Neurotoxicity in central nervous system tumors treated with CAR T cell therapy: a review

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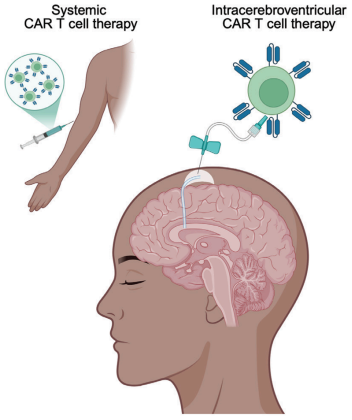

ICANS	TIAN	MNTs	CAR T cell related cognitive impairment
Global toxicity	Localized toxicity	Localized toxicity	Global toxicity
Can occur with both IV and ICV infusions, but more commonly seen with IV infusions	Can occur with both IV and ICV infusions, but more commonly seen with ICV infusions	Can occur with both IV and ICV infusions	Can occur with both IV and ICV infusions
Often preceded by CRS	May occur with or without concurrent CRS	Typically occurs after the resolution of CRS and ICANS	May occur with or without concurrent CRS
Associated with encephalopathy, tremors, dysgraphia, seizures, apraxia, aphasia, acalculia, cerebral edema	Associated with transient worsening of existing or new neurological symptoms from a patient's baseline (Type 2 TIAN) OR clinical signs/symptoms of increased intracranial pressure (Type 1 TIAN)	Associated with bradykinesia, micrographia, tremor, cogwheel rigidity, motor dysfunction, speech disturbances, gait changes, reduced attention, memory impairment, flat affect, reduced facial expression, apathy	Associated with neurocognitive slowing and memory changes
Treatment can include anakinra, corticosteroids and tocilizumab when there is concurrent CRS	Treatment can include anakinra, corticosteroids, and neurocritical care measures and CSF removal	Treatment can include corticosteroids and if severe, cyclophosphamide	Treatment consists of supportive care, as there is no toxicity-specific treatment

Abstract

Background

Chimeric antigen receptor (CAR) T cell therapy has revolutionized treatment for hematologic malignanciesand is now being applied to central nervous system (CNS) tumors. As experience grows, distinct neurotoxicities are emerging that differ from those observed in systemic CAR T cell therapy. Understanding these toxicities is critical for optimizing safety and advancing clinical translation.

Methods

We reviewed preclinical data and early-phase clinical trials of CAR T cell therapy for CNS tumors, focusing on the characterization, mechanisms, and management of treatment-associated neurotoxicity. Three major categories were examined: immune effector cell–associated neurotoxicity syndrome (ICANS), tumorinflammation–associated neurotoxicity (TIAN), and other non-ICANS neurotoxicities (NINTs), including movement and neurocognitive treatment-emergent events.

Results

ICANS reflects a global, cytokine-mediated process, whereas TIAN represents localized inflammation at the tumor site, producing either mechanical (type 1) or electrophysiologic (type 2) neurologic dysfunction. TIAN is common across phase I trials of locoregional CAR T cell therapy for CNS tumors, often transient and reversible, and may require

corticosteroids, IL-1 blockade, or cerebrospinal fluid diversion. ICANS remains uncommon in this setting. Emerging data also suggest microglial activation and neurocognitive effects paralleling chemotherapy-related cognitive impairment.

Conclusion

CAR T cell therapy for CNS tumors induces unique neurotoxicities reflecting local immune activation within the brain. Differentiating ICANS from TIAN is essential for appropriate management. Standardized grading criteria, prospective neurocognitive monitoring, and rational CAR design are critical next steps in safely advancing CAR T cell therapy in neuro-oncology.

No datasets were generated or analysed during the current study.

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Additional information

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