Worcestershire NHS
Acute Hospitals NHS Trust

Guideline for the management of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) associated with Bispecific Antibody Treatments

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

T-cell engaging bispecific antibodies are a class of systemic anti-cancer therapy (SACT) designed to simultaneously bind to two antigens e.g. T cells via CD3 and surface antigens on cancer cells. This dual binding mechanism activates and redirects T cells against the cancer cell, leading to the release of granzymes, perforins, and pro-inflammatory cytokines, which facilitate HLA-independent T-cell-mediated tumour cell killing. A variety of bispecific antibodies are currently approved by NICE, targeting different antigens on tumour cells, with notable tumour-associated antigens including BCMA (Teclistamab and Elranatamab) and CD20 (Glofitamab and Epcoritamab.)

Bispecific agents have demonstrated significant efficacy in the treatment of haematological malignancies; however, their use is associated with potentially life-threatening toxicities that necessitate specialized monitoring and prompt intervention. Among these toxicities, Cytokine Release Syndrome (CRS) and Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) are particularly critical, requiring timely diagnosis, grading, and management.

For this reason, patients undergoing treatment with bispecific agents require vigilant monitoring for CRS and ICANS. This guideline aims to provide guidance on the monitoring requirements, acute and ongoing management of patients who develop CRS and/or ICANS whilst receiving bispecific antibody treatment.

This guideline is for use by the following staff groups:

Staff providing care for patients receiving Bi-specific anti-cancer medication e.g. Haematology, Pharmacy, Intensive Care, Emergency Care, Acute Oncology Service.

Lead Clinician(s)

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Approved by Haematology and Palliative Care Governance on:	20th November 2024
Approved by Medicines Safety Committee on:	11th December 2024
Chemotherapy Advisory Group	6th December 2024
This guideline should not be used after end of:	11th December 2027

Key amendments to this guideline

Date	Amendment	Approved by:
11/12/24	New guideline	MSC / Haem Governance

Cytokine Release Syndrome (CRS)

CRS is an intensified immune response that can occur following bispecific antibody treatment that activates or engages T-cells and other immune effector cells. While symptoms may vary in presentation and severity, CRS is usually characterised by fever. Patients may also present with hypotension, hypoxia, and/or multi-organ toxicity. Typically, CRS occurs within hours to days after the initial doses of treatment.

It is important to note that the common symptoms associated with CRS are not exclusive to this syndrome. Clinicians must exercise caution to rule out other potential causes of fever, hypotension, hemodynamic instability, and respiratory distress, including severe infections. Currently, there are no specific laboratory tests for CRS; changes in inflammatory markers, such as C-reactive protein (CRP) and ferritin, may lag behind clinical manifestations by up to 12 hours and are not specific to CRS. Therefore, the diagnosis of CRS should be made clinically, taking into account the timing of symptom onset and the overall clinical picture.

If CRS is suspected, it should be managed based on American Society for Transplantation and Cellular Therapy (ATSCT) consensus grading (1). Appendix 1 outlines the grading and initial and ongoing management of patients suspected of having CRS.

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

The precise pathophysiological mechanisms underlying ICANS are still being elucidated. ICANS is believed to be triggered by the passive diffusion of cytokines into the central nervous system (CNS), along with the trafficking of T cells, monocyte recruitment, and macrophage activation. It frequently occurs concurrently with or following CRS and is characterised by varying degrees of diffuse encephalopathy, which may include focal neurological signs, intracranial hypertension, and seizures.

ICANS typically presents as toxic encephalopathy, with initial symptoms including diminished attention, language disturbances, and impaired handwriting. Other manifestations may involve confusion, disorientation, agitation, aphasia, somnolence, and tremors. In more severe cases (grade >2), patients may experience seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral oedema. The syndrome can exhibit a biphasic pattern; the first phase often coincides with high fever and other CRS symptoms, while delayed neurotoxicity—such as seizures or confusion—may arise during the third or fourth week post-treatment.

Baseline Assessment

Before initiating bispecific antibody treatment, a thorough neurological baseline assessment should be conducted. This includes cognitive function tests and documentation of any pre-existing neurological conditions.

Regular Monitoring

During treatment, particularly during the step-up dosing phase and following the initial full dose, patients should be monitored twice daily for signs of ICANS. Monitoring should be performed by clinical professionals trained in recognising ICANS symptoms.

Grading

ICANS severity is assessed using a 10-point neurological assessment tool known as the Immune Effector Cell-associated Encephalopathy Score (ICE Score, previously CARTOX-10):

- **Orientation to year, month, city, hospital** (4 points total)
- **Follows commands** (1 point)
- **Naming three nearby objects** (3 points total)
- **Writing a standard sentence** (1 point)
- **Counting backwards from 100 in tens** (1 point)

A patient with normal cognitive function would score a total of 10. Additional parameters, including conscious level, seizures, motor findings, and evidence of increased intracranial pressure, further contribute to the grading of ICANS. The ICE score should be performed twice daily. Clinical findings and ICE scores should be documented in the medical record.

