Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) from CAR-T Therapy

BACKGROUND

Neurotoxicity from CAR-T therapy can occur as part of cytokine release syndrome (CRS) or as an independent process. The underlying pathophysiology for neurologic toxicity from CAR-T therapy is not fully understood. CAR-T cells in the CNS may play a role. However, the heightened systemic inflammatory and cytokine state resulting from CAR-T therapy may also be a factor.

The symptoms and manifestations of neurotoxicity are broad and range from confusion/altered mental status to seizures. Routine monitoring is critical in patients receiving CAR-T therapy to identify neurologic symptoms early and neurology should be consulted for any patients that exhibit early signs/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

These guidelines were developed based on the package inserts for the currently FDA approved CAR T cell products and published consensus guidelines from several clinical oncology and cancer immunology organizations.[1-4] They are intended to provide a framework for the management of neurotoxicity in CAR-T patients. They are not intended to replace clinical judgement and provider discretion. Each patient should be evaluated, and an attending physician should be notified at the first signs/symptoms of neurotoxicity and should be involved in each therapeutic decision.

Immune Effector Cell-Associated Encephalopathy (ICE) Score

The ICE score is a neurological assessment score that quantifies the severity of neurologic impairment. Each item in the assessment is associated with the point value indicated. The higher the score the better, with an ICE score of 10 indicating a normal neurological assessment. The score should then be considered with other assessments to accurately grade the patients ICANS as is outlined in management of ICANS below.

Table 1. ICE Score

Assessment	Score (10 = No impairment)
Orientation	
• Year	1
• Month	1
• City	1
• Hospital	1
Name 3 objects (example: point to clock, pen, and button)	3
Ability to follow simple commands (e.g. “Show me 2 fingers” or “Close your eyes and stick out your tongue”	1
Ability to write a standard sentence	1
Ability to count backwards from 100 by 10	1
Total	10

ICANS Management: Corticosteroid Therapy

Grade	Intervention
Grade 1 ICE Score: 7-9 (mild impairment) Level of consciousness: awakens spontaneously Seizure: none motor Findings: none elevated ICP/cerebral edema: none	All patients with ICANS should receive levetiracetam 500 mg po bid. See below for taper details* Consult Neurology Service Supportive care as outlined below
Grade 2 ICE Score: 3-6 (moderate impairment) Level of consciousness: awakens to voice Seizure: none motor Findings: none elevated ICP/cerebral edema: none	All patients with ICANS should receive levetiracetam 500 mg po bid. See below for taper details* Administer dexamethasone 10 mg IV every 6 to 12 hours until improvement to grade 1 ICANS. Then taper‡
Grade 3 ICE Score: 0-2 (severe impairment) Level of consciousness: awakens only to tactile stimulus Seizure: any clinical seizure (focal or generalized) that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention Motor Findings: none ICP/cerebral edema: elevated ICP; focal/local edema on neuroimaging	All patients with ICANS should receive levetiracetam 500 mg po bid. See below for taper details* Guidelines regarding management of *seizures, cerebral edema and elevated intracranial pressure* are included in **Appendix 1** Give dexamethasone 10 mg IV every 6 hours until improvement to grade 1 ICANS. Then taper‡ Can increase to 20 mg IV every 6 hours if there is evidence of focal seizure

Grade 4 ICE Score: critical condition, and/or obtunded and cannot perform assessment of tasks Level of consciousness: unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma Seizure: 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 Elevated ICP/Cerebral edema: diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; cranial nerve VI palsy; papilledema; Cushing's triad	All patients with ICANS should receive levetiracetam 500 mg po bid. See below for taper details* Methylprednisolone IV 500 mg every 12 hours x 3 days. Then taper: 250 mg every 12 hr x 2 days 125 mg every 12 hr x 2 days 60 mg every 12 hr x 2 days

* Suggested levetiracetam taper: 500 mg PO BID x 2 weeks, then taper to 250 mg BID x 1 week, then 250 mg daily x 1 week, then stop.

‡ Suggested steroid taper: once returned to baseline neurologic function, aim to taper steroids over 2-5 days, with decrease of 25-50% every 24-48 hours

Special Considerations:

A*nti-CD19* directed CAR T cell products with *CD28 costimulatory domains*: **Yescarta** (axicabtagene ciloleucel) and **Tecartus** (brexcabtagene autoleucel)

Yescarta: In January 2022, the FDA approved a new label update for Yescarta that allows the use of prophylactic steroids to aid in the management of CRS and ICANS. Based on these recommendations and the observation of high rates of ICANS in patients receiving Yescarta, the following orders have been added to the treatment plan for DLBCL receiving Yescarta:

- Administer levetiracetam 500 mg po bid starting on the day of Yescarta infusion. Taper is outlined below.
- Administer dexamethasone 10 mg daily x3 days starting on the day of Yescarta infusion for patients with DLBCL, *not follicular lymphoma.*

Tecartus: Tecartus uses the same chimeric antigen receptor construct as Yescarta. The following order has been added to the treatment plan for patients receiving Tecartus:

- Administer levetiracetam 500 mg po bid starting on the day of Tecartus infusion. Taper is outlined below.

