg IV 6 hourly (3 days with progressive tapering within 3-7 days) • If refractory for >24 hours manage as Grade 4 CRS • If hypotension persistent perform daily ECHO to assess cardiac function
GRADE 4	• Administer tocilizumab (8mg/kg infused over 1 hour, maximum single dose 800mg, **maximum 4 doses**) • Transfer to Intensive care urgently (transfer not to delay administration of tocilizumab) • Administer high dose methylprednisolone 1g/day for 3 days followed by progressive tapering eg 250mg BD for 2 days, 125mgBD for 2 days then 60mg BD for 2 days • In the absence of improvement at **8 hours** repeat tocilizumab (8mg/kg infused over 1 hour, maximum single dose 800mg, **maximum 4 doses**) • If refractory for >24 hours or deteriorating consider additional therapies as below • If hypotension persistent perform daily ECHO to assess cardiac function
If refractory to tocilizumab consider siltuximab (11mg/kg IV as a single dose) OR anakinra (2mg/kg SC daily for 3-5 days / 100mg SC for 7 days) OR alternative agents such as anti-TNF	

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