

The intent of this handout is to provide background information regarding neurotoxicity and grading system management guidelines. This handout is not intended to provide treatment guidance for patients.

NEUROTOXICITIES ASSOCIATED WITH IMMUNOTHERAPY

Immuno-oncology therapies are associated with neurologic adverse events affecting the central and peripheral nervous systems including¹⁻³:

- Encephalitis
- Demyelinating disease (eg, Guillain-Barré syndrome)
- Neuropathies
- Neurodegenerative disorders (eg, parkinsonism)

Therapies such as checkpoint inhibitors, CAR-T, and bispecific antibodies may lead to serious and life-threatening neurotoxicity.^{2,4}

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS is a pathologic process involving the central nervous system following immunotherapy that activates endogenous or infused T-cells and/or other immune effector cells.⁴

Neurotoxicity symptoms include^{4,5}:

Consistent with ICANS

- Aphasia
- Altered consciousness level
- Agitation
- Delirium
- Seizures
- Encephalopathy
- Cognitive skill impairment/difficulty concentrating
- Motor weakness

Inconsistent with ICANS

- Headache
- Tremor
- Myoclonus
- Parkinsonism
- Asterixis
- Hallucinations
- Peripheral neuropathy

Consider advising patients receiving treatment for multiple myeloma about the risks of neurotoxicity, as well as the signs and symptoms associated with it.

Potential clinical factors associated with neurotoxicity^{2,6-11}

Clinical factors associated with neurotoxicity are best described following CAR-T therapy. Due to potential T-cell involvement in other immunotherapies, the following considerations may apply.



Patient/therapy-related

- Age
- High disease burden
- Preexisting neurologic comorbidities and autoimmune diseases
- Therapy dose and/or combinations
- CRS onset and severity



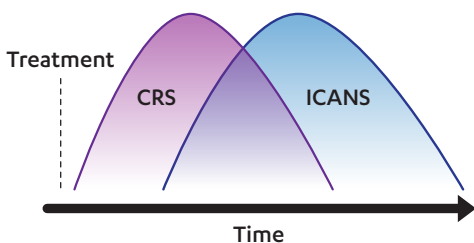
Biomarkers

LDH | CRP | Fibrinogen | Ferritin

Timing and pathophysiology of ICANS^{4,6,12-21}

The timing and pathophysiology of ICANS are best described following CAR-T therapy. Coexisting evidence of consistent symptoms of CRS and ICANS suggests similar pathophysiology for other immuno-oncology therapies.

Onset and duration of CRS and ICANS



- ICANS typically occurs after or concurrent with CRS
- In ICANS, proinflammatory cytokines associated with CRS may leak into the vasculature, disrupting the BBB and causing neuronal injury

BBB, blood-brain barrier; CAR-T, chimeric antigen receptor-T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LDH, lactate dehydrogenase.

Consider monitoring symptoms⁴

- Impairment in motor function (eg, handwriting changes)
- Changes in sensation (eg, numbness)
- Headache
- Speech disorders
- Convulsions
- Disturbances in consciousness
- Confusion
- Disorientation

Consider diagnostic testing²

- Serologic testing
- Brain MRI
- Lumbar puncture
- EEG
- EMG

Counsel your patients to seek medical attention for any signs and symptoms of ICANS.

ASTCT ICANS Consensus Grading for Adults⁴

CTCAE v5.0 grading is used to evaluate all neurotoxicity. The ASTCT recommends using the ICANS grading criteria (shown below), and CTCAE v5.0 to grade events that are not part of or consistent with the ICANS definition criteria.

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient unarousable and unable to perform ICE assessment)
Depressed level of consciousness[†]	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	NA	NA	Any clinical seizure, focal or generalized, that resolves rapidly; or nonconvulsive 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	NA	NA	NA	Deep focal motor weakness, such as hemiparesis or paraparesis [‡]
Elevated ICP/cerebral edema	NA	NA	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 patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable. [†]Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication). [‡]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. [§]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0. Table reprinted from *Biol Blood Marrow Transplant*, 25(4), Lee DW et al, ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells, 625-638, Copyright (2019), with permission from Elsevier.

