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The Cognitive Footprint of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) in Chimeric Antigen Receptor T-Cell Therapy (CAR-T): A Systematic Review

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Abstract:
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) presents a significant side-effect of CAR-T cell therapy, with cognitive dysfunction emerging as a core manifestation that can impact patient quality of life and their functional outcomes.To systematically review current evidence on the clinical impact, underlying mechanisms, assessment methodologies, and management strategies of ICANS-related cognitive dysfunction in CAR-T recipients.A systematic literature search was conducted across PubMed, EMBASE, Google Scholar and Web of Science databases following PRISMA guidelines. Studies reported ICANS affects 26.9% of CAR-T recipients overall, with cognitive dysfunction representing the most prevalent manifestation. Deficits in attention, memory, executive function, and language processing were consistently reported, with varying degrees of persistence ranging from days to months post-treatment.ICANS-related cognitive dysfunction represents a significant clinical concern requiring standardized assessment protocols and targeted interventions. Further research is needed to establish predictive biomarkers and effective management strategies.

Keyword: ICANS, Human Cognition, CAR-T Cell Therapy, Oncology

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy is a groundbreaking form of adoptive cellular immunotherapy that has transformed the treatment of hematologic malignancies since the first FDA approval of tisagenlecleucel in 2017.[1] To date, six CAR-T products have received regulatory approval, and approximately 1,000 clinical trials have been registered worldwide over the past eight years. These efforts have demonstrated remarkable outcomes, with complete response rates ranging from 39% to 81% in large B-cell lymphomas.[2] Reflecting its growing clinical significance and adoption, the global CAR-T therapy market is projected to reach $128.55 billion by 2034.[3]

Despite these advances, CAR-T therapy is frequently complicated by Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Overall, ICANS affects about 26.9% of recipients, with 10.5% experiencing high-grade neurotoxicity.[4] Among its diverse manifestations, cognitive dysfunction stands out as a critical concern. Recent studies have reported persistent neurocognitive impairments particularly

in memory, executive function, attention, and language processing that may profoundly affect patients' quality of life and functional outcomes.[5][6]

The mechanisms underlying ICANS-related cognitive decline remain incompletely understood. Current evidence points to immune-mediated neuroinflammation, cytokine-driven disruption of the blood–brain barrier, and direct cellular infiltration into the central nervous system as contributing factors.[7][8] Nevertheless, standardized neurocognitive assessment protocols are not consistently implemented across CAR-T treatment centers, and available therapeutic strategies to prevent or manage cognitive dysfunction remain largely exploratory.[9][10]

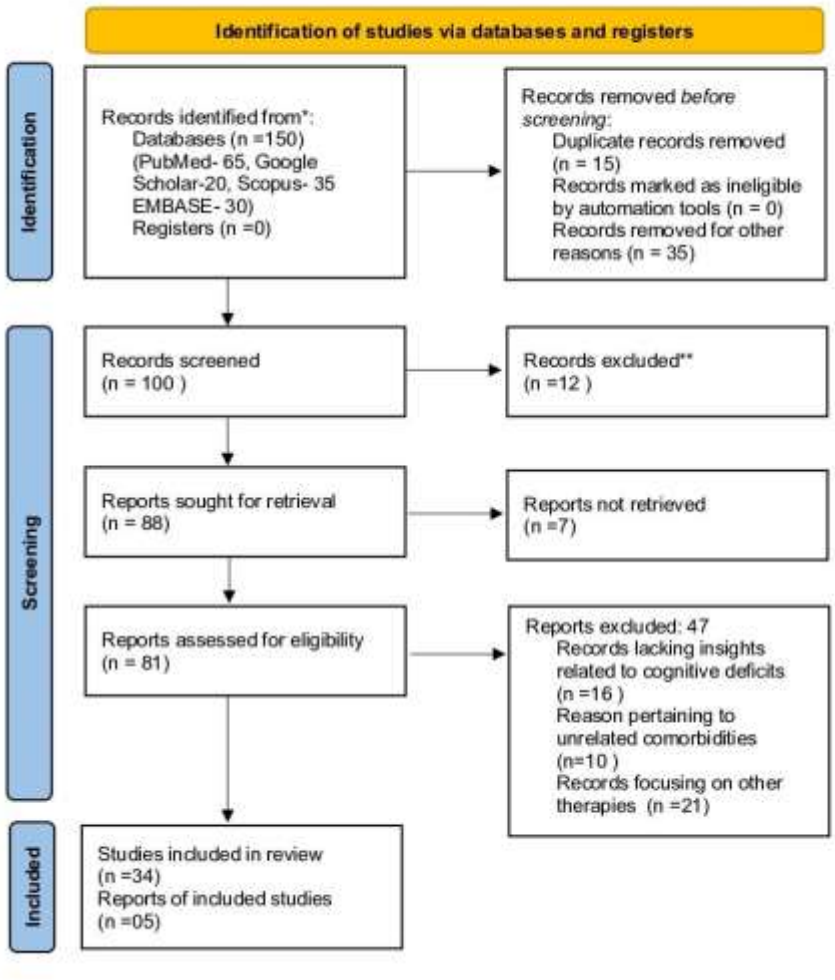
Given the expanding use of CAR-T therapy and the potential for long-term cognitive consequences, this systematic review aims to critically evaluate the current evidence regarding the clinical impact, underlying mechanisms, assessment approaches, and comparative outcomes of ICANS-related cognitive dysfunction in CAR-T recipients. By identifying knowledge gaps and synthesizing existing findings, this review seeks to inform clinical practice and guide future research directions to optimize cognitive outcomes in this vulnerable patient population.

Material and methods

This systematic review was conducted in accordance with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[11] A comprehensive literature search was performed using the electronic databases PubMed, Embase, Web of Science, and PsycINFO. All studies published upto July 2025 were considered.The primary search terms included: "Immune Effector Cell-Associated Neurotoxicity Syndrome" OR "ICANS" OR "CAR-T therapy neurotoxicity" AND "cognition" OR "cognitive function" OR "neurocognitive outcomes." In addition, reference lists of relevant papers and review articles were manually screened to identify any further eligible studies.Two independent reviewers screened titles and abstracts, followed by full-text screening of articles against predefined inclusion and exclusion criteria. Any disagreements were resolved through consensus. Studies not meeting the minimum quality threshold were excluded, with reasons documented and presented in the PRISMA flow diagram (Figure 1).

Figure: 01

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Inclusion Criteria

1. Peer-reviewed empirical papers published in English.
2. Studies that assessed cognitive functions in patients who developed ICANS due to CAR-T treatment.
3. Articles where ICANS was clearly identified, diagnosed and evaluated.

Exclusion Criteria

1. Non-quantitative papers such as editorials, commentaries, or narrative reviews.
2. Studies focusing on interventions unrelated to ICANS or cognition (e.g., deep brain stimulation, transcranial stimulation, psychotherapy, or assessments of psychological constructs not linked to cognitive functioning).
3. Papers that did not specifically assess cognitive outcomes or neurocognitive functioning in the context of ICANS.

Data Extraction

Data extracted included study characteristics, patient demographics, ICANS incidence and grading, cognitive assessment tools, cognitive domains affected, duration of impairment, and recovery patterns.

Result and Discussion

ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome) is a neurological side effect of CAR-T (Chimeric Antigen Receptor T-cell) therapy that significantly affects many patients, with cognitive dysfunction as a primary symptom. It's crucial to understand the nature of this cognitive impairment, including which domains are affected, how long the symptoms last, and how severity correlates with long-term effects.

Clinical Impact of ICANS on Cognition

ICANS occurs in approximately 26.9% of CAR-T recipients, with 10.5% experiencing high-grade neurotoxicity. [4] Cognitive dysfunction is the most common manifestation, occurring in nearly all patients who develop neurotoxicity. [7] ICANS is characterized by several symptoms, such as confusion, language disturbance, delirium, dysgraphia, and diminished attention, among others. [13]

Multiple studies show that ICANS-related cognitive impairment affects several domains. Attention and concentration deficits are the most commonly reported issues, affecting 73-85% of patients. [14] Memory impairment, particularly affecting short-term memory and verbal learning, is documented in 35% of patients. [7] Additionally, patients may experience executive dysfunction, which includes difficulties with problem-solving, decision-making, and working memory. [7] Other commonly reported symptoms include aphasia, word-finding difficulties, and writing impairments (agraphia). [14]

Transient vs. Persistent Cognitive Impairments

Most cognitive symptoms present within the first two weeks post-CAR-T infusion, with the median onset of ICANS at 8 days. While most symptoms resolve within 1-4 weeks [15], there is concern that ICANS may have long-term negative consequences on patients' cognition. Cognitive impairment is common after cancer treatment and cellular therapies, with up to 75% of survivors reporting cognitive issues. [13] A relevant number of patients suffer from long-lasting cognitive deficits, such as impairments in memory, word-finding, and attention. [12] Approximately 10-37.5% of patients report ongoing cognitive difficulties beyond 6 months. [7] While complete cognitive recovery is observed in most patients by 6-12 months, some deficits may persist. [16] Regarding changes in perceived cognition over time, from baseline to day 90, there were no statistically significant changes in global cognition or any cognitive domain. [17] In contrast, from day 90 to day 360, participants reported worsening mean-level global cognition, memory, language, organization, and divided attention. At day 90, 12% of participants reported a clinically significant worsening in cognition relative to baseline, while at day 360, this number increased to 25%. [17]

Correlation Between ICANS Severity and Cognitive Dysfunction

The severity of ICANS correlates with the extent of cognitive dysfunction. Results indicated that patients with higher-grade ICANS (Grade 2 or above) reported significantly worse cognition at day 360 relative to those with low-grade ICANS (Grade 0 or 1).There were no differences in cognition by CRS at any time point or disease status (response versus progression) at day 360. [17] These findings suggest that more severe acute neurotoxicity is associated with more pronounced and persistent cognitive issues.

Mechanistic Basis of ICANS-Related Cognitive Deficits

The pathophysiology of ICANS-related cognitive deficits involves a complex series of neuroinflammatory

events. A key proposed mechanism is the cytokine-mediated neuroinflammation, where elevated levels of cytokines such as IL-6, GM-CSF, and TNF-α have been directly correlated with the severity of cognitive symptoms. [18] This neuroinflammatory cascade also leads to the disruption of the blood-brain barrier (BBB) through endothelial activation and increased vascular permeability. [9] Additionally, studies have identified persistent neuroinflammation characterized by reactive microglial phenotypes. [12]

Pre-infusion factors, such as high disease burden, advanced age, and baseline cognitive status, can help predict the likelihood of developing ICANS. [19] Biomarkers like elevated CD27 serum proteins in patients with a high disease burden [20] and specific cerebrospinal fluid (CSF) markers also show predictive potential. [21]

Neuroimaging and Biomarker Evidence of Brain Changes

Neuroimaging and biomarker studies provide significant evidence of the structural and functional brain changes associated with ICANS. Neuroimaging studies have revealed white matter changes, with T2/FLAIR hyperintensities in 78% of cases, commonly affecting the pons, thalamus, and corpus callosum.Functional alterations, such as generalized electroencephalogram (EEG) slowing, are observed in 80% of cases. [22] Furthermore, single-nucleus sequencing of the frontal lobe from patients who underwent CAR-T therapy confirmed the presence of reactive microglia and oligodendrocytes after treatment. [23]

A study highlights that patients with ICANS Grade 2 or higher show a significantly higher peak concentration of serum neurofilament light chain (sNfL) on day 7 post-infusion, even before symptoms appear. This suggests potential neuroaxonal injury in moderate-to-severe ICANS and indicates that sNfL could serve as a real-time biomarker for guiding early interventions. [24]

Clinical and Radiographic Progression of Neurotoxicity:

Case studies and serial imaging demonstrate the dynamic and progressive nature of ICANS-related neurotoxicity. One case, in particular, showed severe neurotoxicity on MRI, including cerebral edema and mass effect, despite the patient experiencing only low-grade ICANS symptoms. The delayed onset of a seizure in this case proved that neurotoxicity can progress long after CAR-T therapy is discontinued. [25]

MRI findings illustrate a dynamic progression of neurotoxicity, with a small focus of restricted diffusion in the splenium of the corpus callosum aligning with known neuroinflammation patterns. The development of susceptibility artifacts in the lentiform and caudate nuclei over time correlates with microhemorrhage or hemosiderin deposition. The presence of these artifacts up to 250 days after the initial MRI provides rare evidence of chronic injury from ICANS.This chronic neuroinflammation is also suggested by the increased size and heterogeneity of signal abnormalities in the caudate nuclei even 99 days later. [25]

While some foci in areas like the hypothalamus and ependymal regions may show partial recovery, new lesions in the septum pellucidum, hippocampus, and caudate nuclei indicate ongoing inflammation and continued impact of ICANS. [25] The delayed appearance of new lesions in the hippocampus is particularly concerning due to their potential impact on cognition and memory. These findings underscore the importance of long-term serial imaging to assess the extent of neurotoxicity and guide treatment. Further research is needed to develop a consensus for interpreting neuroimaging in ICANS patients to improve diagnostic accuracy and enhance the understanding of its pathophysiology. [25]

Prophylactic Measures and Associated Risks

CAR-T cell therapy is a highly promising treatment for hematological cancers, but it carries a risk of life-threatening adverse events like cytokine release syndrome (CRS) and ICANS. CRS is mediated by cytokines such as IL-1 and IL-6, which can cause fever and hypotension. To mitigate the risk of CRS and neurotoxicity, the FDA approved the use of tocilizumab, a humanized anti-IL-6 receptor antibody, for CAR-T cell therapy.Elevated cytokine levels during CD19-CAR T cell therapy have been linked to pretreatment tumor burden.[1]

Methodological Approaches and Clinical Practice Implications

The assessment and treatment of ICANS are heavily dependent on a clinician's ability to accurately and promptly diagnose the syndrome and evaluate its severity. In 2019, the American Society for Transplantation and Cellular Therapy (ASTCT) published a consensus grading scheme for ICANS that includes a standardized assessment tool, the Immune Effector Cell-Associated Encephalopathy (ICE) score. [26]

Assessment Tools and Their Limitations The ICE score, a five-item assessment, evaluates a patient's cognitive function by measuring their orientation, ability to name three objects, follow a simple command, perform sentence writing, and complete serial 10s subtraction. [26] A patient with a score of less than 10 is classified as having ICANS. [26] While the ICE score is a valuable tool for monitoring, its validity is dependent on the patient's ability to engage with the test, requiring adequate motor, auditory, and visual sensory function, as well as proficiency in the language of administration. This presents a significant challenge for clinicians assessing older patients, who are often eligible for CAR-T therapy and may have sensory or physical impairments, or for non-native-speaking patients. [26]

Because of these limitations and the subjective nature of bedside exams, other tools have been explored. While biomarkers such as serum proteins (CRP, LDH, and ferritin) have been associated with increased ICANS severity, they lack specificity since they are also elevated in cytokine release syndrome (CRS). [27] Furthermore, neuroimaging, like CT and MRI scans, typically does not show abnormalities except in severe cases with cerebral edema.[27] However, an interesting case study highlighted how serial imaging can reveal a dynamic progression of neurotoxicity, including white matter changes and microhemorrhage, even in patients with low-grade symptoms, indicating chronic injury. [25] Electroencephalography (EEG) shows promise as a potential biomarker for ICANS, as changes in EEG patterns, such as delta and theta slowing, have been shown to correlate with symptom severity. However, findings to date are limited by small sample sizes and are not yet widely adopted in clinical practice. [27]

