[Clinic or Hospital Logo]

SOP #	[Number]
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Owner	[Name]
Department	[Name]
Tags	[Tags]
Applicability	[Name of sites]

Adult Monitoring and Management of Neurotoxicity Associated with Bispecific T-Cell Engagers (Example 1)

Where Did This Resource Come From?	
Clinic/Hospital Type	Academic medical center
What's Unique?	• Considers use of anti-seizure prophylaxis • Considers Neurology consult in lower grade • More frequent dexamethasone dosing interval in lower grade • Provides guidance on how to approach subsequent doses (e.g. inpatient administration) • Provides a higher dose range for anakinra and more frequent dosing interval

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.
- **Immune Effector Cell Encephalopathy (ICE) Score**: A clinical scoring tool for assessing the severity of neurological symptoms associated with immune effector cell therapies.
- **Neurotoxicity**: Side effects that impact the nervous system, including those caused by immunotherapy.

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, electrocephalogram (EEG), MRI, or lumbar puncture, as appropriate
- Assess for concurrent symptoms of CRS; 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

Grade	ICE Score	Level of Conscious-ness	Seizure	Motor Findings	Raised intracranial pressure / Cerebral Edema	Management
Any Grade						-Withhold agent until ICANS resolves; -Consider non-sedating, antiseizure medication for seizure prophylaxis (e.g., levetiracetam)
Grade 1 Appropriate patients may be considered for outpatient management	7-9	Awakens spontaneously				-Consider observation/monitoring in outpatient setting -Consider dexamethasone IV 10 mg x 1 dose -Monitor neurologic symptoms and consider neurology consult
Grade 2	3-6	Awakens to voice				-Administer dexamethasone 10 mg IV every 6-12 hours until resolution to grade 1 or less, then taper -Monitor neurologic symptoms and consider neurology consult -With next dose, consider hospitalization for ICANS monitoring

Grade 3	0-2	Awakens only to tactile stimulus	Any clinical seizure, focal or generalized, that resolves rapidly or non-convulsive seizure on EEG that resolve with intervention		Focal / local edema on neuroimaging	-Administer dexamethasone 10 mg IV every 6 hours until resolution to grade 1 or less, then taper -Admit to ICU for neurologic monitoring -Neurology consult mandatory If **1st occurrence** of grade 3 ICANS: -Withhold agent until ICANS resolves -With the next dose of agent, required hospitalization for ICANS monitoring If **recurrent** grade 3 ICANS: -Permanently discontinue agent
Grade 4	0 (unable to perform ICE score)	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma	Life-threatening prolonged seizure (>5 minutes) or repetitive clinical or electrical seizures without return to baseline in between	Deep focal motor weakness, such as hemi-paresis or paraparesis	Diffuse cere-bral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Crushing's triad	-Permanently discontinue agent -Admit to intensive care unit (ICU) for neurologic monitoring -Administer dexamethasone 10 mg IV every 6 hours until resolution to grade 1 or less, then taper. -Consider changing to methylpred-

						nisolone 1000 mg IV daily x 2-3 days if unstable, not improving, or deteriorating -Neurology consult mandatory -Consider anakinra 100-200 mg IV TID x 72 hours (consult clinical pharmacist for management) if persistent symptoms. Rapid taper with clinical improvement.

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