[Clinic or Hospital Logo]

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Adult Monitoring and Management of Neurotoxicity Associated with Bispecific T-Cell Engagers (Example 2)

Where Did This Resource Come From?	
Clinic/Hospital Type	Large community oncology clinic
What's Unique?	• CRS management takes into consideration presence/absence of ICANS • Includes plan for neuroimaging for higher grades of ICANS

1. Purpose

To provide a framework for the monitoring and management of neurotoxicity in patients receiving bispecific T-cell engager (BTCE) therapy in the inpatient setting.

2. Scope

This Standard Operating Procedure (SOP) outlines the responsibilities, procedures, and monitoring requirements for all clinical staff involved in the inpatient management of patients receiving BTCEs, with a specific focus on the identification, assessment, and management of neurotoxicity.

3. Definitions

- **Bispecific T-Cell Engager (BTCE)**: Synthetic proteins that bind two distinct antigens: one targets the CD3 protein on T cells, and the other targets a specific cancer antigen, redirecting T cells to activate an antitumor immune response.
- **Cytokine Release Syndrome (CRS):** A potentially severe inflammatory response that occurs when immune effector cell therapy leads to the release of cytokines into the bloodstream. This syndrome causes symptoms such as fever, hypotension, hypoxia, chills, tachycardia, dyspnea, nausea, rash, headache, and myalgia.

- **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** A neurological complication caused by inflammation in the central nervous system following immune effector cell therapy. Symptoms can range from mild, such as headache and confusion, to severe, including seizures and coma, which may be life-threatening.
- **Neurotoxicity**: Side effects that impact the nervous system, including those caused by immunotherapy.
- **Cytokine Release Syndrome (CRS):** A potentially severe inflammatory response that occurs when immune effector cell therapy leads to the release of cytokines into the bloodstream. This syndrome causes symptoms such as fever, hypotension, hypoxia, chills, tachycardia, dyspnea, nausea, rash, headache, and myalgia.
- **Immune Effector Cell Encephalopathy (ICE) Score**: A clinical scoring tool for assessing the severity of neurological symptoms associated with immune effector cell therapies.

4. Workup[2]

- Pertinent history and physical exam
- Review medications including last dose of antipyretic therapy, steroids, or anti-cytokine therapy
- Perform ICE score (see below) on all patients with neurologic symptoms
- Assess for alternate cause of symptoms; consider performing CT head, electroencephalogram (EEG), MRI, or lumbar puncture, as appropriate
- Assess for concurrent symptoms of CRS (e.g., fever, hypoxia, and hypotension); treatment of CRS can occur concurrently if appropriate
- If any concern for neurological adverse effects (AE) exists, patient should be evaluated in outpatient center or emergency department (ED). If any worsening symptoms (e.g., somnolence, worsening confusion, weakness, etc.), patients should be promptly referred to the ED
- As neurological adverse events have been uncommonly observed across BTCE clinical trials, *routine* neurologic testing for patients who are asymptomatic with normal neurological examination at baseline is not required.

ICE Scoring:

Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backward from 100 by 10	1 point

5. Management

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is arousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is arousable or requires vigorous or repetitive tactile stimuli to arouse Stupor or coma
Seizure			Any clinical seizure focal or generalized that resolves rapidly; or non-convulsive 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				Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure (ICP) / Cerebral Edema			Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or Cranial nerve VI palsy; or papilledema; or Cushing's triad

[a] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

[b] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication).

ICANS Grade	Concurrent CRS	No Concurrent CRS
Grade 1 (ICE 7-9)	• Should be evaluated in office • Dexamethasone 16 mg PO X 1 • Administer tocilizumab 8 mg/kg (max 800 mg) IV. May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total. • Observation	• Supportive care and observation
Grade 2 (ICE 3-6)	• **Admit to hospital for monitoring** • Administer tocilizumab 8 mg/kg (max 800 mg) IV. May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total. • If no improvement after tocilizumab, administer dexamethasone 10 mg IV every 6 hours until grade ≤1	• **Admit to hospital for monitoring** • Supportive care • Dexamethasone 10 mg IV, repeat every 6 hours if no improvement until grade ≤1
Grade 3 (ICE 0-2)	• **ICU care is recommended** • Administer tocilizumab 8 mg/kg (max 800 mg) IV. May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total. • Administer dexamethasone 10 mg IV with first dose of tocilizumab and repeat every 6 hours until ≤1 or may use methylprednisolone 1 mg/kg IV every 12 hours	• **ICU care is recommended** • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity

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Grade 4 (ICE 0)	• **ICU care** • Administer tocilizumab 8 mg/kg (max 800 mg) IV. May repeat every 8 hours to a max of 3. doses in 24 hours and 4 doses total • Methylprednisolone 1000 mg/day IV for 3 days followed by a rapid taper • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines	• **ICU care** • Consider mechanical ventilation • Methylprednisolone 1000 mg/day IV for 3 days • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines

6. Records and Documentation

- Document any neurologic toxicity in electronic medical record including adverse event grade, ICE score, medications, neurology consultation (if applicable), and any ICU stays.

7. References

1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.
2. 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.

8. Revision History

Version #	Date	Description of Changes	Reviewed / Approved By