Recommendations for Monitoring and Management of Bispecific Antibody-Related CRS and Neurotoxicity

Contents

1. Scope and Purpose 1
1a. Introduction 1
1b. Bispecific antibodies (BsAbs) 1
2. Cytokine Release Syndrome (CRS) 2
2a. Planning treatment 2
2b. Monitoring of CRS 2
2c. Clinical presentation of CRS 3
2d. Clinical assessment 3
2e. CRS grading 3
2f. CRS Management 4
3. Neurological toxicities 5
3a. Clinical assessment and monitoring 5
3b. ICANS Management 6
4. Appendix 1 – CRS grading and management crib sheet 8
5. References: 9

1. Scope and Purpose

1a. Introduction

This document is meant to be used in conjunction with individual bispecific antibodies protocol on ARIA. The aim of this document is to suggest a standardised approach to management of cytokine release syndrome (CRS) and neurological toxicity in patients receiving bispecific antibody treatment.

1b. Bispecific antibodies (BsAbs)

Bispecific antibodies are a group of molecules that can recognised two different antigens or epitopes simultaneously (as opposed to monoclonal antibodies that bind to one target site). In the haemato-oncology setting, one of the antigen binding sites is usually a T-cell receptor, which activates the immune system to target tumour cells. Consequently, patients receiving BsAbs can experienced toxicities related to immune activation: specifically, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

2. Cytokine Release Syndrome (CRS)

CRS is an acute systemic inflammatory response and can be life-threatening in severe cases. The risks can be mitigated by ensuring patients have pre-medications prior to infusion, adequate monitoring for signs of CRS and timely intervention when it occurs.

2a. Planning treatment

- Education to patients and caregivers on potential side-effects of BsAbs is essential prior to starting treatment.
- The table below illustrates the timing of mandatory hospitalization and median time to CRS onset post-infusions for the current NICE approved BsAbs and those accessible via Early Access to Medicines Scheme (EAMS).
- CRS can occur minutes into infusion or after patient is discharged.
- The highest risk is usually during the step-up infusion period. The risk is significantly reduced with subsequent cycles.

Bispecific antibody	Hospitalization (mandated)	Median time to CRS onset	Notes
Lymphoma			
Epcoritamab	Cycle 1 Day 15 (24 hours post-dose)	21 hours	Subsequent admissions may be needed if patients developed CRS grade 2 or above
Glofitamab	Cycle 1 Day 8 (24 hours post-dose)	14 hours	
Myeloma			
Elranatamab	Cycle 1 Day 1 (first step-up dose) and Day 4 (2nd step-up dose)	Two days	Patients should be hospitalized for 48 hours after first step-up dose and for 24 hours after second step-up dose
Small cell cancer (EAMS scheme)			
Tarlatamab	Cycle 1 Day 1 (step-up dose) and Day 8 (target dose)	13.5 hours	Patients should be hospitalised for 24 hours from start of infusion. Recommend that patients remained within one-hour from hospital for 48 hours from start of infusion.

2b. Monitoring of CRS

- Patients will be admitted to hospital for CRS monitoring as specified in individual BsAbs protocol.
- During the inpatient stay, patients will have routine 4-hourly observations from time of treatment administration. This includes measuring of temperature, heart rate, blood pressure, oxygen saturations and respiratory rate.
- Frequency of monitoring will need to be increased in the event of CRS as outlined in table below. (Please see CRS grading in section 2e)

CRS grade	0	1	2	3-4
Observations	4-hourly	2-hourly	2-hourly	Continuous

2c. Clinical presentation of CRS

- CRS typically presents with a fever (temp ≥38 °C).
- General symptoms: malaise, rigors, fatigue, anorexia, myalgia, headache, rash, arthralgia
- Organ dysfunction: Hypotension, circulatory collapse, tachycardia, tachypnoea, hypoxia, renal failure

2d. Clinical assessment

- All patients who spiked a temperature requires immediate medical review.
- Clinical review: Assess patient for symptoms/signs of infection, neurological changes, evaluate other causes of fever.
- Blood tests: Send blood cultures, full blood count, U&E, liver function test, bone profile, phosphate, magnesium, LDH, CRP, ferritin, and coagulation profile.
- Other investigations (if indicated): Chest x-ray, ECG, viral respiratory swab.
- Start empirical antibiotics in neutropenic patients and consider antibiotics in non-neutropenic patients if unable to exclude sepsis.
- Differential diagnosis: CRS symptoms can mimic infection and therefore it is essential septic screen is done. Other differentials include haemophagocytic lymphohistocytosis (HLH)/macrophage activation syndrome (MAS), tumour lysis syndrome, disease progression.