Appendix 2 outlines the grading and initial and ongoing management of patients suspected of having ICANS.

Tocilizumab

Tocilizumab binds specifically to IL-6 receptors. IL-6 is a pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation.

Dose

Tocilizumab should be administered by IV infusion at a dose of 8mg/kg (maximum 800 mg) for patients weighing >30 kg, over 60 minutes (2). This can be repeated every 8 hours up to a maximum of 4 doses.

3 adult doses of Tocilizumab are kept on the inpatient haematology ward. Additional doses are available from the Emergency Drug Cupboard (EDC) next to pharmacy if needed out-of-hours.

Tocilizumab is funded by NHSE and a blueteq application MUST be filled out for each patient receiving treatment for this indication. This can be done retrospectively if the completion of a form would delay patient receiving treatment.

Anakinra

Anakinra blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.

Anakinra is a second-line option for patients who have not responded to at least 2 doses of tocilizumab (3). It is licensed for use in rheumatoid arthritis and other inflammatory syndromes but therapy for CRS and/or ICANS is an off-label use of the drug for all routes.

Dose

100 mg once daily (increasing in 100 mg intervals to a maximum of 10 mg/kg/day according to response (3).) Anakinra is given subcutaneously unless contra-indicated/ unsuitable (e.g. platelets < $20x10^9$/L (4)), in which case the IV route may be considered (see administration advice below.)

Treatment should be continued until 24 hours after resolution of symptoms (3).

Anakinra should be used with caution in patients with moderate renal impairment (CrCl 30-59 mL/min) and in severe renal impairment (CrCl <30 mL/min) consider administration every other day (5).

Subcutaneous Injection

- Anakinra pre-filled syringes are sterile unpreserved solutions for single use only
- Do not shake. Allow the PFS to reach room temperature before injecting.
- Before administration, visually inspect the solution for particulate matter and discolouration. Only clear, colourless-to-white solutions that may contain some product-related translucent-to-white amorphous particles should be injected. The presence of these particles does not affect the quality of the product (5).

Intravenous bolus

- Use pre-filled syringe to administer Anakinra as a slow IV bolus (over 1-3 minutes) followed by a NaCl 0.9% flush OR
- Use pre-filled syringe to add Anakinra dose to 50 mL NaCl 0.9% before infusing intravenously, over 30 minutes.
- Anakinra should not be administered concomitantly via Y-site or mixed with any other medications due to a lack of compatibility data

Continuous intravenous infusion

- Intravenous infusion administration is reserved for patients who are critically unwell or unresponsive to preferred Anakinra routes
- Inject 100-200 mg by slow IV bolus over 1-3 minutes (as a loading dose) followed by a continuous IV infusion set at 2mL/hour (see table below.) Suggested upper limit of 400 mg per day (excluding loading dose.) (4)
- Infusion must be changed every 6 hours due to limited stability data
- Change to subcutaneous administration as soon as clinically appropriate

Drug	Concentration	Diluent	Rate of infusion	Dose
Anakinra	100 mg in 12 mL total volume	Sodium chloride 0.9%	2 mL/hour	400 mg/day Syringe must be changed every 6 hours

References

1. Lee, DW et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity. Biol Blood Marrow Transplant. 2019. Vol. 25, 4.

2. Summary of Product Characteristics (SPC). RoActemra 20mg/ml Concentrate for Solution for Infusion. Electronic Medicines Compendium (eMC). [Online] [Cited: 30 10 2024.] https://www.medicines.org.uk/emc/product/6673/smpc.

3. The Christie NHS Foundation Trust. Guidelines for management of cytokine release syndrome. Cellular Therapy and Transplant Programme.

4. University College London Hospitals NHS Foundation Trust. Anakinra in the Treatment of Secondary Haemophagocytic Lymphohistiocytosis (sHLH). 2020.

5. Summary of Product Characteristics (SPC) - Kineret 100 mg solution for injection in a pre-filled syringe. Electronic Medicines Compendium (eMC). [Online] 30 10 2024. https://www.medicines.org.uk/emc/product/559/smpc.

6. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. Crombie, JL et al. 16, s.l. : Blood, 2024, Vol. 143.

7. Group, Equity in Multiple Myeloma Bispecific Research and Access (EMMBRAce) Bispecific Antibody Implementation. Consensus Framework for the Optimal Delivery of Bispecific Antibodies for patients with Multiple Myeloma (Version 1.0). [Online] October 2024. [Cited: 06 November 2024.] https://www.ucl.ac.uk/lifesciences-faculty/sites/lifesciences_faculty/files/consensus_framework_for_the_optimal_delivery_of_bispecific_antibodies_for_patients_with_multiple_myeloma_v1_oct_2024.pdf.

