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.

Evolving Landscape of CAR-T Therapy and Associated Toxicities

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. As CAR-T platforms diversify beyond CD19-targeted therapies, the observed neurotoxicity phenotypes are also broadening beyond the classical ICANS presentation1.

Emerging Non-ICANS Neurotoxicities

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.

Furthermore, 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. This underscores the necessity for indication-specific monitoring and attribution frameworks to accurately identify and manage these complications1.

Multilayered Pathophysiology of Neurotoxicity

Converging evidence indicates a complex, multilayered pathophysiology underlying CAR-T-associated neurotoxicity. 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.

Monitoring and Management Challenges

Given the frequency of these complications, active research is underway to identify clinical, functional, and biological signals that could predict and improve their management. However, most potential biomarkers remain investigational, lacking prospective validation and straightforward clinical utility in current practice1.

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.

Clinical Implications for Practice Today

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.

Limitations and Future Directions

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. Continued investigation into the specific inflammatory contexts and neurotoxicity patterns associated with different CAR-T targets and indications will be crucial for optimizing patient safety and outcomes1.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Pagliuca S, Jacquet C, Rubio MT, Sorrentino P. The neurotoxic legacy of CAR-T cells: where do we stand? Ther Adv Neurol Disord. 2026;19:17562864261440261. doi:10.1177/17562864261440261

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com