Treatment and Management of ICANS

The treatment for ICANS largely relies on a clinician's ability to diagnose it accurately and in a timely manner. Steroids like dexamethasone may be beneficial for treatment [27], but prolonged use may diminish the desired effect of CAR-T cell therapy on the underlying cancer[27]. Another consideration is that tocilizumab, a common treatment for CRS, may potentially worsen ICANS. [27]

Given these treatment limitations, the need for a reliable and readily available ICANS biomarker is critical. Such a biomarker could improve patient outcomes and provide a cost-saving tool for management. [27] Unfortunately, an objective, accessible, and reliable biomarker has yet to be identified. While MRI, CSF profiles, and serum cytokine concentrations have been explored with some success, their expense and the difficulty of obtaining them limit their widespread use in clinical practice. [27] Consequently, current

ICANS assessment procedures rely on frequent, standardized bedside examinations, which can be subjective and resource-intensive. [27]

Current Assessment Approaches

Several tools are currently used to assess cognitive function in patients with Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), each with its own strengths and limitations.

The **ICE score** is a standardized 10-point bedside assessment tool endorsed by the American Society for Transplantation and Cellular Therapy. It evaluates five components: orientation, naming, following commands, writing, and serial 10s subtraction. [26] While it is the current standard for ICANS assessment, the ICE score has poor sensitivity for detecting mild cognitive dysfunction, especially in patients with high baseline cognitive function. [5] Patients can have a perfect score of 9-10/10 yet still exhibit significant deficits in areas like attention, processing speed, and learning. [28] The tool also requires modification for patients with visual or hearing impairments or for non-native speakers. [26]

The **Montreal Cognitive Assessment (MoCA)** is a more sensitive tool than the ICE score for detecting subtle cognitive changes. It evaluates a wider range of cognitive domains, including executive function, visuospatial skills, attention, language, and memory. [5] In a study of 360 CAR-T patients, a positive MoCA result (indicating cognitive impairment) was a significant predictor of ICANS, with higher scores being associated with a lower risk. [10]

Neuropsychological batteries offer the most comprehensive assessment of cognitive function. These include tests like the Hopkins Verbal Learning Test (HVLT) for memory, the Mini-Mental State Examination (MMSE) for basic screening, and domain-specific tests such as the Wisconsin Card Sorting Test for cognitive flexibility, the Trail Making Test for processing speed, and the Stroop Test for inhibitory control. [5] Additionally, the CAR-T Neurotoxicity Screener (CART-NS) is a specialized tool developed to address the limitations of traditional methods. It consists of eight abbreviated neurocognitive tests and two symptom questionnaires administered at 8-hour intervals. The CART-NS has predictive capability, with early Stroop test changes showing a high predictive accuracy (AUC=0.857) for ICANS within 36 hours. [29]

Evidence for Early Screening and Monitoring

There is strong evidence to support the use of early screening protocols for detecting cognitive decline in ICANS patients. Pre-infusion assessment with the MoCA has been shown to stratify ICANS risk, as patients with a score below 26 have a significantly higher rate of neurotoxicity. [10] This allows for targeted surveillance and proactive management. During the acute phase, frequent serial testing with tools like the CART-NS can sensitively detect subtle cognitive changes. [29] Routine use of the ICE score provides a standardized method for bedside monitoring, although its limited sensitivity highlights the need for a multimodal screening approach. [26]

Collectively, a strategy combining pre-infusion MoCA, frequent CART-NS assessments, and the use of the ICE grading system enables the early detection of cognitive decline, optimizes the timing of interventions, and helps to mitigate long-term neurocognitive issues in CAR-T recipients. [10] [26] [29]

Current Evidence on Cognitive Recovery Patterns

The trajectory of cognitive recovery following ICANS is highly variable, with significant implications for long-term care and rehabilitation. While acute cognitive symptoms typically appear within the first two

weeks after CAR-T infusion, recovery patterns are often heterogeneous and unpredictable. [30]
Most cognitive symptoms associated with ICANS improve within the first month, and the majority of patients show cognitive stabilization by three months post-infusion. However, it's worth noting that performance-based measures can reveal more subtle changes. One prospective study found that patients might show declines on objective cognitive tests in the first month, even while subjectively reporting stable function. [31]Long-term cognitive outcomes are generally favorable, but a notable minority of patients continue to experience persistent difficulties. Quality of life assessments indicate that while overall cognitive function returns to near-baseline levels by six months, approximately 18-22% of patients report clinically significant cognitive symptoms, depression, or anxiety at this time point. [32] An important factor in recovery is treatment response: patients with progressive disease show worse perceived cognition over time. [13]

Fig: X Emerging themes from the review:

Theme	Sub-Theme	Codes
1. **Clinical Impact of ICANS on Cognition**	a. Incidence and Prevalence	- 26.9% CAR-T recipients affected - 10.5% high-grade neurotoxicity - Cognitive dysfunction in nearly all ICANS patients
	b. Cognitive Domain Impairments	- Attention/concentration deficits - Memory impairment - Executive dysfunction - Language impairments (aphasia, agraphia) - Word-finding difficulties
2. **Pathophysiological Mechanisms**	a. Neuroinflammatory Processes	- Cytokine-mediated neuroinflammation - IL-6, GM-CSF, TNF-α elevation - Blood-brain barrier disruption - Microglial activation - Endothelial activation
	b. Biomarker Evidence	-Elevated serum neurofilament light chain - CD27 serum proteins - CSF proteomics markers

			- EEG abnormalities (80% cases)
3.	**Assessment and Monitoring**	a. Current Assessment Tools	- ICE score (standardized bedside assessment) - Montreal Cognitive Assessment (MoCA) - Neuropsychological batteries (HVLT, MMSE) - CAR-T Neurotoxicity Screener (CART-NS) - Domain-specific tests
4.	**Treatment and Management**	a. Current Interventions	- Corticosteroids (dexamethasone) - Tocilizumab limitations - Supportive care measures - Seizure prophylaxis - Symptom-based management
		b. Prophylactic Measures	-CRS risk mitigation - Cytokine monitoring - Pretreatment tumor burden assessment - Early biomarker detection - Risk-based interventions

One notable case report described the use of pharmacological agents oxiracetam and GV-971, which yielded gradual cognitive improvement in a CAR-T recipient with persistent cognitive deficits post-ICANS. [7] . More commonly, clinical management adopts a multidisciplinary rehabilitation framework integrating occupational therapy to support daily living activities and energy conservation, speech-language pathology targeting language and memory deficits, physical therapy for mobility impairments, and neuropsychological consultation for comprehensive cognitive assessment and strategy training [33] Systematic pre-infusion cognitive screening using validated tools such as the Montreal Cognitive Assessment (MoCA) demonstrates promise in predicting ICANS risk and should be integrated into oncology protocols to enable early risk stratification and patient education**.** Furthermore, emerging tools like the CAR-T Neurotoxicity Screener (CART-NS) provide sensitive detection of early cognitive changes during acute monitoring and facilitate timely therapeutic interventions. [29] Longitudinal cognitive monitoring extending beyond the acute phase, with defined thresholds for rehabilitation referral, is essential for optimizing survivorship care.

Conclusion

This systematic review reveals that ICANS-related cognitive dysfunction is a significant and multifaceted clinical challenge, impacting multiple cognitive domains with highly variable recovery trajectories. The underlying pathophysiology involves complex neuroinflammatory cascades that lead to blood-brain barrier disruption and microglial activation. A complete understanding of this condition is currently limited by the heterogeneity of assessment methods, a lack of standardized outcome measures, and insufficient long-term longitudinal data, which collectively impede the establishment of universal guidelines for rehabilitation and care.[34]To address these critical gaps, future research must prioritize the development and validation of standardized assessment protocols and the identification of reliable predictive biomarkers to enable earlier and more effective intervention. Furthermore, the establishment of evidence-based therapeutic interventions and standardized care models will be pivotal for improving long-term cognitive outcomes and enhancing the overall quality of survivorship for CAR-T patients affected by ICANS.

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