8. Rodriguez-Otero, P et al. . International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. The Lancet Oncology. 2024. Vol. 25, 5.

9. Newcastle upon Tyne Hospitals NHS Foundation Trust. Management of CRS, Neurotoxicity and CAR-T related encephalopathy syndrome (CRES) post chimeric antigen recepton (CAR) T-cell therapy. Version 2.1. 2021.

Appendix 1: A summary of the management of CRS (6) (7)

All reactions grade 1 or above should be discussed with a Consultant Haematologist.
Grade 2 reactions: Outreach Nurses Bleep #421/422
Grade 3 or 4 reactions: ITU Registrar Bleep #702

Presenting Symptoms	Initial management	Ongoing management
Grade 1 CRS		
Temperature ≥38°C No hypotension No Hypoxia	• Interrupt bispecific • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • Supportive care e.g. IV fluids and oxygen as appropriate • Consider **tocilizumab*** for persistent fever or at first onset of fever in patients at high risk of CRS • Consider **dexamethasone 10 mg PO stat** in ambulatory setting or if patient has bone pain (tumour flare), not controlled with analgesia	• Ensure symptoms are resolved for >72 hours prior to next bispecific and consider slower rate for infusions • If symptoms recur, discontinue bispecific • If symptoms persist for >3 days or refractory fever, treat as Grade 2 CRS • Consider **antifungal prophylaxis** in patients receiving steroids
Grade 2 CRS – Inform ICU and Consider Transfer		
Temperature ≥38°C **AND** Hypotension responsive to fluids **AND/OR** Hypoxia requiring <6L/min oxygen	• Discontinue current bispecific • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • IV fluids bolus 500-1000 mL to maintain SBP >90mm/Kg and oxygen as appropriate • Administer **tocilizumab*** • Consider **Dexamethasone 10 mg IV 6 hourly** if no clinical improvement after 6-8 hours of 1st tocilizumab dose. Continue until symptoms have resolved. Consider taper. • If hypotension persistent after 2 x fluid boluses and tocilizumab, consider low-dose vasopressor	• Ensure symptoms are resolved for >72 hours prior to next bispecific and consider slower rate for infusions • Inpatient monitoring for next bispecific • If no improvement within 24 hours, treatment as Grade 3 CRS • Consider **antifungal prophylaxis** in patients receiving steroids

Grade 3 (Medical Emergency) – Transfer to ICU		
Temperature ≥38°C **AND** Hypotension requiring vasopressors **AND/OR** Hypoxia requiring >6L/min oxygen	• Discontinue current bispecific • Manage fever and constitutional symptoms as per Grade 1 and 2 CRS • Administer vasopressors and oxygen as required • Administer **tocilizumab*** • Start **Dexamethasone 10 mg IV 6 hourly.** If no improvement within 6-8 hours, increase to **Methylprednisolone IV 1mg/kg BD**. Consider taper once symptoms resolved. • Consider **Anakinra**** if no clinical improvement after two doses of tocilizumab and regular high-dose corticosteroid	• Ensure symptoms are resolved for >72 hours prior to next bispecific and consider slower rate for infusions • Inpatient monitoring for next bispecific • If grade ≥3 CRS recurs, stop bispecific and permanently discontinue therapy • Consider **antifungal prophylaxis** in patients receiving steroids
Grade 4 (Medical Emergency) – Transfer to ICU		
Temperature ≥38°C **AND** Hypotension requiring multiple vasopressors **AND/OR** Hypoxia requiring CPAP/BiPAP/Ventilation	• Discontinue current bispecific • Manage fever and constitutional symptoms as per Grade 1 and 2 CRS • Provide positive pressure support (e.g. CPAP) as needed • Administer **tocilizumab*** • Administer **methylprednisolone 1g/day IV** for 3 days**.** • Consider **Anakinra**** if no clinical improvement after two doses of tocilizumab and regular high-dose corticosteroid	• Permanently discontinue bispecific antibody • Consider **antifungal prophylaxis** in patients receiving steroids

***Tocilizumab Guidance (20mg/mL concentration solution for infusion)**

- 8mg/kg (max. 800 mg per dose) IV over 60 minutes
- Repeat dose every 8 hours if no improvement. Maximum 4 doses.
- Stock on Laurel 3, ITU and Pharmacy Emergency Drug Cupboard
- Blueteq required (can be done retrospectively)

****Anakinra Guidance (100mg/0.67 mL solution for injection PFS)**

- 100 mg daily SC or via slow IV bolus if platelets <20.
- Can increase in 100 mg increments to a maximum dose of 10mg/kg/day as needed
- Continue until 24 hours after resolution of CRS (usually no more than 3-5 days required.)
- Stock in pharmacy

Monitoring:

- NEWS score hourly
- FBC, U&Es, LFTs, Ca2+, Mg2+, PO43- , uric acid, LDH, CRP, lactate, PT/APTT
- 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 (See ICANS.)

