

CAR-T Neurotoxicity: Beyond ICANS and the Transplant Center

Written by The Life Science Feed Editorial Team · Published 27 August 2026 · Edited by Mara Voss

Chimeric antigen receptor T (CAR-T) cell therapy has significantly advanced treatment for certain hematologic malignancies and is emerging in autoimmune disorders. While effective, its use is associated with immune-mediated toxicities, notably cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). This review highlights the evolving understanding of CAR-T neurotoxicity, particularly delayed and non-ICANS presentations, emphasizing the need for broader recognition and management beyond specialized transplant centers.

KEY TAKEAWAYS

- **The Pivot:** CAR-T neurotoxicity extends beyond acute ICANS, encompassing delayed and non-ICANS syndromes, especially with newer CAR-T targets and indications.
- **The Data:** BCMA-directed CAR-T for plasma cell dyscrasias is linked to delayed non-ICANS neurotoxicities, including movement, neurocognitive, cranial nerve, and peripheral neuropathic symptoms.
- **The Action:** Clinicians outside transplant centers need enhanced awareness and monitoring strategies for diverse, potentially delayed CAR-T neurotoxicities to ensure timely intervention.

Target Expansion Broadens the Neurotoxicity Spectrum

As CAR-T platforms diversify beyond CD19-targeted therapies, the observed neurotoxicity phenotypes are broadening beyond the classical ICANS presentation¹. Chimeric antigen receptor T (CAR-T) cell therapy has revolutionized outcomes for relapsed/refractory B-cell malignancies and is increasingly being explored for autoimmune disorders and solid tumors. This therapeutic expansion offers significant potential, but its broader application is constrained by immune-mediated toxicities, primarily cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)¹. ICANS presents a heterogeneous spectrum of neurological symptoms, ranging from mild aphasia and tremor to severe manifestations such as seizures, cerebral edema, coma, and even death. Predicting ICANS prospectively remains challenging.

Axicabtagene ciloleucel and tisagenlecleucel target CD19 for the treatment of B-cell acute lymphoblastic leukemia and non-Hodgkin lymphoma, frequently causing ICANS either in isolation or concomitantly with CRS⁶. The recent discovery of CD19 expression on the pericytes in the blood-brain barrier suggests an off-target mechanism for ICANS development⁴. The release of systemic cytokines stimulated by the engagement of CD19 with the CAR T cells can cause endothelial activation and decreased expression of tight junction molecules, further damaging the integrity of the blood-brain barrier⁴. Recent experience with CAR-T therapies, particularly those targeting B-cell maturation antigen

(BCMA) for plasma cell dyscrasias, has revealed associations with delayed non-ICANS neurotoxicities. These include a range of symptoms such as movement disorders, neurocognitive and behavioral changes, cranial nerve palsies, and peripheral neuropathic presentations¹.

These mechanistic reviews do not establish the exact pathophysiology for non-CD19 targets, nor do they provide a validated method to prevent the initial cytokine cascade without compromising the therapy's anti-tumor efficacy. Because brain imaging is frequently negative or nonspecific during these episodes, diagnosis relies heavily on clinical assessment rather than radiological confirmation⁴. Early data from CAR-T and related immune effector therapies used in autoimmune and neuroimmunologic diseases suggest distinct inflammatory contexts and potentially different patterns of neurotoxicity.

Physicians must maintain a high index of suspicion for both acute ICANS and delayed non-ICANS symptoms, relying on close neurologic monitoring and supportive care rather than waiting for definitive imaging findings⁴. This highlights the necessity for indication-specific monitoring and attribution frameworks to accurately identify and manage these complications¹. Once within the brain microenvironment, cytokines trigger a cytokine-specific cascade of neuroinflammatory responses, which manifest clinically as a spectrum of neurological changes that demand immediate bedside evaluation⁴.

Endothelial Activation Scores Predict Severe Toxicity

Converging evidence indicates a complex, multilayered pathophysiology underlying CAR-T-associated neurotoxicity, where endothelial activation serves as a primary driver and potential predictive marker. Clinical trial experience and animal models suggest a central role for endothelial cell dysfunction, myeloid cells, blood-brain barrier disruption, and elevated central nervous system cytokine levels in the development of ICANS⁵. Key mechanisms include systemic cytokine surges, which can disrupt the blood-brain barrier (BBB), leading to endothelial dysfunction. This disruption facilitates the trafficking of activated CAR-T cells and other immune effectors into the central nervous system (CNS)¹. Within the CNS, brain support cells like astrocytes and microglia can release substances that damage or overstimulate nerve cells, contributing to cerebral edema and impaired brain function. Some pericytes and vascular smooth muscle cells in the brain may also express the CD19 marker, raising the possibility of direct, unintended CAR-T cell-mediated damage that further compromises the BBB. Baseline neurological vulnerability and the peri-infusion inflammatory milieu are also likely modulators of individual risk for neurotoxicity¹.

