BC Cancer Protocol for Immune Effector Cell-Associated Neurotoxicity Syndrome Management

Protocol Code	*SCICANS*
Tumour Group	*Supportive Care*
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Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS is associated with certain immune therapies including T-cell engaging bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy. Clinical symptoms indicative of ICANS are **headache, confusion, disorientation, speech disturbances, altered levels of consciousness, seizures and motor weakness**. Symptoms may also include, but are not limited to: lethargy, aphasia, difficulty concentrating, agitation, tremor, and rarely cerebral edema.

When starting immune therapies associated with a risk of ICANS, patients must be closely monitored for early neurological signs and symptoms indicative of ICANS. At initial presentation of altered mental state, consider other differential diagnoses of encephalopathy including infection/sepsis, intracranial hemorrhage, metabolic derangements, and medication-associated encephalopathy.

Neurologic toxicity may occur alone or concurrently with cytokine release syndrome (CRS), often 2 to 4 days after the onset of CRS. Patients with signs of ICANS should also be monitored closely for concurrent CRS. **See the *Supportive Care Cytokine Release Syndrome (SCCRS)* protocol for specific treatment recommendations for CRS.**

ICANS Assessment:

- **At baseline, twice daily during admission, and as indicated during treatment** by nursing or clinical team: Clinical assessment with the ICE (immune effector cell-associated encephalopathy) tool (see Table 1 below)

TESTS:

For ICANS Grade 2 or higher:

- CBC & Diff, platelets, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, uric acid, albumin, creatinine, ALT, alkaline phosphatase, LDH, total bilirubin, lactate, CRP, ferritin, INR, PTT, fibrinogen
  - **If there are any abnormalities:** Labs should be repeated Q4H or at provider discretion and must be repeated prior to discharge
- Consider CT or MRI head and/or EEG to assess for alternate etiologies. Repeat assessment if any persistent abnormalities or if any further clinical changes.
- Consider lumbar puncture. If done, recommend including opening pressure, evaluation for infectious etiologies as well as standard testing including protein, glucose, cell count and differential, as well as flow cytometry for underlying disease if appropriate

Table 1. Immune effector cell-associated encephalopathy (ICE) score (See Appendix 1):

Category	Points
1. Orientation: orientation to year, month, city, place*	4 points
2. Naming: ability to name 3 objects (i.e., pen, cup, glasses)*	3 points
3. Following commands: ability to follow simple command (i.e., “Close your eyes and stick out your tongue”)	1 point
4. Writing: ability to write a standard sentence (i.e., “The flag is red and white”)	1 point
5. Attention: ability to count backwards from 100 by 10	1 point

*1 point for each item

Table 2. American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Severity Grading for ICANS in Adults*

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7 to 9	3 to 6	0 to 2	0 (patient is unrousable and unable to do ICE testing)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable or requires vigorous or repetitive tactile stimulus to awaken
Seizures	N/A	N/A	Any seizure (focal, general) that resolves rapidly. Non-convulsive seizure on EEG that resolve with intervention.	Life-threatening prolonged seizures (>5min). Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging (excluding intracranial hemorrhage)	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; papilledema; cranial nerve VI palsy; Cushing's triad (irregular/decreased respirations, bradycardia, and systolic hypertension)

*ICANS Grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

TREATMENT: A physician must be notified at the first signs of ICANS.

ICANS	Management
Grade 1	**Immediately stop administration of treatment medication.** **Page the admitting physician or covering physician.** **Admit the patient for further monitoring if not already admitted.** Early administration of steroids may decrease severity of ICANS. Steroids may not be required for Grade 1 ICANS, however low threshold to give a single dose of dexamethasone if concerning features such as ataxia or ICE score of 7. Steroid dosing: • Consider dexamethasone 10 mg IV once and reassess (can be repeated Q6H, as per Grade 2 dosing) Supportive Care: • Point of care glucometer testing QID • Seizure precautions • Fall precautions • Elevate head of bed 30 degrees • Aspiration precautions - assess swallowing. Convert all medications to IV if impaired • NPO, meds with sips • Avoid medications that cause CNS depression • Bedside fundoscopic evaluation • Consider Neurology consultation • If concurrent CRS, consider tocilizumab. See SCCRS protocol. • LORazepam 1mg IV Q5mins PRN for seizures, to a maximum of 4mg Monitor for ICANS symptoms including an ICE score every 12 hours until normalization using Tables 1 and 2, above. Monitor vitals Q4H for concurrent CRS.