Appendix 2: A summary of the management of ICANS (7) (8)

All reactions grade 1 or above should be discussed with a Consultant Haematologist.
Grade 2 reactions: Outreach Nurses Bleep #421/422
Grade 3 or 4 reactions: ITU Registrar Bleep #702

Presenting Symptoms	Initial management	Ongoing management
Grade 1 and Grade 2 ICANS- Inform ICU and Consider Transfer		
Grade 1: ICE score 7–9 Awakens Spontaneously **Grade 2:** ICE score 3–6 Awakens to voice	• Interrupt bispecific • Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines and fluids and assess swallowing. Liaise with pharmacist for medicines that need converting from oral preparations. • Avoid sedating medications if possible • Initiate regular neurological observations • ICE score TDS- QDS • Initiate consultation with a neurologist • Consider non-sedating, anti-seizure medicinal products **(Levetiracetam IV 500mg BD, or up to 2000 mg BD)** • Consider **Dexamethasone IV 10 mg every 6 hours** until symptom resolution, then taper. • Consider **Tocilizumab**, if neurotoxicity is associated with CRS. • If ICANS persistent (>48 hours), consider **Anakinra**	• Early EEG ideally within 24 hours, repeated if condition deteriorates • Fundoscopic exam to assess for papilloedema • Consider MRI brain and CT brain; diagnostic LP including opening pressure; MRI spine if focal neurological deficits; CT brain can be performed if MRI brain not feasible • Consider **antifungal prophylaxis** in patients receiving steroids
Grade 3 ICANS (Medical Emergency) – Transfer to ICU		
ICE score 0–2 Awakens only to tactile stimulus Clinical seizures that resolve rapidly or non-convulsive seizures on EEG that resolve with intervention Focal cerebral oedema on imaging	• Supportive care, treatment and neurological work-up as indicated for Grade 1 and Grade 2 ICANS • For steroid treatment, consider **methylprednisolone 1mg/kg IV every 12 hours**. Taper when symptoms improve.	• Repeat MRI brain for refractory or worsening ICANS • For first occurrence of Grade 3 ICANS, bispecific may be re-introduced once symptoms have resolved according to protocol • For recurrent Grade 3 ICANS, discontinue bispecific therapy permanently

Grade 4 ICANS (Medical Emergency) – Transfer to ICU		
ICE score 0 Un-rousable Prolonged (>5 minutes) or frequent seizures Motor weakness Diffuse cerebral oedema on imaging or symptoms of oedema	• Supportive care, treatment and neurological work-up as indicated for Grade 1 and Grade 2 ICANS • For steroid treatment, consider **methylprednisolone 1000 mg IV OD for 3 days.** Taper when symptoms improve. • Consider hyperosmolar therapy with mannitol	• Consider repeat neuroimaging every 2-3 days for persistent ICANS • Permanently discontinue bispecific therapy

ICE Assessment Tool	
Question	**Points**
What year is it?	1
Which month is it?	1
Which city/town are we in?	1
Which hospital are we in?	1
Follow an instruction e.g. touch your nose	1
Name 3 objects (point to three different objects)	3
Write a sentence	1
Count backwards from 100 in 10's	1

Monitoring Tool

This should include realistic goals, timeframes and measurable outcomes.

How will monitoring be carried out?

Who will monitor compliance with the guideline?

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
Page 3	Tocilizumab is used appropriately for CRS/ICANS for specific patients and appropriate NHSE funding applications are in place.	Follow up on blueteq applications for dispensing records of tocilizumab where not submitted	12 times a year	High-cost drugs pharmacy team	High-cost drugs pharmacy team	12 times a year

Contribution List

This key document has been circulated to the following individuals for consultation;

Designation
Keith Hinton (Lead Pharmacist and Clinical Team Lead – Surgery, Theatres and ITU)
Dr. Salim Shafeek (Haematology Consultant)
Dr. Sian Bhardwaj (Consultant in Anaesthesia and Intensive Care Medicine)

This key document has been circulated to the chair(s) of the following committees / groups for comments;

Committee
Haematology and Palliative Care Governance
Medicines Safety Committee
Chemotherapy Advisory Group

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

		Yes/No	Comments
1.	**Does the policy/guidance affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	N/A	
4.	**Is the impact of the policy/guidance likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this key document, please refer it to Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact Human Resources.

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue?	No
3.	Does the implementation of this document require additional manpower?	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff?	No
	Other comments:	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval