

Neurological complications in patients receiving CAR T-cell therapies

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ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 or B cell maturation antigen has revolutionized the treatment of patients with relapsed lymphoma, acute lymphoblastic leukemia, and multiple myeloma. However, this therapy is associated with both short- and long-term immune-mediated toxicities. Among them, neurological complications represent a distinct and clinically significant category, with a wide range of presentations. In this paper, we describe the different types of immune effector cell-associated neurotoxicity syndrome (ICANS) and non-ICANS neurological toxicities, including their clinical features, recommended diagnostic evaluations, underlying mechanisms, and available treatment approaches.

Keywords: Cellular Therapies. ICANS. Non-ICANS Complications.

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapies targeting CD19 or B-cell maturation antigen (BCMA) have transformed the treatment landscape for patients with relapsed lymphoma, acute lymphoblastic leukemia, and multiple myeloma¹, with expanding global use and indication in earlier lines of therapy. However, these therapies are associated with both acute- and long-term immune-mediated toxicities^{2,3}, which may be particularly challenging to manage in resource-variable settings⁴. Among these adverse events, neurological complications constitute a distinct and clinically significant category, with a broad spectrum of manifestations⁵⁻⁷, including immune effector cell-associated neurotoxicity syndrome (ICANS), as well as other non-ICANS neurological toxicities.

In this review, we discuss both common and uncommon presentations of ICANS, with an emphasis on clinical features, diagnostic approaches, and management strategies, and with particular attention to patients in Brazil and Latin America (Chart 1).

SEARCH METHOD

A structured narrative literature review was conducted using PubMed/MEDLINE and recent major society guidelines to identify relevant publications on neurological complications associated with CART-cell therapies. Searches included articles published through December 2025 using combinations of the terms “CAR T-cell,” “ICANS,” “neurotoxicity,” “ICU,” “mortality,” “movement disorders,” “myelopathy,” “peripheral neuropathy,” “cranial nerve palsy,” and “tumor inflammation-associated neurotoxicity.” Priority was given to prospective clinical trials, large retrospective series, consensus guidelines, and high-impact review articles. Additional references were identified through manual review of bibliographies from selected publications. Emphasis was placed on clinically relevant data regarding incidence, presentation, biomarkers, diagnostic evaluation, management strategies, and considerations applicable to Brazil and Latin America.

Chart 1. Practical perspective: Latin America and Brazil.

Key regional challenges
CAR T-cell access concentrated in a limited number of tertiary centers
Public reimbursement remains variable or limited
Long manufacturing/import timelines may prolong vein-to-vein time
ICU beds, EEG, urgent MRI, and neurology consultation may not be uniformly available
Referral delays may increase disease burden before infusion
Practical recommendations
Establish institutional ICANS monitoring pathways using ICE scores
Predefine transfer criteria to higher-complexity centers
Use tele-neurology when on-site specialists are unavailable
Include infectious disease consultation early for CNS differential diagnosis
Adapt workup to endemic infections (tuberculosis, cryptococcosis, neurocysticercosis, arboviruses, Chagas disease when relevant)
Standardize corticosteroid, seizure, and CRS escalation protocols
Train nursing staff in early neurotoxicity recognition

CAR: chimeric antigen receptor; ICU: intensive care unit; EEG: electroencephalogram; MRI: magnetic resonance imaging; ICANS: immune effector cell–associated neurotoxicity syndrome; ICE: immune effector cell encephalopathy; CNS: central nervous system; CRS: cytokine release syndrome. Source: Elaborated by the authors.

IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME IN CELLULAR THERAPIES

Definition and classification

ICANS is the most frequently observed neurological complication and occurs with every approved CAR T-cell product (Table 1), typically between days 5 and 10 following cell infusion^{8–15}. The most common presentation is encephalopathy, accompanied by headaches, language impairment, tremors, and handwriting deficits, but clinical manifestations can vary widely and may also include motor weakness, ataxia, insomnia, anxiety, agitation, and psychosis. Tonic-clonic seizures and cerebral edema are less common and occur in 2–3% of patients. The presence and severity of ICANS are assessed using the standardized immune effector cell encephalopathy (ICE) score (Table 2), a 10-point scale that includes tests of orientation, naming, writing, attention, and the ability to follow commands¹⁶, as well as evaluation of other neurological domains, including level of consciousness, motor symptoms, seizures, or cerebral edema/evaluated intracranial pressure. All these data combined leads to the American Society for Transplantation and Cellular Therapy ICANS Consensus Grading Guidelines for Adults (Table 3).