2e. CRS grading

- In patients suspected of having CRS, severity is grade based on ASTCT Consensus grading as outlined in table below.
- Management will depend on the grade 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		
Hypotension	None	Responsive to IV fluids	Requiring a vasopressor	Requiring multiple vasopressors
		And/or		
Hypoxia	None	Oxygen requirement <6 L/min	Oxygen requirement ≥6 L/min	Requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

2f. CRS Management

- Please also refer to local Trust Policy of CRS management
- **All patients with CRS regardless of grade should be discussed with a consultant.**
- Early management of CRS may prevent progression to a higher grade.
- The table below summarises the management of CRS according to grade.

CRS	Grade 1	Grade 2	Grade 3	Grade 4
Management	Ward based monitoring	Alert Intensive Care Unit	Transfer to Intensive Care Unit	
	Medical review, initiate septic screen and consider empirical antibiotics. Treat symptoms with paracetamol and/or intravenous fluid			
	-If lasts >48 hours, consider tocilizumab **-**Consider early tocilizumab in selected cases (see notes)	-Give tocilizumab -Consider corticosteroids	Administer tocilizumab and corticosteroids	
Subsequent treatment	Ensure resolution of symptoms prior to next treatment	-Ensure resolution of symptoms prior to next treatment -Consider slower infusion rate -Monitor patients for at least 24 hours post infusion	**First episode:** Ensure resolution of symptoms prior to next infusion. Hospitalization for at least 24 hours (48 hours for elranatamab) **Recurrent Grade 3 CRS:** Permanently discontinue	Permanently discontinue

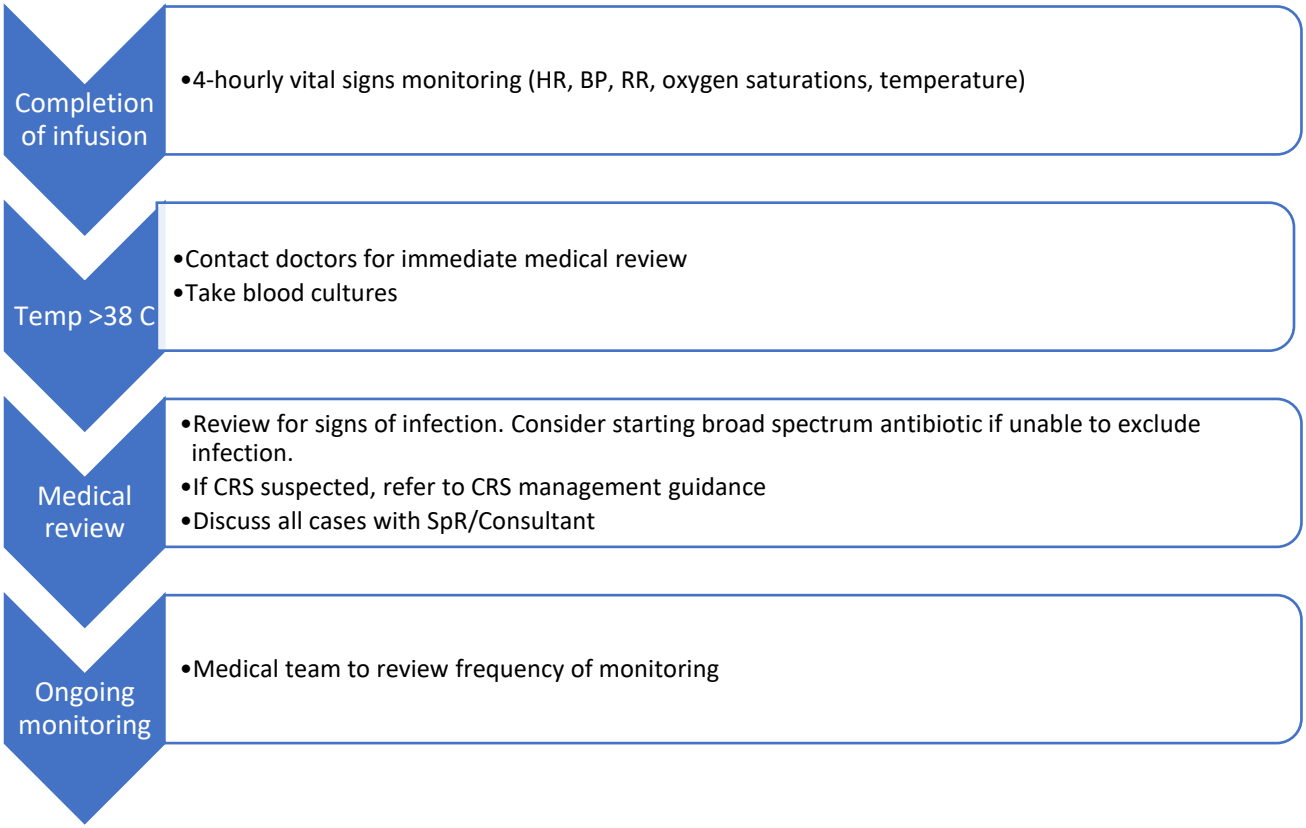
- <u>Tocilizumab</u>
  - Ensure a dose of tocilizumab is immediately available on the ward or pre-specified location prior to starting BsAbs treatment. Access to an additional dose of tocilizumab within 8 hours of use of the previous dose must be ensure.
  - Tocilizumab dose 8 mg/kg (maximum dose 800 mg) is administered over 60 minutes.
  - Another dose can be repeated after 8 hours. If no improvement in symptoms after 2 doses, consider starting corticosteroids.
  - In total, up to 4 doses can be used with interval between doses of at least 8 hours.
  - Tocilizumab should be considered earlier in older and/or more frail patients who might tolerate higher grade CRS less well.