Consider management strategies^{2,4,7,8,10,22-25}

Multiple versions for ICANS management have been implemented in clinical trials with interventions as per the investigator's discretion. Given the onset of ICANS in relation to CRS, guidelines have included management based on CRS manifestation in addition to toxicity grade.

Consider partnering with a neurologic specialist to discuss supportive therapy and ICU requirements.

Shown below are select pharmacological management strategies for ICANS from established guidelines.^{23,24} For more comprehensive guidance on supportive care related to CRS and neurotoxicity management, refer to your institutional guidelines and established guidelines (eg, ASCO²³, CARTOX²⁴).

⊕ CONCURRENT WITH CRS

- Consider administration of
 - Nonsedating antiepileptics
 - Corticosteroids
 - Anti-cytokine therapy (eg, anti-IL-6R)

⊖ NOT CONCURRENT WITH CRS

- Consider administration of
 - Nonsedating antiepileptics
 - Corticosteroids

ASCO, American Society of Clinical Oncology; ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, CAR T-cell therapy-associated toxicity; CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events; EEG, electroencephalography; EMG, electromyography; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; ICU, intensive care unit; IL-6R, interleukin-6 receptor; MRI, magnetic resonance imaging; NA, not applicable.

References: 1. Guidon AC, Burton LB, Chwalisz BK, et al. *J Immunother Cancer*. 2021;9(7):e002890. 2. Burton LB, Eskian M, Guidon AC, Reynolds KL. *Neurooncol Adv*. 2021;3:v108-v120. 3. Van Oekelen O, Aleman A, Upadhyaya B, et al. *Nat Med*. 2021;27(12):2099-2103. 4. Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. 5. Cohen AD, Parekh S, Santomasso BD, et al. *Blood Cancer J*. 2022;12(2):32. 6. Stein AS, Schiller G, Benjamin R, et al. *Ann Hematol*. 2019;98(1):159-167. 7. Salvaris R, Ong J, Gregory GP. *J Pers Med*. 2021;11(5):355. 8. Maus MV, Alexander S, Bishop MR, et al. *J Immunother Cancer*. 2020;8(2):e001511. 9. Wang Z, Han W. *Biomark Res*. 2018;6:4. 10. Rivera AM, May S, Lei M, et al. *Crit Care Nurs Q*. 2020;43:191-204. 11. Grant SJ, Grimshaw AA, Silberstein J, et al. *Transplant Cell Ther*. 2022;28(6):294-302. 12. Morris EC, Neelapu SS, Giavridis T, Sadelain M. *Nat Rev Immunol*. 2022;22:85-96. 13. Schuster SJ, Bartlett NL, Assouline S, et al. *Blood*. 2019;134(1):6. 14. Budde LE, Sehn LH, Matasar M, et al. *Lancet Oncol*. 2022;23(8):1055-1065. 15. Moreau P, Garfall AL, van de Donk NWCJ, et al. *N Engl J Med*. 2022;387(6):495-505. 16. Schadendorf D, Wolchok JD, Hodi FS, et al. *J Clin Oncol*. 2017;35(34):3807-3814. 17. Spain L, Walls G, Julve M, et al. *Ann Oncol*. 2017;28(2):377-385. 18. Johnson DB, Manouchehri A, Haugh AM, et al. *J Immunother Cancer*. 2019;7(1):134. 19. Postow MA, Chesney J, Pavlick AC, et al. *N Engl J Med*. 2015;372(21):2006-2017. 20. Larkin J, Hodi FS, Wolchok JD. *N Engl J Med*. 2015;373(13):1270-1271. 21. Ceschi A, Nosedà R, Palin K, Verhamme K. *Front Pharmacol*. 2020;11:557. 22. Puzanov I, Diab A, Abdallah K, et al. *J Immunother Cancer*. 2017;5:95. 23. Santomasso BD, Nastoupil LJ, Adkins S, et al. *J Clin Oncol*. 2021;39:3978-3992. Erratum in: *J Clin Oncol*. 2022;40:919. 24. The University of Texas MD Anderson Cancer Center. IEC Therapy Toxicity Assessment and Management (also known as CARTOX) - Adult. Published September 15, 2020. Accessed September 9, 2022. <https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf> 25. Mayo Clinic. mSMART. Accessed March 10, 2023. Available at <https://www.msmart.org/mm-treatment-guidelines>