Treatment Guideline: Management of Cytokine Release Syndrome

INTRODUCTION

This document has been developed to assist management of patients receiving T-cell engaging bispecific antibodies for malignant haematology therapy, who are at risk of developing cytokine release syndrome (CRS). It is primarily intended for patients receiving:

- Glofitamab[1] or Epcoritamab[2] for the treatment of relapsed/refractory high-grade B-cell lymphoma.
- Elranatamab or Teclistamab for relapsed myeloma[5].
- Blinatumomab for the treatment of relapsed[3] or MRD positive[4] B-cell acute lymphoblastic leukaemia.

Some aspects of this guideline are likely to apply to patients treated with alternative T-cell engaging bispecific antibody therapy or chimeric antigen receptor T-cell therapy, but drug-specific guidelines should be followed in the first instance.

Bispecific antibodies have two binding sites, one targets an antigen expressed on the malignant cell surface, and one targets a T-cell surface marker (CD3). This interaction enhances host cytotoxic T-cell activity against malignant cells. Specific toxicities related to this mode of action are seen, including CRS. Bispecific antibodies are also associated with immune cell associated neurotoxicity syndrome (ICANS), for which there is a separate Trust guideline: https://www.gloshospitals.nhs.uk/media/documents/ICANS_guideline.pdf

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 intravenous infusion, or within 24 hours of subcutaneous administration, but CRS onset has been reported over 7 days after administration. 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) or 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. Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome.

RISK OF CRS

The frequency of CRS according to key clinical trials:

- Epcoritamab: any grade CRS 50%, grade ≥3 in 3%[6]
- Glofitamab: any grade 63%, grade ≥3 in 4%[7]
- Elranatamab: any grade CRS 58%, grade ≥3 in 0%[10]
- Teclistamab: any grade 71%, grade ≥3 0.6%[18]

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- Blinatumomab: in relapsed/refractory B-ALL any grade CRS not reported, grade ≥3 in 5%[8]; MRD positive B-ALL any grade CRS 3%, grade ≥3 in 2%[9]

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/injection.
- Pharmacy to ensure tocilizumab is available on ward.
- Inform DCC at CGH that treatment is due before 08:30 on day of infusion, call ext. 4013 or 8954.
- Administration should start no later than 12:00 noon.
- The duration of patient admission may differ depending on the bispecific antibody used, but patients should be monitored for minimum 24 hrs from start of infusion/injection. If they remain well then discharge with advice for symptoms to be weary of in case of late reaction.
- Once a patient is established on treatment the ongoing risk of CRS is low and ongoing treatment is 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.
- Of note, the highest risk of CRS with epcoritamab occurs with the third dose and the initial 2 doses may be given as an outpatient depending on the patient's risk profile.

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[11] (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.

Table 2. CRS management guidance *(excludes patients receiving blinatumomab)*

	Grade 1	Grade 2	Grade 3	Grade 4
Immediate actions	Treat symptoms[¥] Consider broad spectrum antibiotics	Treat symptoms[¥] Hypotension – 0.9% saline fluid challenge in 500ml boluses. If >1000 ml administered, consider vasopressor support Hypoxia – administer oxygen Consider broad spectrum antibiotics	Treat symptoms[¥] Symptomatic management of organ toxicities **Admit to DCC** for vasopressor and/or respiratory support Give broad spectrum antibiotics	Treat symptoms[¥] Symptomatic management of organ toxicities **Admit to DCC** for vasopressor and/or respiratory support Give broad spectrum antibiotics
Cortico-steroids	Consider initial single dose dexamethasone 10 mg IV and increase frequency up to 6-hrly if ongoing concern[θ]	Administer dexamethasone 10 mg IV, consider frequency up to 6-hrly if ongoing concern[θ]	Administer dexamethasone 10 mg IV 6-hrly	Administer dexamethasone 10 mg IV 6-hrly If refractory grade 4 CRS consider methylprednisolone 1 g OD for 3 days
Tocilizumab	Consider if ongoing clinical concern following dexamethasone[θ]	Administer tocilizimab (dosing below*****)	Administer tocilizimab (dosing below*****)	Administer tocilizimab (dosing below*****)
If CRS occurs during glofitamab 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

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

* **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)[12].

Θ **Teclistamab SPC[13]** recommends use of tocilizumab prior to steroids, but following review the GHNHSFT Haematology department feel it reasonable to adopt a uniform approach for elranatamab, epcoritimab, glofitamab and teclistamab.

Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as 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

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 tociluzimab 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[17].

Table 3. Management of next dose following episode of CRS *(excludes patients receiving blinatumomab)*

	Grade 1	Grade 2	Grade 3	Grade 4
Glofitamab	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.	Permanently discontinue bispecific antibody
Epcoritimab	Withhold treatment until CRS resolves	Withhold treatment until CRS resolves	Withhold treatment until CRS resolves If grade 3 CRS duration >72 hours permanently discontinue If grade ≥ 3 CRS recurs permanently discontinue therapy	
Elranatamab and Teclistimab	Withhold treatment until CRS resolves	Withhold treatment until CRS resolves	Withhold treatment until CRS resolves. If grade ≥ 3 CRS recurs permanently discontinue therapy	

Table 2 and 3 CRS management guidance is based on the SPC for elranatanab, epcoritimab, glofitamab and teclistamab[13-16].

MANAGEMENT OF CRS FOR PATIENTS RECEIVING BLINATUMOMAB

Some aspects of the general guideline table also apply for patients receiving blinatumomab but there are specific differences as set out in the product SPC[19]. Blinatumomab differs to other bispecific antibodies as it is given as a continuous infusion and has a short half-life. The median time to onset of a CRS event was 2 days, and typically occurs with cycle 1 or 2. CRS symptoms normally resolve quickly on discontinuing the blinatumomab infusion.

Use of TOCILIZUMAB to manage CRS is not described in the blinatumomab SPC, and cannot be reimbursed via the high-cost drugs fund.

Table 4. Management of CRS for patients receiving blinatumomab

Grade 1	• Continue blinatumomab and administer supportive care¥. Steroids are not indicated.
Grade 2	• The infusion of blinatumomab must be stopped immediately. • Administer supportive care¥. • Re-start infusion once CRS resolves to grade ≤1. • Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Grade 3	• The infusion of the blinatumomab must be stopped immediately. • Dexamethasone should be administered IV at a dose 8 mg TDS for up to 3 days. • The dexamethasone dose will then be reduced step-wise over up to four days. • Hold blinatumomab until resolves to grade ≤1, then resume drug at 9 mcg/day for one week. If toxicity remains grade ≤1, increase dose to 28 mcg/day to complete 28-day cycle of therapy. • Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients much receive 20 mg of dexamethasone IV. • If grade 3 CRS recurs after blinatumomab is resumed, stop drug permanently. • If the initial adverse event lasts for ≥ 2 weeks without improvement, then blinatumomab will be permanently discontinued.
Grade 4	• Blinatumomab should be discontinued permanently

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

Table 4 guidance is based on the SPC for blinatumomab[19] and the E1910 trial protocol[20]

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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