Management of Immune Cell Associated Neurotoxicity Syndrome (ICANS)

INTRODUCTION

This document has been developed to assist management of Immune Cell Associated Neurotoxicity Syndrome (ICANS) in patients receiving bispecific antibody therapy. It is primarily intended for patients receiving:

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

It will also provide a guide for patients treated with alternative bispecific antibody therapy or chimeric antigen receptor T-cell therapy, although drug-specific guidelines should be followed in the first instance.

Bispecific antibody therapies target antigens expressed cancer cells (e.g. CD20) and T-cells (CD3). The interaction between tumour cell, bispecific antibody and host T-cell enhances cytotoxic T-cell activity against cancer cells. Although efficacious, it is important to recognise that they are associated with specific toxicities related to their mode of action, including Cytokine Release Syndrome (CRS) and Immune cell Associated Neurotoxicity Sydrome (ICANS). The management of CRS is covered in a separate treatment guideline: https://www.gloshospitals.nhs.uk/media/documents/Cytokine_Release_Syndrome_Guideline.pdf

IMMUNE CELL ASSOCIATED NEUROTOXICITY SYNDROME

ICANS is defined as a disorder characterised by a pathological process involving the CNS following any immune effector therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells[5]. It can initially manifest as a tremor, dysgraphia, expressive dysphasia and inattention, headache and lethargy; it may subsequently progress to global aphasia, altered consciousness, weakness, seizures and cerebral oedema.

The pathology of ICANS is poorly understood, but is thought to relate to pro-inflammatory cytokines, disruption of the blood brain barrier and subsequent neuronal injury. ICANS typically occurs 2-4 days after the onset of severe CRS, although can occur independently of CRS.

The frequency of neurotoxicity varies between bispecific products:

- Epcoritamab – all grades: 6%, grade ≥3: 1%[6]
- Glofitamab – all grades: 8%, grade ≥3: 3%[7]
- Blinatumumab – all grades: 45-53%, grade ≥3: 9-13%[8,9]
- Elranatamab – all grades: 3%, grade ≥3: none[10]
- Teclistamab – all grades 3%, grade ≥3: none[11]

ICANS should be suspected in anyone presenting with new onset neurological symptoms or signs following bispecific antibody or CAR-T cell therapy. The ICE score (Table 1) is a validated assessment of encephalopathy that is easy to perform at the bedside[12]. Example ICE assessment record sheets are in **Appendix 1**.

Table 1. ICE score

Orientation	Orientation to year, month, city, hospital **(4 points)**
Naming	Name 3 objects e.g. point to clock, pen, button **(3 points)**
Following commands	Follow simple commands e.g. close your eyes and stick out your tongue **(1 point)**
Writing	Write a standard sentence e.g. the cow jumped over the moon **(1 point)**
Attention	Count backwards from 100 by 10 **(1 point)**

ICANS is graded according to American Society for Transplantation and Cellular Therapy (ASTCT) grading system[12] (Table 2):

Table 2. ASTCT ICANS Consensus Grading

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2 *or* awake with global aphasia	Unrousable
Consciousness†	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus only	Unrousable or requires vigorous or repetitive tactile stimuli
Seizure	n/a	n/a	Any clinical seizure focal or generalised that resolves rapidly *or* nonconvulsive seizure on EEG that resolves with intervention	Life-threatening prolonged seizure (>5 min) *or* repetitive clinical or EEG seizure without return to baseline in between
Motor findings	n/a	n/a	n/a	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP / cerebral oedema	n/a	n.a	Focal/local oedema on neuroimaging*	Diffuse cerebral oedema on neuroimaging, decebrate or decorticate posturing, cranial nerve VI palsy, papilloedema or Cushing's triad

† A depressed level of consciousness should be attributed to no other cause e.g. sedating medication

* Intracranial haemorrhage with or without associated oedema is not considered neurotoxicity

ICE SCORE MONITORING

Monitoring for ICANS using the ICE score is mandated for:

- Baseline pre-treatment for all bispecifics
- Any patient with suspected ICANS – 8-hourly
- Elranatamab – twice daily as inpatient and for 48 hours as an outpatient for the first cycle
- Blinatumumab – twice daily for 14 days

For Glofitamab, Epcoritamab and Teclistamab, routine ICE score monitoring is not mandated, but should be started 8-hourly for any patient with suspected ICANS.

MANAGEMENT OF IMMUNE CELL ASSOCIATED NEUROTOXICITY SYNDROME

All reactions grade 1 or above should be discussed with a Consultant Haematologist.

