

Management of Bispecific Antibody-Mediated Immune Toxicities



TARGET AUDIENCE	Secondary care
PATIENT GROUP	Haemato-oncology patients receiving Bispecific Antibody Therapies

Clinical Guidelines Summary

- Bispecific antibody (BsAb) therapy is a novel approach in the treatment of haematological malignancies including lymphomas and myeloma.
- Due to engagement of the host immune system against malignant cells, specific toxicities can occur with BsAb which are not seen with conventional chemotherapy treatments. These include cytokine release syndrome (CRS) and immune effector cell-mediated neurotoxicity syndrome (ICANS).
- This clinical guideline outlines the management for patients receiving BsAB and how CRS and ICANS should be managed in NHS Lanarkshire.

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Guideline Body

Introduction

Bispecific antibody (BsAb) therapy is a novel approach in the treatment of haematological malignancies. BsAbs have two binding sites, one for endogenous T-cells (via the CD3 receptor) and one for the malignant cell. They promote activation and expansion of endogenous T-cells as well as T-cell mediated lysis of malignant cells via specific receptors.

BsAbs used in treatment of B-cell non-Hodgkin lymphoma include **Epcoritamab**, **Glofitamab** (both SMC-accepted as monotherapy for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy), **Mosunetuzumab** and **Odronextamab** (currently available in clinical trials only). These bind via the CD20 receptor of malignant B cells.

Phase 2 studies analysing BsAbs in DLBCL have shown promising efficacy, with overall response rates of up to 60% and complete response rates of approximately 30-40% in patients with relapsed/refractory disease. Ongoing clinical trials are investigating earlier incorporation of these agents, including in the first-line setting.

In myeloma, **Elranatamab** and **Teclistamab** promote T-cell mediated lysis of malignant plasma cells via the B-cell maturation antigen (BCMA). They are both SMC accepted as monotherapy for patients with relapsed/refractory disease who have received at least three prior therapies (including an immunomodulatory agent, proteasome inhibitor and anti-CD38 antibody) and progressed on the most recent therapy.

Due to engagement of the host immune system against malignant cells, specific toxicities can occur which are not seen with conventional chemotherapy treatments. These include cytokine release syndrome (CRS) and immune effector cell-mediated neurotoxicity syndrome (ICANS). Both are seen in patients receiving other types of immunotherapy, including CAR-T cell therapy.

Blinatumomab is a BsAb directed against CD19+ cells in B-cell acute lymphoblastic leukaemia. This drug can also cause CRS and ICANS, however has a different administration and toxicity profile to the BsAbs used for lymphomas and myeloma. Please refer to separate, specific guidance for Blinatumomab administration and toxicity management.

It is important to note that frequency and severity of CRS with BsAbs is typically less than that seen with CAR-T, and ICANS is seen rarely. However, without prompt identification and treatment, these complications can cause significant adverse effects and can be fatal. It should be noted that each of the different licensed BSAB has subtle differences within their Summary of Product Characteristics (SPC) in the management of CRS. A standardised approach to managing these patients is therefore essential. Please note that individual product [West of Scotland SACT protocols](#) should be referred to in conjunction with this guideline.

Cytokine release syndrome

CRS is an acute systemic inflammatory syndrome occurring due to over-stimulation of the immune system by the interaction of tumour cells and immune effector cells. There is rapid and massive

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cytokine release which, in severe cases, can precipitate multi-organ dysfunction. Interleukin 6 (IL-6) is often implicated in CRS and is a specific target for therapy.

The incidence of CRS with BsAb therapy has been reported at 40-60%. The median time to onset is variable depending on the BsAb used but is predominantly within the first 48 hours (see **Appendix 1**). CRS can be graded depending on severity (see below) with most cases being mild.

Fever must be present for CRS. Other symptoms can include (but are not limited to) chills, sweating, rash, nausea, restlessness, dizziness, BP changes, dyspnoea, myalgia and headache. Important differential diagnoses to consider include anaphylaxis and infection/sepsis.

There should be a low threshold to consider commencement of broad-spectrum antibiotics, particularly in this immunocompromised cohort of patients.