Appendix:

ICANS Management: Supportive Care, Consultations and Management of Seizures, Elevated ICP and Cerebral Edema

Supportive Measures:

- Supportive Care; aspiration precautions; IV hydration
- Withhold oral intake and assess swallowing. Convert medications and nutrition to IV administration if swallowing is impaired
- Avoid medications causing CNS depression
- Agitation: haloperidol 0.5 mg IV every 6 hours or lorazepam 0.25-0.5 mg IV every 8 hours (monitor closely)
- For Grade 2 consider transfer to ICU, Grade 3 and above requires transfer to ICU; Grade 4 requires ICU support/monitoring; consider mechanical ventilation for airway protection

Consultation/Examination (Begin with Grade 1 ICANS)

- Consult Neurology with Grade 1 or higher Neurotoxicity
- Consider fundoscopic exam to assess for and grading of papilledema
- Consider optic nerve sheath ultrasound to assess for elevated intracranial pressure, optic nerve edema
- Consider brain MRI with and without contrast if able to tolerate. If unable to tolerate prolonged study due to agitation, consider fast sequence brain MIR (including DWI, ADC, Flair, SWI) if feasible. Obtaining imaging should not interfere with direct therapeutic interventions.
- Consider continuous video EEG monitoring following discussion with Neurology
- If EEG demonstrates non-convulsive status epilepticus, treat as outlined in Grade 3
- Consider repeat CT or MRI every 2-3 days if ≥ grade 3 ICANS persists or if new focal neurological deficits develop

Seizures

- Prophylaxis
    - Levetiracetam 500 mg PO BID from cell infusion day through day +14, then taper to 250 mg BID x 1 week, then 250 mg daily x 1 week, then stop. Indications include:
        - DLBCL patients receiving Yescarta
        - Patients receiving Tecartus
        - High risk patients defined as: history of seizure, prior stroke, previous traumatic brain injury, CNS disease involvement, and/or history of seizure with alcohol withdrawal
- Grade 3 (focal or single isolated seizures with return to baseline)
    - Assess airway breathing, and circulation
    - Check blood glucose
    - Lorazepam 2 mg IV; give additional 2 mg IV every 5 min prn up to a total of 0.1 mg/kg to break seizures
    - Levetiracetam 20 mg/kg IV bolus, followed by 1000 mg IV every 12 hr maintenance dosing for seizure control
    - If seizures persist, transfer to ICU if not already and treat with fosphenytoin 20 mg/kg load followed by 100 mg IV every 8 hours to achieve free level of ~ 2
    - Continuous EEG monitoring for refractory seizures and further guidance per neurology consult
- Grade 4
    - If non-convulsive, treat as outlined for management of seizures in Grade 3
    - If convulsive: Lorazepam 2mg IV if weight <60kg, 4mg IV if > 60kg; give additional 2 mg IV every 5 min prn up to a total of 0.1 mg/kg to break seizures
    - Levetiracetam 60 mg/kg IV bolus (max dose 4.5 gm), followed by 1000 mg IV every 12 hr to control seizures

- If seizures persist, add fosphenytoin 20 mg/kg load followed by 100 mg IV every 8 hours to achieve free level of ~ 2
- Continuous EEG monitoring for refractory seizures and further guidance per neurology consult

Elevated ICP/Cerebral edema

- Grade 3
  - Elevate head end of patient's bed to 30 degrees
  - Acetazolamide 1000 mg IV, followed by 250 – 1000 mg IV every 12 hr (adjust dose based on renal function and acid-base balance, monitored 1-2 times/day)
- Grade 4
  - High dose corticosteroids as outlined above
  - Elevate head end of patient's bed to 30 degrees
  - Hyperventilation: goal partial pressure of arterial carbon dioxide (PaCO2) of 28-30 mmHg (maintain for no longer than 12 hr)
  - Hyperosmolar therapy (mannitol or hypertonic saline)
    - Mannitol (20g/dl solution): initial dose 0.5-1 g/kg; maintenance dose 0.25-0.5 g/kg every 6 hr; monitor metabolic profile and serum osmolality every 6 hr. Withhold mannitol if serum osmolality is ≥320 mOsm/kg or the osmolality gap is ≥20
    - Hypertonic saline: 250 mL of 3% hypertonic saline bolus over 15 minutes followed by maintenance at 50-75 mL/hr with target sodium goal as recommended by neurology consultant; monitor electrolytes every 4 hr. Withhold infusion if serum Na reaches ≥155 mEq/L. If imminent herniation – initial 30 mL of 23.4% hypertonic saline over 10-15 minutes via central access or intraosseus access
  - If Ommaya reservoir present, drain CSF to target opening pressure of <20 mmHg
  - Consider Neurosurgery consult for CSF diversion or intracranial monitoring
  - Consider IV anesthetics for burst-suppression pattern on EEG
  - Metabolic profiling every 6 hr
  - Daily CT of head
  - Adjust medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

References:

1. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol 2022;33(3):259-275. DOI: 10.1016/j.annonc.2021.12.003.
2. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2019;25(4):625-638. DOI: 10.1016/j.bbmt.2018.12.758.
3. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer 2020;8(2). DOI: 10.1136/jitc-2020-001511.
4. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol 2021;39(35):3978-3992. DOI: 10.1200/JCO.21.01992.