Table 1. Rates of ICANS and non-ICANS neurological toxicities based on cellular therapy products.

Cellular product	Indications	ICANS incidence (95%CI)	ICANS G3/G4 Incidence (95%CI)	Non-ICANS prevalence
Axicabtagene ciloleucel	DLBCL, FL	77% (47–95%)	20% (14–28%)	Unknown
Brexucabtagene autoleucel	MCL, B-ALL	65% (49–80%)	31% (22–43%)	Unknown
Lisocabtagene maraleucel	DLBCL, CLL/SLL, FL, MCL, MZL	24% (3–75%)	9% (1–45%)	Unknown
Tisagenlecleucel	B-ALL, DLBCL	20% (7–43%)	3% (0–8%)	Unknown
Ciltacabtagene autoleucel	MM	20% (2–74%)	5% (0–80%)	12%
Idecabtagene vicleucel	MM	22% (3–73%)	3% (1–10%)	Unknown

ICANS: immune effector cell–associated neurotoxicity syndrome; 95%CI: 95% confidence interval; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; MZL: marginal zone lymphoma; MM: multiple myeloma. Source: Elaborated by the authors.

Table 2. Immune effector cell encephalopathy (ICE) scoring and grading: part 1.

Domain	Points
Orientation: year, month, city, hospital	4
Name three objects (e.g., point to clock, pen, button)	3
Follow simple command	1
Write a standard sentence	1
Count backward from 100 by tens	1

ICE scoring: 10 = normal; 7–9 = mild impairment; 3–6 = moderate impairment; 0–2 = severe impairment. Source: adapted from the ASTCT grading criteria¹⁶.

Table 3. Differences between immune effector cell–associated neurotoxicity syndrome (ICANS) and tumor inflammation-associated neurotoxicity (TIAN).

Feature	ICANS	TIAN
Full term	Immune effector cell-associated neurotoxicity syndrome	Tumor inflammation-associated neurotoxicity
Primary mechanism	Systemic inflammation, endothelial activation, blood-brain barrier disruption, cytokine-mediated CNS toxicity	Local on-tumor, on-target inflammatory reaction at sites of CNS disease involvement
Typical population	Any patient receiving CAR T-cell therapy	Most often patients with primary or secondary CNS lymphoma or CNS tumor involvement
Time of onset	Usually days 1–10 after infusion, often concurrent with or after CRS	Often early after infusion, variable timing depending on tumor burden/location
Association with CRS	Common	May occur with or without CRS
Common symptoms	Encephalopathy, aphasia, confusion, inattention, tremor, seizures, reduced consciousness	Headache, focal deficits, cranial neuropathies, worsening pre-existing neurologic deficits, symptoms of raised ICP
Neurologic exam	Diffuse cortical dysfunction common	Often focal/localizing findings
ICE score	Commonly abnormal and used for grading	May be normal unless diffuse dysfunction coexists
MRI findings	Often normal or nonspecific; FLAIR/T2 changes in severe cases	Lesion-centered edema, mass effect, hydrocephalus, localized inflammatory changes
CSF findings	Often nonspecific inflammatory changes	Variable; may reflect tumor/inflammatory involvement
Key diagnostic clue	Diffuse encephalopathy after CAR T-cell therapy	Neurologic worsening anatomically corresponding to known CNS disease
Initial management	Corticosteroids, seizure monitoring, ICU support if severe	Corticosteroids, ICP management, neurosurgical consultation when indicated
Role of tocilizumab	Helpful for CRS; limited CNS penetration for isolated ICANS	Usually limited unless CRS coexists
Prognosis	Often reversible with prompt treatment	Depends on location, tumor burden, ICP complications

CNS: central nervous system; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; ICP: intracranial pressure; ICE: immune effector cell encephalopathy; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid. Source: Elaborated by the authors.

Relationship with cytokine release syndrome, biomarkers, and pathogenesis

ICANS commonly occurs concurrently with or following cytokine release syndrome (CRS) and appears largely product independent. This temporal relationship suggests that ICANS may result from a combination of systemic hyperinflammatory response, endothelial activation, blood-brain barrier disruption, and trafficking of immune effector cells and cytokines into the central nervous system rather than from direct CAR T-cell target recognition within neural tissue alone^{17–20}. Although ICANS has been reported with all commercially available CAR T-cell products, differences in incidence and severity may be partially impacted by CAR construct design, particularly in the co-stimulatory domain. Specifically, CD28-based products generally demonstrate faster expansion kinetics and a more robust early cytokine surge compared with 4-1BB-based constructs, which may contribute to higher observed ICANS rates in some studies²¹.

Several biomarkers have emerged as potential tools for risk stratification, and early predictors have been developed to help predict ICANS severity (Chart 2). Markers of endothelial injury are among the most

consistently associated with toxicity, including the serum angiopoietin 2 to angiopoietin 1 (Ang-2/Ang-1) ratio at day 7, Willebrand factor, soluble thrombomodulin, and ferritin, supporting the central role of vascular permeability and capillary leak¹⁷. The modified endothelial activation and stress index (m-EASIX) score, which incorporates lactate dehydrogenase, platelet count, and C-reactive protein values, has also shown promise as a pragmatic bedside predictor of both CRS and ICANS severity at early timepoints²². Elevated inflammatory cytokines such as interleukin (IL)-6, IL-10, interferon- γ , tumor necrosis factor (TNF)- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1/CCL2) have also been associated with neurotoxicity¹⁷, while increased CSF concentrations of IL-10, MCP-1, and other chemokines may reflect intrathecal immune activation²³. Biomarkers of neuronal injury, including neurofilament light chain (nFL), glial fibrillary acidic protein (GFAP), and S100B, are increasingly recognized as markers of astrocytic injury, axonal damage, and blood-brain barrier dysfunction^{19,23}. Elevated baseline plasma nFL prior to CAR T-cell infusion has been associated with subsequent ICANS, suggesting some patients may have pre-existing neurologic vulnerability²⁴.

Chart 2. Immune effector cell encephalopathy (ICE) scoring and grading: part 2.

Finding	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 and unarousable / severe global dysfunction
Depressed consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous/repeated stimulus
Seizure	None	None	Any brief seizure resolving rapidly	Life-threatening, prolonged, repetitive, status epilepticus
Motor findings	None	None	Focal weakness	Deep focal weakness, diffuse weakness
Cerebral edema	None	None	Focal/local edema	Diffuse edema, signs of raised intracranial pressure, herniation risk

Source: adapted from the ASTCT grading criteria¹⁶.

From a practical clinical standpoint, no single biomarker is sufficient for routine standalone use yet, but serial monitoring can complement bedside assessment. Patients at higher risk may benefit from trending C-reactive protein (CRP), ferritin, complete blood count, coagulation parameters, liver and renal function, and m-EASIX scores during the first 7–14 days after infusion, particularly when CRS is present. Rapid rises in inflammatory markers, thrombocytopenia, worsening coagulopathy, or escalating ferritin may precede neurologic deterioration. Clinically, the most important monitoring remains structured neurologic examination using the ICE score, handwriting changes, language dysfunction, inattention, tremor, altered level of consciousness, and seizure surveillance.

Future prospective studies are needed to validate combined biomarker panels integrating endothelial, inflammatory, and neuronal injury markers to enable earlier intervention and personalized ICANS prevention strategies.

DIAGNOSTIC APPROACHES AND MANAGEMENT

Recognition and management of ICANS require multidisciplinary collaboration among hematology, neurology, intensive care, and infectious disease specialists. This is particularly important in Latin America, where tuberculosis, endemic fungal infections, viral encephalitis, and other tropical diseases may mimic or coexist with ICANS. Accordingly, the differential diagnosis should be tailored to local epidemiology rather than relying exclusively on U.S.- or Europe-based diagnostic algorithms (Chart 3).

Grade 1 ICANS is typically managed with close clinical monitoring and frequent neurological examinations. In contrast, evaluation of grade ≥ 2 ICANS should also include brain magnetic resonance imaging (MRI) and electroencephalogram (EEG). EEG should be considered early in patients with encephalopathy, as non-convulsive seizures can occur. Patients with low-grade ICANS often have normal MRI findings, whereas those with higher-grade ICANS may demonstrate reversible T2-weighted or fluid-attenuated inversion recovery

Chart 3. Biomarkers for ICANS and non-ICANS neurological toxicities.

Biomarker	Category	Proposed significance	Clinical use status	Level of evidence
CRP	Systemic inflammation	CRS/inflammation included in m-EASIX	Routinely available, nonspecific	Moderate-High
Ferritin	Hyperinflammation/macrophage activation	Severe inflammation, higher toxicity risk	Routinely available	Moderate-High
LDH	Tissue injury/tumor burden	Included in m-EASIX	Routinely available	Moderate
Platelet count	Endothelial consumption/coagulopathy	Included in m-EASIX	Routinely available	Moderate
Angiopoietin-2 / Angiopoietin-1 ratio	Endothelial activation	BBB dysfunction, capillary leak, ICANS risk	Investigational	Moderate/experimental
Von Willebrand factor	Endothelial injury	Supports vascular activation	Investigational	Low-moderate/experimental
IL-6	Cytokine surge	CRS-related inflammation	Limited routine use	High association/moderate biomarker utility
IL-10	Anti-inflammatory/cytokine dysregulation	Associated with severe ICANS in some studies	Investigational	Low-moderate
MCP-1 (CCL2)	Monocyte trafficking/CNS inflammation	Associated with CSF neuroinflammation	Investigational	Low-moderate
Neurofilament light chain (nFL)	Axonal injury	Baseline vulnerability/neuronal injury	Emerging	Moderate/experimental
GFAP	Astrocytic injury	CNS glial injury marker	Emerging	Low-moderate/experimental
S100B	BBB/glial injury	May reflect barrier disruption	Investigational	Low/experimental
Absolute lymphocyte count	CART-expansion surrogate	May correlate with delayed non-ICANS toxicity in BCMA CART	Emerging	Low-moderate depending on ICANS or non-ICANS

ICANS: immune effector cell-associated neurotoxicity syndrome; CRP: C-reactive protein; LDH: lactate dehydrogenase; IL: interleukin; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; BBB: blood-brain barrier; CSF: cerebrospinal fluid; CNS: central nervous system. Source: Elaborated by the authors.

(FLAIR) hyperintensities. Lumbar puncture should be considered in atypical or prolonged cases to exclude alternative etiologies, with diagnostic testing adapted to local epidemiology, including opportunistic fungal infections (e.g., cryptococcosis or aspergillosis), endemic viral infections (such as arboviruses as Dengue fever, Zika virus infection, and Chikungunya fever), toxoplasmosis, neurocysticercosis, and Chagas disease. Preemptive seizure treatment (e.g., levetiracetam 750 mg twice daily) may be considered for patients with grade 3–4 ICANS, although evidence supporting routine seizure prophylaxis remains mixed^{25,26}.

Management of ICANS is guided by disease grading and clinical persistence. Low-grade ICANS (grades 1–2) is typically treated with corticosteroids, most commonly intravenous (IV) dexamethasone 10 mg with repeat dosing every 6–12 hours depending on clinical response. Higher-grade ICANS (grades 3–4) should be managed with high-dose steroids, either IV dexamethasone 10 mg every 6 hours or IV methylprednisolone 1 mg/kg. For steroid-refractory ICANS, additional interventions may be considered, including the IL-1 receptor antagonist anakinra and intrathecal chemotherapy. Ruxolitinib and the interferon- γ -blocking antibody emapalumab have shown promise in preclinical models and have also been used in selected patients²⁷.

It should be emphasized that, aside from corticosteroids, the evidence supporting these second- and third-line agents remains limited. No randomized controlled trials have evaluated the management of steroid-refractory ICANS or non-ICANS neurological toxicities, and current recommendations regarding anakinra, ruxolitinib, emapalumab, and cyclophosphamide are largely derived from preclinical studies, case reports, and small retrospective series. Accordingly, these options should be regarded as reasonable but low-certainty strategies requiring individualized clinical judgment and, whenever feasible, implementation within a multidisciplinary framework or evaluation in the context of a clinical trial.

While grade 1 can generally be monitored on a regular medical service, patients with grade 2 ICANS may require transfer to the intensive care unit (ICU), often for close observation, particularly in the setting of rapidly deteriorating symptoms²⁸. Admission to a medical or neurological ICU is usually recommended for patients with grade 3–4 ICANS, rapid neurological decline, sustained seizures or status epilepticus, and when specialized monitoring or endotracheal intubation for airway protection is required due to reduced levels of consciousness. While established centers may offer round-the-clock neurology consultation, neurocritical care, MRI, EEG, and advanced cerebrospinal fluid diagnostic testing, these resources are not uniformly available throughout the region. Accordingly, practical institutional protocols are essential, including routine ICE score surveillance, early corticosteroid and tocilizumab escalation algorithms, structured seizure recognition and management pathways, and predefined referral and transfer pathways to higher-complexity centers when necessary.

ICANS is reversible in most patients and typically resolves without major neurological sequelae; reported mortality varies and is most often related to infectious complications or other concurrent medical conditions²⁹. However, a subset of patients experience persistent neurological symptoms, including cognitive impairment (e.g., memory loss or aphasia), motor deficits (such as parkinsonism-like tremors), peripheral neuropathy, or autonomic dysfunction manifested as orthostatic hypotension^{30,31}.

Beyond the acute period, the long-term neurological trajectory of CAR T-cell recipients remains incompletely characterized, although emerging survivorship data suggest that a meaningful minority of patients experience persistent cognitive impairment and reduced quality of life. Prospective and cross-sectional studies have described lingering difficulties with memory, attention, processing speed, and executive function, as well as fatigue, anxiety, depression, and sleep disturbances, which may persist for months after infusion and appear to correlate with the severity of prior CRS and ICANS^{30,31}. These deficits are often subtle and may not be detected by routine bedside neurological assessments, underscoring the importance of formal neurocognitive evaluation and the incorporation of patient-reported outcome measures in long-term follow-up. Structured neurological surveillance, including cognitive screening, functional assessment, and evaluation for late-onset movement, sensory, autonomic, and neuropsychiatric symptoms, is increasingly advocated, particularly for patients who experienced higher-grade acute neurotoxicity. Longitudinal studies using standardized neurocognitive assessments and quality-of-life instruments are needed to better define the incidence, duration, reversibility, and predictors of long-term neurological impairment and to inform evidence-based survivorship care.

OTHER NEUROLOGICAL COMPLICATIONS WITH CELLULAR THERAPIES

Beyond ICANS, an emerging group of less well-described complications have been reported and collectively described as non-ICANS neurological toxicities. These include tumor inflammation-associated neurotoxicity (TIAN), movement and neurocognitive toxicity (MNT), cranial nerve palsies, ischemic stroke, myelopathy, and peripheral neuropathy⁵.

TIAN is a neurologic complication distinct from ICANS that results from CAR T-cell-related on-tumor, on-target inflammation at sites of the central nervous system (CNS) malignant involvement (Table 3). It has been reported in patients with CNS lymphoma treated with anti-CD19 CAR T-cell therapy, and its clinical presentation varies depending on the location of the lesions³². Since features of TIAN can overlap with those of ICANS, it should be included in the differential for all patients with CNS disease. Two clinical subtypes of TIAN have been described. Type 1 TIAN, or mechanical neurotoxicity, is characterized by elevated intracranial pressure (ICP) due to cerebral edema or CSF outflow obstruction resulting from on-tumor, on-target inflammation. Patients with posterior fossa tumors are at particularly high risk for this subtype because of anatomical constraints and should be considered for external ICP monitoring. Clinical presentation can range from mild headaches to severe manifestations of cerebral herniation, including altered mental status, cranial nerve dysfunction, focal sensorimotor deficits, and respiratory compromise. Type 2 TIAN refers to localized

CNS on-tumor, on-target inflammation that results in electrophysiological dysfunction and worsening of pre-existing neurological symptoms related to underlying CNS disease involvement. Management of both subtypes relies on close neurological examination, with MRIs considered as needed, although radiographic findings often lag behind clinical changes. Treatment of Type 1 TIAN focuses on reducing ICP through CSF diversion or hyperosmolar therapy, along with corticosteroids to reduce inflammation. Refractory cases warrant neurosurgical consultation. Type 2 TIAN typically requires close observation with serial neurological examinations, although corticosteroids, with or without anakinra, may be considered for patients with progressive or severe symptoms^{5,33}.

MNT is characterized by a new-onset movement disorder, most commonly resembling parkinsonism, with features such as bradykinesia, cogwheel rigidity, motor dysfunction, gait disturbances, speech disturbances, and diminished facial expression. It may also include cognitive changes (*e.g.*, attention, or memory impairment) and personality changes (apathy, flat affect). MNT typically emerges after the resolution of CRS and ICANS, with a median onset of 36 days (range, 14–914 days) after CAR T-cell infusion^{34,35}. This neurotoxicity has been associated with anti-BCMA CAR T-cell therapy possibly related to BCMA expression within the CNS, particularly in the basal ganglia. Like ICANS or CRS, measurement of absolute lymphocyte count can help differentiate MNT from a primary movement disorder, as lymphopenia or absent CAR T-cells would argue against MNT. Specifically, after anti-BCMA CAR T-cell infusion, a day-14 peripheral acute lymphocyte count $\geq 2.4 \times 10^3$ per microliter has been shown to be associated with MNT development, as well as cranial nerve palsies³⁶. In addition to neurology consultation, a trial of levodopa can be informative, as MNT is typically not responsive to dopamine replacement and clinical improvement would suggest a primary movement disorder. MRI can help exclude structural etiologies, and lumbar puncture can also be performed to assess the presence of CAR T-cells in the CSF. In immunocompromised patients developing parkinsonism after cellular therapy, infectious etiologies including tuberculosis, neurocysticercosis, cryptococcosis, or arboviruses should be excluded before attributing symptoms to delayed neurotoxicity or neurodegeneration. Dexamethasone is recommended as first-line therapy, followed by high-dose systemic cyclophosphamide (2 g/m²) for refractory cases. Other options include ruxolitinib, etoposide or other lymphodepleting chemotherapy, and intrathecal chemotherapy^{5,20,27}.

Cranial nerve palsies represent another non-ICANS neurological complication, most observed following anti-BCMA CAR T-cell therapy³⁷. Although the underlying mechanism remains poorly defined, CAR T-cell-related inflammation is thought to contribute, while some cases may occur in the context of TIAN for anti-CD19 CAR T-cell therapies. Cranial nerve VII (the facial nerve) is the most frequently affected and may present unilaterally or bilaterally, often with an earlier onset than MNT, with a median of 22 days following CAR T-cell infusion. Palsies of cranial nerves III and IV have also been reported. Diagnostic evaluation should include brain MRI and lumbar puncture to exclude alternative etiologies, such as plasmacytoma or leptomeningeal disease. Corticosteroids, either prednisolone 25 mg twice daily or prednisone 1 mg/kg daily for 7–10 days, are recommended as first-line therapy and have been reported to resolve approximately 90% of cases. Intravenous immunoglobulin (IVIG) may be considered in refractory cases.

Although classified as non-ICANS neurological complications, ischemic strokes can occur in the setting of severe ICANS, as well as following prior episodes of ICANS. Ischemic stroke represents a clinically significant complication of CAR T-cell therapy, with reported non-relapse mortality rates ranging from 2–6%^{38,39}. Accordingly, ischemic stroke should be considered in any patient with new neurological symptoms, including those attributed to ICANS, and particularly in the presence of acute focal deficits. Consultation with stroke specialists is recommended, with no specific deviation in management from standard, non-CAR T-cell-related stroke care.

Similarly, acute myelopathy typically occurs after ICANS, most often within 5–27 days of ICANS onset. It presents as a sudden, severe motor or sensory deficit, including flaccid quadriplegia or paraplegia, neurogenic bladder, and hypoesthesia. Several mechanisms have been proposed, including inflammation-induced