- <u>Corticosteroids</u>
  - When indicated for CRS, start dexamethasone IV 10-20 mg every 6 hours or methylprednisolone 1-2 mg/kg/day. If no improvement, escalate to

methylprednisolone 1000 mg/day. Consider addition of other immunosuppressive agents if persistent CRS.
    - Steroids can be used concurrently with tocilizumab.
    - Review and taper corticosteroid dose once CRS is controlled. Please discuss with consultant prior to dose reduction.

- Supportive management
    - Start paracetamol PO/IV 1 g QDS.
    - IV fluids replacement if hypotensive and oxygen if hypoxic.
    - Consider starting broad spectrum antibiotic if unable to exclude concurrent infection.

Flow chart summarising CRS monitoring procedure.



3. Neurological toxicities

Neurologic toxicities associated with BsAbs are usually mild and less frequent compared to CAR-T cells therapy. This term encompassed a wide range of adverse events including headache, dizziness, confusion, tremor, neuropathy, encephalopathy and ICANS.

3a. Clinical assessment and monitoring

- ICANS and ICANS-like symptoms can occur without preceding CRS.
- Clinical symptoms: Confusion, delirium, deterioration in handwriting, expressive and receptive aphasia, loss of attentiveness, agitation, depressed level of consciousness, tremor, loss of motor coordination and seizures.
- Patients and their caregivers should be educated on these symptoms and alert medical team if symptomatic.

- **Routine ICE testing is not required in the absence of neurological signs or symptoms.**
- Immune Effector Cell Encephalopathy (ICE) score should be performed if patients developed neurological symptoms.
- ICE scoring system: This is a 10-point neurological assessment tool and one point is assigned to each of the following:

Domain	Year	Month	City	Hospital	Object 1	Object 2	Object 3	Follow command	Hand-writing	Attention*	Total
Score											/10
	Handwriting:										

***** Attention to count backward from 100 by 10

3b. ICANS Management

- **All patients suspected of having ICANS should be discussed with a consultant.**
- Management will depend on the grade of ICANS.
- The table below summarises ICANS grading according to ASTCT criteria.