Prevention

- Step-up dosing – the drug dose is increased upon each administration until the maximum dose is established
- Premedication – paracetamol, an antihistamine and steroid are given as standard practice
 - See Appendix 1/individual drug SPC for dosing and pre-medication of each BsAb

Initial assessment and management

- If CRS occurs during treatment, stop infusion
- Assess patient to determine grade of CRS (see **Table 1**), but also ensure alternative causes for fever, hypoxia and hypotension are considered
- Regular observations – minimum hourly until CRS resolves
- Symptomatic treatment – paracetamol 1g, chlorphenamine 10mg IV (if not already given), consider ibuprofen for refractory fever if no significant thrombocytopenia, coagulopathy or renal impairment
- Baseline investigations if CRS grade ≥ 2 :
 - Bloods – FBC, U&Es, LFTs, CRP, LDH, bone profile, urate, ferritin, coagulation & fibrinogen
 - Infection screen – blood cultures, urine culture, sputum culture, COVID-19 PCR, and consider extended viral swabs
 - Chest x-ray – if respiratory symptoms or hypoxia
- ECG – baseline at onset of CRS, repeat as necessary depending on clinical features
- Inform Haematology doctor oncall:
 - Monday to Friday (0900-1700)
 - University Hospital Monklands phone 404666
 - University Hospital Wishaw bleep 065
 - University Hospital Hairmyres 01355 58 (4320)
 - Out of hours (1700-0900 and weekends) – contact Haematology consultant via switchboard
- Haematology doctor to discuss any CRS of grade ≥ 2 with Haematology consultant
 - This is the attending consultant in normal working hours, or the on-call consultant if out of hours
- Discuss with the patient’s responsible consultant in working hours for adverse event reporting

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Drug treatment

- Decisions on use of anti-cytokine and/or corticosteroid therapy should be based on CRS severity (see **Tables 1 and 2**) and on discussion with consultant
- **Anti-cytokine therapy** – Tocilizumab 8mg/kg (maximum 800mg per dose) (off label use*). Can be repeated after at least 8 hours. Maximum of 2 doses in 24 hours and not more than 3 doses in a 6-week period.
 - Must be discussed with consultant prior to giving
 - 4 doses are always kept in Ward 15, University Hospital Monklands (UHM). Please see **Appendix 2** for details on how to access Tocilizumab out of hours
 - If CRS is refractory to Tocilizumab and corticosteroid, consider Anakinra 100mg SC twice daily (can continue for 3-7 days) (off label use*) (4 doses are kept in Ward 15, UHM)
 - **No anti-cytokine therapy is licensed for the treatment of BsAb related CRS. However, the licensing of BsAbs recommends anti-cytokine therapy be available for management*
- **Corticosteroid therapy:**
 - Dexamethasone is the preferred corticosteroid for pre-medication and initial CRS management. See **Table 2** for dosing considerations which will depend on individual patient factors and CRS grading
 - If refractory CRS, Dexamethasone can be increased to 20mg IV 6-hourly or alternatively, consider Methylprednisolone 1000mg IV per day
 - Consider early use in suspected ICANS (see below)
 - In myeloma, consider prophylactic use in those at risk of spinal cord compression due to tumour flare (in those with significant extramedullary disease)
 - Can be used in myeloma patients developing bone pain due to tumour flare

CAUTION: fever and CRP are unreliable markers of CRS once patients are treated with steroids or anti-cytokine therapy. If hypotension or hypoxia persist, consider ongoing CRS and manage accordingly.

Grading of CRS

Grading is determined by the most severe event. There is no specific cut-off for hypotension, but this will be determined on a case-by-case basis in the context of systolic blood pressure (SBP), mean arterial pressure (MAP) and the patient's baseline BP. Management of CRS depending on grade is detailed in **Table 2**.

Table 1 – CRS grading

	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥38°C	≥38°C	≥38°C	≥38°C
with				
Blood pressure	Normal	Low, responds to IV fluids	Low, requiring 1 vasopressor	Low, requires 2+ vasopressors
and/or				
O2 saturation (≥94%)	Normal	Requires low-flow O2 (≤6L)	Requires high-flow O2 (>6L)	Requires positive pressure ventilation

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Table 2 – CRS management

	Grade 1	Grade 2	Grade 3	Grade 4
Supportive care	<ul style="list-style-type: none"> - Withhold subsequent doses until CRS resolves, or stop infusion if ongoing - Give paracetamol and IV chlorphenamine - Consider IV fluids - Consider broad-spectrum antibiotics, particularly if neutropenic 	<ul style="list-style-type: none"> - Follow grade 1 recommendations - Inform on-call consultant - Monitor closely: regular observations, fluid balance, consider catheter and telemetry - Hypoxia: treat with oxygen - Hypotension: 2x 500ml IV crystalloid fluid boluses. If poor response despite this and the drug therapy below, consider vasopressor therapy - Discussion with HDU/ITU on a case-by-case basis 	<ul style="list-style-type: none"> - Follow grade 2 recommendations - Give broad-spectrum antibiotics - Monitor organ function: fluid balance, catheter, telemetry, consider invasive BP monitoring if vasopressor required - Hypoxia: treat with oxygen - Hypotension: vasopressor support if IV crystalloid fluid boluses and anti-IL-6/steroid fail to maintain BP - Transfer to HDU/ITU. Haematology consultant to discuss with critical care consultant re. suitability for transfer to critical care 	<ul style="list-style-type: none"> - Follow grade 3 recommendations - Mechanical ventilation and/or renal replacement therapy may be required - Consider and assess for MAS/HLH²
Drug therapy	<ul style="list-style-type: none"> - Consider tocilizumab +/- dexamethasone (e.g. 10mg once daily PO) if grade 1 CRS persists >24h despite symptomatic management, or for those with significant comorbidities (e.g. cardiac impairment, limited pulmonary reserve) 	<ul style="list-style-type: none"> - Give tocilizumab - Consider addition of dexamethasone (e.g. 10mg IV every 12 hours for 1-3 days or resolution to grade ≤1) if no response following 2 doses of tocilizumab 	<ul style="list-style-type: none"> - Give tocilizumab - Give dexamethasone (e.g. 10mg IV every 6 hours for 1-3 days or resolution to grade ≤1) - If refractory, consider alternative anti-cytokine therapy (e.g. anakinra) +/- increasing dose of steroid 	<ul style="list-style-type: none"> - Give tocilizumab - Give dexamethasone (e.g. 20mg IV every 6 hours for 1-3 days or resolution to grade ≤1, with taper over 3-7 days) - If refractory, consider alternative anti-cytokine therapy (e.g. anakinra) +/- methylprednisolone 1000mg IV once daily for 3 days
Other considerations	<ul style="list-style-type: none"> - If CRS occurs during IV infusions, treatment can be re-started at 50% of initial rate if symptoms resolve. If recurrent symptoms despite this, discontinue current IV infusion - Ensure symptoms are resolved prior to next infusion¹ - Consider slower rate of infusion (duration may be up to 8 hours) 	<ul style="list-style-type: none"> - If CRS occurs during IV infusion, discontinue and do not restart - Ensure symptoms are resolved prior to next infusion¹ - Consider slower rate of infusion (duration may be up to 8 hours) 	<ul style="list-style-type: none"> - If CRS occurs during IV infusion, discontinue and do not restart - If no improvement within 24h, consider work-up for possible MAS/HLH² - Ensure symptoms are resolved prior to next infusion¹ - Consider slower rate of infusion - If recurrent grade 3+ CRS, permanently discontinue BsAb 	<ul style="list-style-type: none"> - Permanently discontinue BsAb - If no improvement within 24h, consider work-up for possible MAS/HLH²
Notes	<p>1 – time to next dose depends on the BsAb used:</p> <ul style="list-style-type: none"> - Epcoritamab and Glofitamab – withhold until >72h after resolution of CRS. - Eltranatamab and Teclistamab – refer to drug SPC and discuss with haematology consultant - For newer BsAbs which are not mentioned – refer to drug SPC and discuss with relevant team <p>2 – MAS = macrophage activation syndrome; HLH = haemophagocytic lymphohistiocytosis</p>			

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Immune effector cell-mediated neurotoxicity syndrome (ICANS)

ICANS is a rare neurological complication of immunotherapy which is related to peripheral immune overactivity, in a similar mechanism to CRS. Endothelial activation and subsequent blood-brain barrier dysfunction leads to central nervous system (CNS) inflammation. ICANS is predominantly seen in the setting of CAR-T cell therapy and is rare with BsAb therapy (incidence approximately 5%, mostly at grade 1-2 severity).

ICANS manifests predominantly as a toxic encephalopathy with receptive dysphasia, motor dysfunction and altered consciousness. In severe cases seizures, coma and cerebral oedema can be seen, and this is associated with a high mortality. Grading of ICANS is based on the Immune effector Cell-associated Encephalopathy (ICE) score and the neurological signs and symptoms above. It is based on the most severe event. The CARTOX app, developed for CAR-T cell patients, can help to comprehensively assess patients and aid in management.

ICE score

	Task	Points
Orientation	To year, month, city, hospital	4 (1 for each)
Naming	Name 3 objects	3 (1 for each)
Follow commands	Ability to follow a simple command	1
Writing	Ability to write a standard sentence	1
Attention	Count backwards from 100 by 10	1
Score – 10 = no impairment; 7-9 = grade 1 ICANS; 3-6 = grade 2 ICANS; 0-2 = grade 3 ICANS; if score 0 and patient unrousable and unable to perform		

Grading of ICANS

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0
Depression of conscious level	Awakens spontaneously	Awakens to voice	Awakens to tactile stimuli	Unrousable or requires vigorous or repetitive tactile stimuli; stupor or coma
Seizures	NA	NA	Any clinical seizure (focal or generalised) that resolves rapidly (< 5 minutes) or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (≥ 5 minutes) or repetitive clinical/electrical seizures without return to baseline in between
Motor findings	NA	NA	NA	Deep focal motor weakness e.g., hemiparesis/paraparesis
Cerebral oedema or raised intracranial pressure	NA	NA	Focal/local oedema on neuroimaging	Diffuse cerebral oedema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilloedema, or Cushing's triad

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Initial assessment and management

- Perform neurological exam to calculate ICE score, and assess ICANS grade from table above
- Inform Haematology doctor oncall:
 - Monday to Friday (0900-1700)
 - University Hospital Monklands phone 404666
 - University Hospital Wishaw bleep 065
 - University Hospital Hairmyres 01355 58 (4320)
 - Out of hours (1700-0900 and weekends) – contact Haematology consultant via switchboard
- Consultant discussion is mandatory for any grade ICANS with early consideration of transfer to critical care

- Supportive care:
 - Assess swallow, make nil by mouth if necessary and commence aspiration precautions
 - IV hydration and consider converting oral medication to IV
 - Avoid sedating medication where possible
- **Please refer to individual SACT protocols / summary of product characteristics** for specific investigations and management, including drug treatment with anti-cytokine therapy and corticosteroids as well as neurological interventions

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Acknowledgement

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References/Evidence

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5. Crombie JL, Graff T, Falchi L et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. *Blood*. 2024(143(16)):1565-1575. DOI: <https://doi.org/10.1182/blood.2023022432>

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Appendices

Appendix 1 – further information on bispecific antibodies

	Epcoritamab	Glofitamab	Elranatamab	Teclistamab
Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous
Dosing	C1D1 0.16mg C1D8 0.8mg C1D15 48 mg C1D22 48mg Ongoing full dose of 48mg: Weekly C2-3 Every 2 weeks C4-9 Every 4 weeks C10+	Pretreatment C1D1 with Obinutuzumab C1D8 2.5mg C1D15 10mg C2 30mg Ongoing full dose 30mg every 21 days	C1D1 12mg C1D4 32mg C1D8, D15, D22 76mg Ongoing full dose of 76mg: Weekly C2-6 Fortnightly from C7 if patient has achieved a response	C1D1 0.06mg/kg C1D3 0.3mg/kg C1D5 1.5mg/kg Ongoing full dose of 1.5mg/kg: Weekly, with consideration of dose every 2 weeks if CR or better for 6+ months Dosed on actual body weight
Cycle length	28 days	21 days	28 days	As above
Duration	Continuous until unacceptable toxicity or progression	Maximum 12 cycles, or unacceptable toxicity/progression	Continuous until unacceptable toxicity or progression	Continuous until unacceptable toxicity or progression
Monitoring requirements	Inpatient for first full 48mg dose (C1D15)	Inpatient for 24 hours after first Glofitamab dose (C1D8)	Inpatient for 48 hours following 32mg and first 76mg dose	Inpatient for 48 hours following all step-up doses
Premedication	Paracetamol 1g oral Chlorphenamine 4mg oral, Dexamethasone 16mg oral For cycle 1	Paracetamol 1g oral Chlorphenamine 10mg IV Dexamethasone 20mg IV or methylprednisolone 80mg IV	Paracetamol 1g oral Chlorphenamine 4mg oral Dexamethasone 20mg oral For first three (step-up) doses*	Paracetamol 1g oral Chlorphenamine 4mg oral Dexamethasone 16mg oral/IV For first three (step-up) doses*
Additional medication	Dexamethasone 16mg oral (3 days) Allopurinol (cycle 1) Aciclovir Co-trimoxazole Omeprazole	Allopurinol (cycle 1) Aciclovir Co-trimoxazole Omeprazole	Allopurinol (cycle 1) Aciclovir Co-trimoxazole Omeprazole for first 14 days	Allopurinol (cycle 1) Aciclovir Co-trimoxazole Omeprazole for first 7 days
CRS in Ph2 trials (%pts affected)	49.7% - Grade 1 or 2 2.5% - Grade 3 or 4	59% - Grade 1 or 2 4% - Grade 3 or 4	56.3% - Grade 1 or 2 0% - Grade 3 or 4	56% - Grade 1 or 2 0.6% - Grade 3 or 4
Median time for CRS in trials (from dose)	C1D15 – 20 hours	C1D8 – 13.5 hours	C1 – 48 hours (90.6% with step up doses i.e., C1D4, C1D8)	C1 – 48 hours (most in step-up doses)
Incidence of ICANS in Ph2 trials (% pts affected)	5.8% - Grade 1 or 2 0.6% - Grade 3 or 4	5% - Grade 1 or 2 3% - Grade 3 or 4	3.4% - Grade 1 or 2 0% - Grade 3 or 4	3% - Grade 1 or 2 0% - Grade 3 or 4

* Pre-medication given for BsAbs with SC administration for all step-up doses. If no CRS/ICANS then these can be stopped for subsequent administrations. If previous CRS/ICANS, then ongoing pre-medication may be required. For glofitamab, refer to SPC for detailed advice.

Please refer to each drug specific [Summary of Product Characteristics \(SPC\)](#) for more detailed information

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Appendix 2 – guidance on accessing tocilizumab out of hours

- University Hospital Monklands: contact Ward 15 Haematology on 01698 752045/047 (401045/401047) internally). Four doses are kept in fridge. There are also further vials kept in the emergency cupboard – hospital cover has access.
- University Hospital Wishaw: Two doses are kept in the emergency cupboard – hospital cover has access
- University Hospital Hairmyres: Two doses are kept in the emergency cupboard – hospital cover has access

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1. Governance information for Guidance document

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Distribution	
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CHANGE RECORD

Date	Lead Author	Change	Version No.
		<i>e.g. Review, revise and update of policy in line with contemporary professional structures and practice</i>	1
			2
			3
			4
			5

2. You can include additional appendices with complimentary information that doesn't fit into the main text of your guideline, but is crucial and supports its understanding.

e.g. supporting documents for implementation of guideline, patient information, specific monitoring requirements for secondary and primary care clinicians, dosing regimen/considerations according to weight and/or creatinine clearance

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