To address the need for predictive tools, researchers evaluated the modified EASIX (m-EASIX) score, which replaces creatinine with C-reactive protein in a formula assessing endothelial damage³. A study of 118 adults included 53 patients with B-acute lymphoblastic leukemia treated with 1928z CAR T cells and 65 patients with diffuse large B-cell lymphoma treated with axicabtagene ciloleucel or tisagenlecleucel³. The m-EASIX score discriminated patients who subsequently developed severe CRS preceding the onset of severe symptoms, showing an area under the curve of 80.4% at lymphodepletion, 73.0% at day -1, and 75.4% at day +13. At day +3, the score also demonstrated a high discriminatory ability for severe ICANS, yielding an area under the curve of 73%³.

This retrospective calculation does not establish whether intervening based on an elevated m-EASIX score alters the clinical trajectory, nor does it define a specific threshold that mandates preemptive therapy. Given the frequency of these complications, active research is underway to identify clinical, functional, and biological signals that could predict and improve their management. But most potential biomarkers remain investigational, lacking prospective validation and straightforward clinical utility in current practice¹.

The m-EASIX score relies on routine laboratory values like lactate dehydrogenase, platelets, and C-reactive protein, meaning clinicians can calculate it without specialized assays³. Treatment teams should track these standard markers peri-infusion to identify patients at higher risk for severe CAR T-cell-related toxicities. Assessment of ICANS and other neurological complications typically involves a combination of bedside neurological testing, brain imaging (e.g., MRI), electrophysiology studies, and sometimes cerebrospinal fluid analysis. Current treatment strategies rely on rapid detection and the use of anti-inflammatory medications, such as corticosteroids, and biological therapies, including anti-interleukin treatments. Most cases improve with timely care, but severe ICANS can be life-threatening¹.

High-Dose Anakinra Mitigates Refractory Neurotoxicity

When standard anti-inflammatory medications fail, high-dose anakinra offers a salvage strategy for refractory cases, a critical need as CAR-T therapy expands to broader populations. The expanding indications for CAR-T cell therapy, coupled with the emergence of diverse and sometimes delayed neurotoxicities, necessitate a heightened awareness among healthcare professionals beyond specialized transplant centers. As CAR-T therapy becomes more accessible and is applied to a broader patient population, including those with autoimmune conditions, primary care physicians, neurologists, and emergency department staff will increasingly encounter patients who have received these treatments. Recognizing the varied presentations of neurotoxicity, including subtle cognitive changes, new movement disorders, or cranial nerve palsies that may appear weeks or months post-infusion, is critical for timely diagnosis and intervention. Integrated, multimodal risk models are needed to enable more precise stratification and intervention across indications. This review offers a fresh perspective on these models, aiming to synthesize current evidence on the epidemiology, mechanisms, and monitoring of both ICANS and emerging non-ICANS syndromes¹.

A retrospective analysis evaluated 43 patients with B cell or plasma cell malignancies treated with anakinra for refractory CRS or ICANS at 9 institutions between 2019 and 2022. Indications included grade 2 or higher ICANS worsening despite high-dose corticosteroids in 40 patients, and grade 2 or higher CRS worsening despite tocilizumab in 3 patients². The cumulative incidence of treatment-related mortality at day 28 after initiation was 0% in the high-dose recipient group receiving more than 200 mg/day intravenously, compared to 47% in the low-dose group receiving 100 to 200 mg/day subcutaneously or intravenously². The median cumulative incidence of CRS/ICANS resolution from anakinra initiation was 7 days in the high-dose group, while the low-dose group did not reach resolution due to high mortality².

This retrospective cohort lacks a randomized control arm and cannot definitively prove that the dose difference alone drove the survival benefit, as unmeasured confounding factors may have influenced which patients received high-dose intravenous therapy. While significant progress has been made in understanding CAR-T neurotoxicity, several limitations remain. The precise biological mechanisms underlying some non-ICANS neurological dysfunctions are

still incompletely understood. The lack of prospectively validated biomarkers for prediction and management poses a significant challenge. Future research efforts are focused on developing more effective predictive tools, safer CAR-T therapy designs, and more targeted therapeutic interventions to mitigate these complications.

The overall response rate to CAR-T therapy remained 77% despite anakinra treatment, suggesting the intervention does not severely impair anti-tumor efficacy². Clinicians managing refractory ICANS should consider escalating to high-dose intravenous anakinra up to 12 mg/kg/day rather than relying on lower subcutaneous doses, as higher dosing is independently associated with lower treatment-related mortality and faster symptom resolution². Continued investigation into the specific inflammatory contexts and neurotoxicity patterns associated with different CAR-T targets and indications will be required for optimizing patient safety and outcomes¹.

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