Management of Immune Cell Associated Neurotoxicty Syndrome (ICANS)

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This document has been developed to assist management of Immune Cell Associated Neurotoxicity Syndrome (ICANS) in patients receiving bispecific antibody therapy			
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AMENDMENT HISTORY
(Complete for existing documents that need amendment within their 3 year life span)

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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.

However, drug-specific guidelines should also be followed.

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 Syndrome (ICANS).

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 cells5

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%

Glofitamab – all grades: 8%, grade ≥3: 3%

Blinatumumab – all grades: 45-53%, grade ≥3: 9-13%

Elranatamab – all grades: 3%, grade ≥3: none

Tarlatamab – all grades 7-28%, grade ≥ 3: 0-5%

ICANS should be suspected in anyone presenting with new onset neurological symptoms or signs following bispecific antibody or CAR-T cell therapy.
IMMUNE CELL ASSOCIATED NEUROTOXICITY SYNDROME

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
- For all bispecifics the drug specific protocol should be checked for ICANS risk and monitoring requirements.

MANAGEMENT OF IMMUNE CELL ASSOCIATED NEUROTOXICITY SYNDROME
General Principles:

- **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.
- **Consider seizure prophylaxis** for products known to be associated with ICANS or in patients at higher risk of seizure, such as those with seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions. Consider non-sedating anti-seizure medication (e.g. Levetiracetam 500mg bd, up to 2000mg bd) until ICANS resolves
- **Initiate neurology consultation in patients with signs of neurotoxicity**
- **Neuroimaging of the brain) for ≥ G2 neurotoxicity** (MRI with and without contrast or CT if MRI is not available or feasible. For persistent grade ≥ 3 neurotoxicity, consider repeat neuroimaging (MRI or CT) every 2-3 days if no improvement. ICANS-related MRI abnormalities include T2 fluid-attenuated inversion recovery (T2-FLAIR) hypersignals, diffusion restriction, diffuse pachymeningitis, or cerebral edema.
- **Lumbar puncture for ≥ G3 neurotoxicity** and may consider for G2. Rule out any CNS infections. An increase in CSF protein and cell count in absence of any growth would suggest severity of neuro-inflammation.
- **EEG evaluation for unexplained altered mental status** to assess seizure activity or for ≥ G2 neurotoxicity
- **Monitor and correct severe hyponatremia**
- **Patients should be transferred to HDU/ICU if grade 3/4 toxicity**
- **First treatment is generally high dose intravenous steroids** but is dependent on specific drug SOP
- **Check specific drug protocol for steroid administration guidance.**
- **Consider tocilizumab if concurrent CRS** (Consultant decision – use repeated doses with caution and consider alternative anticytokine therapy, if available).
- **Drug rechallenge decisions should be made by consultant and as per product SPC.**
- **Once sustained clinical improvement is observed steroids can be taper**; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier
- **Prophylactic antibiotics or other antimicrobials as clinically appropriate.**
- **Rigorous control of blood pressure and electrolytes** (particularly calcium and magnesium).

Every patient should have a baseline ICE assessment

Baseline CT or MRI brain is recommended

Undertake a twice daily ICE assessment

If ICANS is suspected, immediately contact the oncology/haematology team

Management should be guided by the haematoncology team in conjunction with a neurologist

If concurrent CRS also follow the CRS management algorithm

If ICANS is suspected a thorough neurological examination should be performed. Investigations should include:

EEG
MRI/CT brain
Frequent monitoring for cognitive function E.g. handwriting tests
Three times daily ICE assessment
Consider LP

Alternative causes of neurological dysfunction such as infection, opioid toxicity, haemorrhage, drugs, electrolyte imbalance or metabolic acidosis should be considered and treated

Supportive Care

Avoid medications that suppress consciousness

Assess swallow (aspiration precautions)
Manage agitation
Assess papillodema
IV hydration

Grade 1 ICANS ICE score 7-9 Awakes spontaneously	• Close monitoring • Neurological examination • Three times daily ICE score • Consider seizure prophylaxis • If persistent symptoms >48hrs discuss treatment options with neurology consultants and consider steroids • Consider tocilizumab if concurrent CRS
Grade 2 ICANS ICE score 3-6 Awakes to voice	• Regular neurological observations • Three times daily ICE score • Administer IV dexamethasone [10mg – 20mg BD – QDS] (Check drug specific SPC) • Inform ICU/outreach team • Consider tocilizumab if concurrent CRS
Grade 3 ICANS ICE score 0-2 Awakes only to tactile stimuli Seizures that resolve rapidly Focal cerebral oedema on imaging	• Consider transfer to ICU/Neuro ICU • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptics for seizures • Administer IV dexamethasone [10mg – 20mg QDS] (Check drug specific SPC) • If refractory, consider IV methylprednisolone 1g or alternative agents (e.g anakinra or siltuximab) • Administer tocilizumab if concurrent CRS
Grade 4 ICANS ICE score 0 Unrousable Prolonged (>5min) or frequent seizures Motor weakness Diffuse cerebral oedema on imaging	• Transfer to ICU/Neuro ICU • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptics for seizures • Check drug specific SPC • Administer IV methylprednisolone 1g and/or alternative agents (e.g anakinra or siltuximab) • Administer tocilizumab if concurrent CRS

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APPENDIX 1

ICE ASSESSMENT RECORD SHEET

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										