ICANS	Management
Grade 2	**Immediately stop administration of treatment medication** **Admit the patient for further monitoring if not already admitted.** Page the admitting physician or covering physician if not already done. Early administration of steroids may decrease severity of ICANS. If Grade 2 ICANS occurs, **administer steroids first,** reserving tocilizumab for concurrent CRS, as tocilizumab does not cross the blood brain barrier. Steroid dosing: • dexamethasone 10 mg IV every 6 hours Continue steroids until event is Grade 1 or less, then taper over 3 days Consider seizure prophylaxis (if not already on), particularly if any concern for clinical seizure and/or epileptiform EEG findings (progression to Grade 3): • levETIRAcetam 1500 mg PO load, then 750 mg PO BID maintenance dose† Supportive care as outlined above for Grade 1, PLUS: • If no resolution of symptoms or no improvement to Grade 1 ICANS after 1 to 2 doses of steroids, consider transfer to higher level of care if required for neurology consultation, EEG and urgent neuroimaging • Consider transfer to intensive care if associated with Grade 2 or higher CRS • Ophthalmology consult to rule out papilledema • Consider lumbar puncture to assess opening pressure and rule out other causes of neurologic deterioration Neurovitals and monitor for ICANS symptoms including an ICE score every 8 hours or more frequently if necessary, using Tables 1 and 2 above. Monitor vitals Q4H for concurrent CRS.

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<td>Grade 3 and Grade 4</td>
<td>
Immediately stop administration of treatment medication
Admit the patient for further monitoring if not already admitted.
Page the admitting physician or covering physician if not already done.
Arrange emergent transfer to higher level of care. Contact ICU to discuss admission.
Steroid:
<table>
<tr><th>Grade</th><th>Steroid Dosing*</th></tr>
<tr><td>3</td><td>Encephalopathy
• dexamethasone 10 mg IV Q6H (increased to 20 mg if not resolved at 24 hours)
Seizure
• dexamethasone 20 mg IV Q6H
Focal cerebral edema
• methylPREDNISolone 1 gram IV daily
• Duration: 3 days if edema involves the brain stem or thalamus. One day for other locations.</td></tr>
<tr><td>4</td><td>methylPREDNISolone 1 gram IV daily or 3 days</td></tr>
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* Continue corticosteroids until event is Grade 1 or less, then taper over 3 days.
Seizure treatment (recommend for Grade 3 to 4 ICANS even if no clinical seizure activity):
• levETIRAcetam 1500 mg PO load, then 750 mg PO BID maintenance dose†
Supportive Care as outlined above for Grades 1 and 2, PLUS:
• EEG to assess for seizures
• Lumbar puncture to assess opening pressure and rule out other causes of neurologic deterioration (if not already performed and no contraindications)
• If seizures, papilledema present on fundoscopy, or edema noted on imaging, consult neurology
• CT/MRI - consider repeating imaging every 2 to 3 days if patient has persistent Grade 3 or higher CRS to monitor for cerebral edema
• ICU monitoring and management of cerebral edema as indicated; consider mechanical ventilation for airway protection
Consider for management of refractory ICANS: anakinra 100 mg IV Q12H (can be escalated to Q6H)
Monitor vitals Q4H for concurrent CRS
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† Empiric seizure prophylaxis is not required for Grade 1 to 2 ICANS. However, low threshold to start anti-seizure medication if concern for clinical seizure and/or epileptiform EEG findings.
levETIRAcetam (KEPPRA®) is the preferred agent, with a load followed by a starting dose of 750 mg PO BID for 30 days. In patients without premorbid seizure history who return to neurologic baseline, advise tapering off as follows: levETIRAcetam 500 mg PO BID for 2 weeks, then 250mg PO BID for 2 weeks, then discontinue levETIRAcetam. Monitor for recurrence of seizure.

REFERENCES

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3. IEC therapy toxicity assessment and management. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf
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 Dec 10;39(35):3978-3992.

Appendix 1: Immune effector cell-associated encephalopathy (ICE) assessment

Category	Points
1. Orientation: orientation to year, month, city, place*	4 points
2. Naming: ability to name 3 objects (i.e pen, cup, glasses)*	3 points
3. Following Commands: ability to follow simple command (ie. “Close your eyes and stick out your tongue”)	1 point
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*1 point for each item

Total Score	10 points

If ICE score is 9 or less (or less than baseline score), notify physician