ICANS should be suspected in anyone presenting with new onset neurological symptoms or signs following bispecific antibody or CAR-T cell therapy. If suspected, perform an neurological examination and ICE score, and treat according to the ASTCT grade (Table 3):

Table 3. ICANS management guidance – Epcoritamab, Glofitamab and Elranatamab

	Grade 1	Grade 2	Grade 3	Grade 4
Supportive care	Close monitoring (neurological examination and ICE score every 8 hours) Rule out other causes of neurological symptoms e.g. infection, haemorrhage, drugs, electrolyte/metabolic disturbance and CNS disease. Refer to Neurology. Consider performing CT head, EEG, MRI or LP, as appropriate. Consider non-sedating anti-seizure medication (e.g. Levetiracetam 500mg bd, up to 2000mg bd) until ICANS resolves Consider tocilizumab if concurrent CRS (Consultant decision – use repeated doses with caution and consider alternative anticytokine therapy, if available). See CRS guideline.			
		Alert DCC	Transfer to DCC	Transfer to DCC
Epcoritamab	Dexamethasone 10mg iv every 12 hours, followed by taper once grade ≤1	Dexamethasone 10mg iv every 12 hours, followed by taper once grade ≤1	Dexamethasone 10-20mg iv every 6 hours, followed by taper once grade ≤1 If no response, Methylprednisolone 1000mg daily iv	Dexamethasone 10-20mg iv every 6 hours, followed by taper once grade ≤1 If no response, Methylprednisolone 1000mg daily iv
	Hold until resolution	Hold until resolution	**First episode**: Delay until complete resolution **Second episode**: Permanently discontinue	Permanently discontinue
Glofitamab	No specific guidance provided by Roche. It is reasonable to follow ICANS management as per Epcoritamab			
Elranatamab	If persistent symptoms >48 hours consider Dexamethasone 10mg iv every 6 hours until resolution to grade ≤1, then taper	Dexamethasone 10mg iv every 6 hours until resolution to grade ≤1, then taper	Dexamethasone 10mg iv every 6 hours until resolution to grade ≤1, then taper If refractory, consider Methylprednisolone 1g daily for 3 days. Taper once symptoms improve	Methylprednisolone 1g daily for 3 days. Taper once symptoms improve
	Hold until resolution	Hold until resolution	**First episode:** Hold until resolution **Second episode**: Permanently discontinue	Permanently discontinue

Teclistamab	-	Dexamethasone 10mg iv every 6 hours until resolution to Grade≤1, then taper	Dexamethasone 10mg iv every 6 hours until resolution to Grade≤1, then taper	Methylprednisolone 1g daily for 3 days. Taper once symptoms improve
	Concurrent CRS: Consider tocilizumab*	**Concurrent CRS:** Administer tocilizumab*. If no improvement, add Dexamethasone 10mg iv every 6 hours until resolution to Grade≤1, then taper	**Concurrent CRS:** Administer tocilizumab*. In addition, add Dexamethasone 10mg iv every 6 hours until resolution to Grade≤1, then taper	**Concurrent CRS:** Administer tocilizumab*. In addition, add Methylprednisolone 1g daily for 3 days. Taper once symptoms improve
	Hold until resolution	Hold until resolution	**First episode:** Hold until resolution **Second episode**: Permanently discontinue	Permanently discontinue

* Tocilizumab 8mg/kg iv over 1 hour (max. 800mg). Repeat every 8 hours as needed. Maximum 4 doses

Blinatumomab[13]	**Management is based on CTCAE grading, which differs from ASTCT**			
	-	Administer dexamethasone 8mg 8 hourly for up to 3 days, then reduce stepwise over 4 days	Administer dexamethasone 8mg 8 hourly for up to 3 days, then reduce stepwise over 4 days	Administer dexamethasone 8mg 8 hourly for up to 3 days, then reduce stepwise over 4 days
	Continue at same dose level	Continue at same dose level	Interrupt infusion until grade ≤1 for at least 3 days and then restart at 9mcg/day. See protocol for full details	Permanently discontinue

CAR-T	Liaise with patient's CAR-T centre (usually Bristol Royal Infirmary)

CONTACTS

- **Haematology**: Bleep 1150. 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
- **Pharmacy:** on-call out of hours via Switchboard

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13. Table 5.2. Table of dose modifications for adverse events possibly, probably, or definitely related to blinatumomab *in:* ECOG-ACRIN Cancer Research Group 2014. A Phase III Randomised trial of blinatumomab for newly diagnosed BCR-ABL-negative B lineage acute lymphoblastic leukemia in adults. Available at: https://cdn.clinicaltrials.gov/large-docs/22/NCT02003222/Prot_SAP_000.pdf [Accessed 17th October 2024]

APPENDIX 1

ICE ASSESSMENT RECORD SHEET

NHS
Gloucestershire Hospitals
NHS Foundation Trust

Name:

Date of Birth: DD / MM / YYYY

MRN Number:

NHS Number:

(OR AFFIX HOSPITAL LABEL HERE)

ICE SCORE	Year	Month	City	Hospital	Object 1	Object 2	Object 3	Command	Writing	Serial 10s	Score
Date and time											
Staff signature	Patient handwriting										
Date and time											
Staff signature	Patient handwriting										
Date and time											
Staff signature	Patient handwriting										
Date and time											
Staff signature	Patient handwriting										