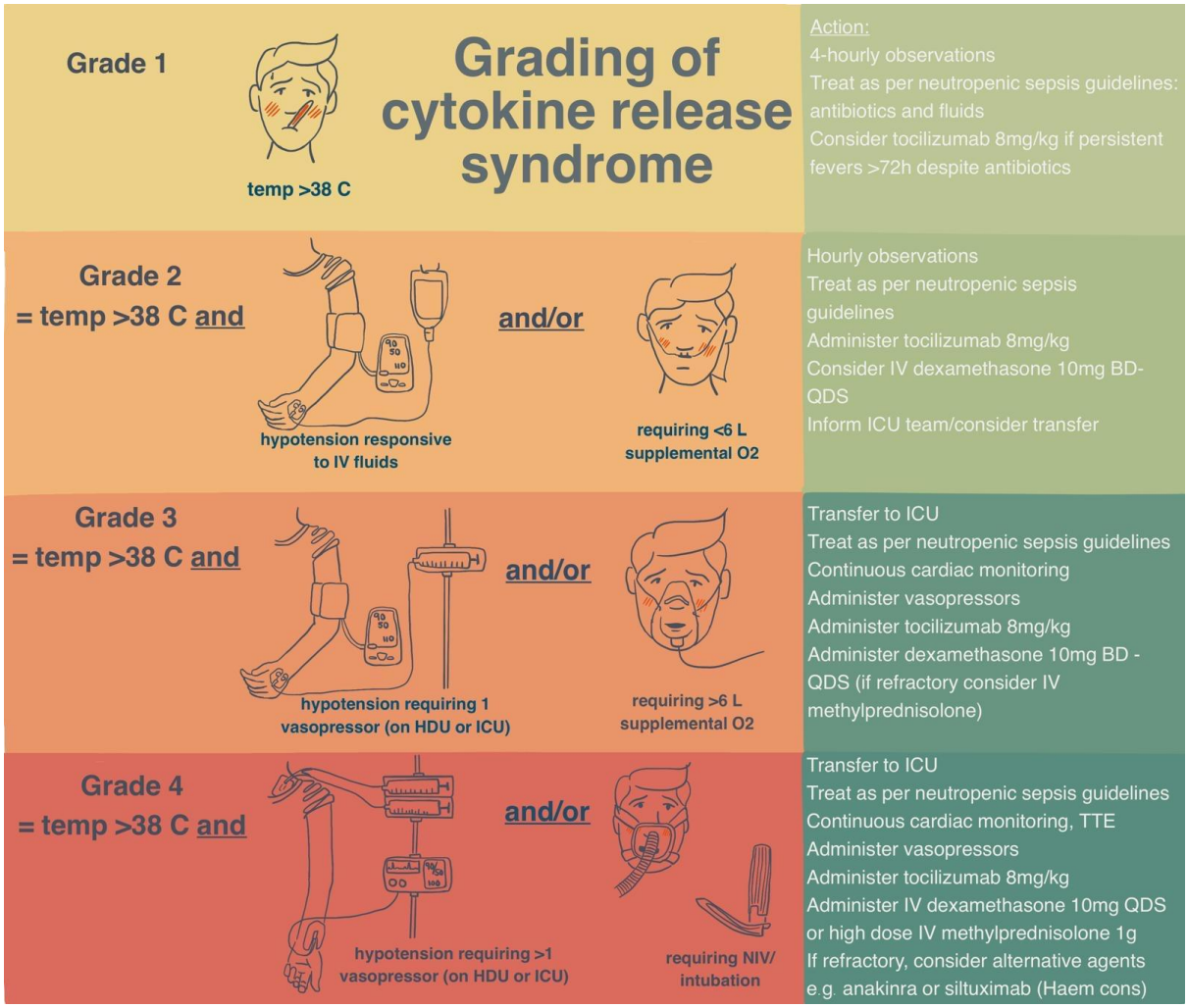
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between.
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP	N/A	N/A	Focal/local oedema on neuroimaging	Cerebral oedema. Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

- The table below summarises ICANS investigations and management according to grade.

<table>
<tr><th></th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td rowspan="2">Monitoring frequency</td><td>4-hourly</td><td>4-hourly</td><td>4-hourly</td><td>4-hourly (where feasible)</td></tr>
<tr><td colspan="4">8 hourly ICE score assessment</td></tr>
<tr><td rowspan="3">Investigations</td><td>Urgent CT head</td><td>Urgent MRI brain</td><td colspan="2">Urgent MRI brain if not previously done. Consider repeat brain imaging if no improvement in >48 hours</td></tr>
<tr><td></td><td>Consider lumbar puncture</td><td colspan="2">Lumbar puncture for cell count, protein, glucose, cytospin, virology (HSV, VZV, CMV, adeno, HHV-6, JC virus)</td></tr>
<tr><td colspan="4">Other investigations after discussion with neurology i.e. EEG</td></tr>
<tr><td rowspan="6">Management</td><td>Alert GICU outreach team</td><td>GICU review</td><td colspan="2">Transfer to GICU</td></tr>
<tr><td colspan="4">Supportive care: Assess swallow, covert oral medications to intravenous if impaired.
Avoid medications causing CNS depression unless required for agitation</td></tr>
<tr><td>-IV dexamethasone 10mg stat (Single dose).</td><td>-IV dexamethasone 10mg bd. If no improvement after 48hrs increase to qds for 1-3 days</td><td>-IV dexamethasone 10mg qds for 1-3 days If no improvement after 48hrs switch to methylprednisolone as per grade 4 ICANS</td><td>-IV Methylprednisolone 1000mg/day for 3 days, then 250mg bd for 2 days, then 125mg bd for 2 days, then 40mg bd for 2 days</td></tr>
<tr><td>N/A</td><td>N/A</td><td colspan="2">Anakinra 200mg s/c od for steroid refractory grade 3/4 ICANS</td></tr>
<tr><td colspan="2">Consider levetiracetam 500 mg BD PO/IV</td><td colspan="2">Levetiracetam 500 mg BD PO/IV
Follow neurology guidance if non-status or status epilepticus present</td></tr>
<tr><td colspan="4">Administer tocilizumab if concurrent CRS</td></tr>
<tr><td>BsAbs treatment</td><td colspan="2">Withhold until resolution of event</td><td>First episode: Ensure resolution of symptoms prior to next dose

Recurrent Grade 3: Permanently discontinue treatment</td><td>Permanently discontinue treatment</td></tr>
</table>

4. Appendix 1 – CRS grading and management crib sheet



With thanks to Dr Sophie Evans

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