Management of Cytokine Release Syndrome

INTRODUCTION

This document has been developed to assist management of patients receiving T-cell engaging bispecific antibodies for lymphoma therapy, who are at risk of developing cytokine release syndrome (CRS). The guideline can also be applied for patients developing late onset toxicity following chimeric antigen receptor (CAR) T cell therapy, usually delivered at our regional centre in Bristol.

T-cell engaging bispecific antibodies are increasingly used in the treatment of B-cell non-Hodgkin lymphoma and glofitamab, epcoritamab and mosunetuzumab have all received FDA approval[1-3]. The first bispecific antibody to gain approval in the NHS is glofitamab[4]. In clinical trial, the risk of any grade CRS was 63%, with grade 3-4 seen in 4%[2]. These therapies typically have two binding sites, one that targets an antigen expressed on the lymphoma cell surface (CD20), and one that targets a T-cell surface marker (CD3). This interaction enhances host cytotoxic T-cell activity against lymphoma cells. Specific toxicities related to this mode of action are seen, including CRS.

CYTOKINE-RELEASE SYNDROME

Mild to moderate presentation of CRS may include symptoms, such as fever, chills, vomiting, dizziness, hypertension, hypotension, dyspnoea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnoea, headache, tumour pain, nausea, and/or myalgia, and may be treated symptomatically with analgesics, antipyretic medicines, and anti-histamines, as indicated. Such reactions typically occur during, or shortly after an infusion or within 24 hours after intravenous drug infusion. The incidence and severity of CRS typically decreases with subsequent infusions. Risk of CRS is increased with bulky disease. CRS may be indistinguishable from an infusion related reaction (IRR).

CRS may be indistinguishable from an anaphylactic reaction. Severe or life-threatening presentations of CRS, such as hypotension, tachycardia, dyspnoea or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated, including the use of high-dose corticosteroids, IV fluids, and other supportive measures. Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome.

PLANNING TREATMENT

As reactions typically occur with first exposure, the first doses will normally be delivered as an inpatient on Rendcomb/Lilleybrook (CGH).

- Admit to Rendcomb or Lilleybrook ward on the evening before infusion.
- Pharmacy to ensure tocilizumab is available on ward. There will always be stock of tocilizumab available on RND.
- If tocilizumab is required, a Blueteq will need to be completed retrospectively.
- Inform DCC at CGH that treatment is due before 08:30 on day of infusion, call ext. 4013 or 8954.
- Infusion needs to start no later than 12:00 noon to make sure staff are present at highest risk period.
- The patient should be monitored for minimum 24 hrs from start of infusion. If they remain well then discharge with advice for symptoms to be weary of in case of late reaction.

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- Once a patient is established on treatment the ongoing risk of CRS is low and infusions will be delivered on the EJU day unit at GRH. If required, tocilizumab can be accessed from the out of hours emergency fridge adjacent to the GRH Pharmacy.

MANAGEMENT OF CYTOKINE RELEASE SYNDROME

Please note: All reactions grade 1 or above should be discussed with a Consultant Haematologist

CRS should be identified based on the clinical presentation. If CRS is suspected, it should be managed based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading[6] (Table 1) according to the CRS management recommendations below (Table 2).

Table 1. ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor ± vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow nasal cannula (≤6 L/min) or blow-by	Requiring high-flow oxygen (>6 L/min) by nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

† Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In patients who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. Cytokine-release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as infections or sepsis. **Consider empiric broad spectrum antibiotics if infection suspected**. Investigations should be guided by degree of clinical concern and include:

- Observation monitoring: Pulse, temperature, blood pressure and respiration rate, pulse oximetry +/- ABG
- Lab studies: FBC, U&Es, LFTs, Ca^{2+}, Mg^{2+}, $PO4^{3-}$, uric acid, LDH, CRP, procalcitonin, lactate, ferritin, PT/APTT, fibrinogen
- Ferritin, procalcitonin and fibrinogen should be monitored daily until CRS has resolved
- Microbiological studies: urinalysis, urine culture, blood cultures, sputum culture if present, COVID19 PCR
- Chest x-ray: if respiratory signs / symptoms or reduced oxygen saturations (urgent mobile)
- ECG: baseline at onset of CRS and then as dictated by clinical signs and symptoms
- Physical examination: to include neurological examination in patients with symptoms

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Table 2. CRS management guidance

	Grade 1	Grade 2	Grade 3	Grade 4
	Treat symptoms[1] Consider corticosteroids[Λ⊖] Consider tocilizumab*[⊖] Consider broad spectrum antibiotics	Treat symptoms[1] Hypotension – 0.9% saline fluid challenge in 500ml boluses. If >1000 ml administered, consider vasopressor support Hypoxia – administer oxygen Administer corticosteroids[Λ] Consider tocilizumab* Consider broad spectrum antibiotics	Treat symptoms[1] Symptomatic management of organ toxicities **Admit to DCC** for vasopressor and/or respiratory support Administer corticosteroids[Λ] Administer tocilizumab* Give broad spectrum antibiotics	Treat symptoms[1] Symptomatic management of organ toxicities **Admit to DCC** for vasopressor and/or respiratory support Administer corticosteroids[Λ] Administer tocilizumab* Give broad spectrum antibiotics
If CRS occurs during infusion	Interrupt infusion Restart infusion at slower rate when symptoms resolve. If symptoms recur, discontinue infusion	Discontinue current infusion	Discontinue current infusion	Permanently discontinue bispecific antibody
For next scheduled bispecific infusion	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate (duration of infusion may be extended up to 8 hours)	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate (duration of infusion may be extended up to 8 hours) Monitor patients post-infusion.	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate (duration of infusion may be extended up to 8 hours) If Grade ≥ 3 CRS recurs at subsequent infusion, immediately stop infusion and permanently discontinue bispecific antibody.	Not applicable - permanently discontinue bispecific antibody

1 **Treat symptoms:** paracetamol 1g IV (if not received within 4 hours), antihistamine (e.g. loratadine 10mg PO, chlorphenamine 10mg IV)

Λ **Corticosteroids dosing:** Start at dexamethasone 10 mg IV given every 6 hours. In refractory grade 4 CRS consider methylprednisolone 1 g once per day.

* **Tocilizumab dosing:** should be administered by IV infusion at a dose of 8 mg/kg for patients weighing ≥ 30 kg only and 12 mg/kg for patients weighing < 30 kg given over 60 minutes (doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of 4 doses)[7].

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- If CRS lasts more than 48 hours after symptomatic management.

Table 2 CRS management guidance is adapted from the Thames Valley Cancer Alliance L.149 Glofitamab EAMS protocol (v1.0)[5].

MANAGING SEVERE CRS (GRADE 3 OR 4)

The development of a severe reaction necessitates immediate notification of the on-call Consultant Haematologist. Tocilizumab and corticosteroids should be readily available on Rendcomb ward and Edward Jenner Unit, but early involvement of pharmacy staff is recommended to confirm access to treatments for refractory CRS. The patient should be referred to DCC for immediate review. If no improvement within 24 hours, initiate work up and assess for signs and symptoms of Haemophagocytic Lymphohistiocytosis (HLH).

Anakinra: If refractory to tocilizumab consider addition of anakinra. If considering use, discuss urgently with on-call pharmacy. For further information on dosage and administration please see SPC for administration details[8].

CONTACTS

- **Haematology Consultant**: If out of hours, contact the on-call Haematology Consultant via Switchboard
- **Department of Critical Care (DCC)**
  - contact Acute Care Response Team (ACRT) via bleep 1700, or contact the on-call DCC consultant via switchboard depending on level of clinical concern
  - To inform DCC that first bispecific antibody infusion is taking place, call ext. 4013 or 8943 prior to 08:30 on day of infusion.
- **Pharmacy:** on-call out of hours via Switchboard

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