Neurovascular/Stroke-Related Safety of CAR-T Cell Products Axicabtagene Ciloleucel, Tisagenlecleucel, and Lisocabtagene Maraleucel for the Treatment of Aggressive B Cell Lymphoma: A Systematic Review.

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Introduction

- CD19-directed chimeric antigen receptor T-cell (CAR-T) therapies such as axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel have revolutionized outcomes in relapsed/refractory aggressive Large B-cell lymphomas (LBCL).
- But the risk of **neurovascular toxicities**, including stroke, immune effector cell-associated neurotoxicity syndrome (ICANS), and cytokine release syndrome (CRS), remains a significant concern.

Methods

- Study Design: A systematic review
- Databases: PubMed, Scopus, Google Scholar (through April 2025)
- Search Terms: "CAR-T," “Axi-cel," “Tisa-cel," “Liso-cel," "B-cell lymphoma," “Stroke," "ICANS,“ “CRS.”
- Inclusion: Adult LBCL studies (trials, cohorts, registries)
- Analysis: Variation in outcome definitions and reporting makes a meta-analysis impractical, leading to a systematic review.

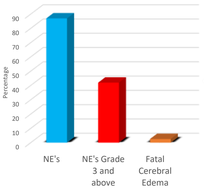
Objective

- To synthesize current evidence on neurovascular adverse events associated with CD19-targeting CAR-T products axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel).

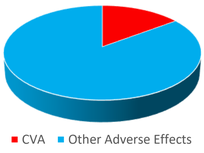
Results

Of 1567 search results, five studies involving 1353 patients with large B-cell lymphoma treated with CD19 CAR-T therapies (axi-cel, tisa-cel) were included. Neurovascular events, particularly **stroke and cerebral edema**, were reported in these studies.

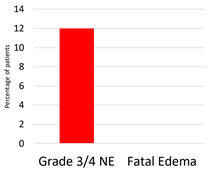
Neurovascular Event Rate in Locke et al., 2024 (axi-cel, n=38)



MACE event types in LBCL in Steiner et al., 2022 (n=27)

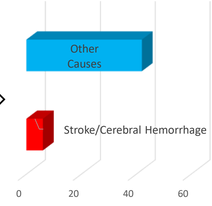


Severe Neurovascular Events in Schuster et al., 2019 (n=93)

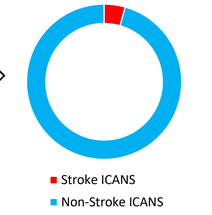


Study	Design / Population	Neurovascular Events	Key Findings
Locke et al., 2024 (ZUMA-1, prophylaxis)[1]	38 r/r LBCL pts, axi-cel	**87% neurologic events**; 42% grade ≥3; 1 fatal cerebral edema	High IL-6 in CSF linked to neuro events despite prophylaxis
Lemoine et al., 2023 (DESCAR-T registry)[2]	957 LBCL pts, axi-cel / tisa-cel	Stroke & cerebral hemorrhage = 6 out of 48 non-relapse deaths. **(12.5%)**	It shows neurovascular events as a significant driver of mortality
Steiner et al., 2022 (single-center)[3]	165 LBCL pts	**16%** of MACE were CVA	Higher CRS grade & older age → ↑ risk
Strati et al., 2020 (cohort, EEG/neuroimaging)[4]	Axi-cel pts with ICANS	Stroke variants in **4.4%**; abnormal EEG’s are frequent	Stroke-like events overlap with ICANS; detectable via imaging/EEG
Schuster et al., 2019 (phase 2, tisa-cel)[5]	r/r DLBCL pts	**12%** severe NEs; no fatal cerebral edema	Severity not always correlated with mortality

Causes of Non-Relapse Death in Lemoine et al., 2023 (n=48)



Strokes in ICANS in Strati et al., 2020 (n=68)



Taken together, these studies reveal a consistent incidence of neurovascular complications following CAR-T therapy, with event characteristics and outcomes influenced by treatment approach, patient risk profile, and associated inflammatory biomarkers.

Discussion

In CD19 CAR-T–treated aggressive B-cell lymphomas, ICANS and CRS are well characterized, but cerebrovascular events are less understood and often overlooked. Recognition is challenging because clinical features frequently overlap with ICANS, and many trials exclude patients with baseline neurologic disease. Higher CRS grade, older age, and elevated CSF IL-6 may indicate increased risk. Vigilance is essential, with early neuroimaging, timely neurology involvement, and use of standardized assessments to aid detection and management.

Summary

Neurovascular events such as stroke and cerebral edema, though uncommon, are important complications of CD19 CAR-T therapy in aggressive B-cell lymphoma. Overlap with ICANS can delay recognition, making early diagnosis and intervention critical. Ongoing research is needed to better define risks and improve patient outcomes.

References

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