blood-brain barrier disruption, spinal cord hypoperfusion due to inflammation-mediated ischemia, and potential CAR T-cell off-tumor targeting of blood-brain barrier-associated cells, such as CD19-expressing mural cells¹⁸. Diagnostic evaluation should include MRI of the brain and spine, as well as lumbar puncture to assess for alternative autoimmune etiologies, including multiple sclerosis, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein–associated disease. In Latin America, infectious causes of acute myelopathy are particularly important in the differential diagnosis because several endemic pathogens can present with transverse myelitis, compressive inflammatory lesions, vascular myelopathy, or post-infectious spinal cord syndromes. Common considerations include tuberculosis (Pott disease with epidural compression, arachnoiditis, intramedullary tuberculoma, or transverse myelitis), human T-lymphotropic virus type 1 associated myelopathy, which is especially relevant in parts of Brazil, Peru, and the Caribbean, schistosomiasis causing schistosomal myeloradiculopathy in endemic areas, neurocysticercosis with spinal involvement, viral infections, and fungal infections such as histoplasmosis and cryptococcosis should also be considered. Because many of these conditions may mimic, evaluation in Latin American patients with acute myelopathy should incorporate local epidemiology, MRI patterns, CSF studies, serologies, and early infectious disease consultation. Metabolic causes should also be excluded (e.g., folate, vitamins B1 and B12, copper, and vitamin E). Treatment parallels the management of autoimmune myelitis, with high-dose corticosteroids (e.g., intravenous methylprednisolone 1 g daily for five days) in the acute phase, while anakinra may be considered in severe or refractory cases^{5,27}.

Peripheral neuropathy has been increasingly reported with both anti-CD19 and anti-BCMA CAR T-cell therapies^{7,40}. This complication includes sensory, motor, or mixed peripheral neuropathy, as well as cases of Guillain-Barré syndrome (GBS). Notably, pre-existing autoimmune neuropathy should not preclude patients from receiving CAR T-cell therapy⁴¹. The etiology of peripheral neuropathy is not well understood, although indirect nerve damage from bystander inflammation has been proposed as a potential mechanism⁵. Diagnostic evaluation for more severe manifestations, particularly GBS, should include MRI imaging, along with CSF and metabolic testing similar to those performed for acute myelopathy. Additional evaluation for anti-GQ1b antibodies in the CSF should be considered if Miller-Fischer syndrome is suspected. Nerve conduction studies and electromyography should also be performed to guide management. For GBS, standard treatment with IVIG is still recommended (400 mg/kg daily for five days), although reported cases have shown limited clinical improvement⁴². Corticosteroids can be considered for other peripheral neuropathies (prednisone 1 mg/kg for 7–10 days).

Finally, cerebellar toxicity has been reported as a non-ICANS neurological complication unique to anti-GPRC5D CART-cell therapy, which is currently in clinical development for the treatment of multiple myeloma⁴³. The underlying etiology may be related to the low-level expression of GPRC5D in the inferior olivary nucleus of the medulla. Diagnostic evaluation and management have not been clearly defined, although limited success has been reported with corticosteroid therapy.

BIOMARKERS AND PREDICTION OF NON-ICANS

Important research gaps remain in the prevention and early detection of non-ICANS neurologic toxicities after CAR T-cell therapy. While ICANS has been relatively well characterized, less is known about delayed and atypical syndromes. In patients with relapsed/refractory multiple myeloma treated with ciltacabtagene autoleucel, rapid and robust CAR T-cell expansion was associated with increased delayed neurotoxicity risk, and early peak absolute lymphocyte count thresholds may serve as a practical surrogate biomarker to identify high-risk patients for preemptive intervention³⁶.

SPECIFIC FOCUS ON LATIN AMERICA

As CAR T-cell therapies expand across Latin America (Chart 1), implementation remains heterogeneous and concentrated in a limited number of specialized centers, with persistent barriers related to reimbursement,

manufacturing timelines, referral pathways, and unequal access to intensive care, EEG, MRI, and neurology expertise. These constraints highlight the need for pragmatic institutional protocols that include routine ICE score monitoring, standardized corticosteroid and CRS escalation pathways, seizure recognition algorithms, and predefined transfer mechanisms to higher-complexity centers when necessary. Early involvement of infectious disease specialists is particularly important in the region, where endemic infections such as tuberculosis, cryptococcosis, neurocysticercosis, arboviruses, and Chagas disease may mimic or coexist with treatment-related neurotoxicity. Future priorities should include regional multicenter registries, local manufacturing initiatives, harmonized treatment algorithms, cost-effectiveness analyses, and long-term survivorship programs to support sustainable growth of cellular therapy programs.

LIMITATIONS

Several limitations of this review should be acknowledged. This is a narrative rather than a systematic review. Although a structured literature search was performed, we did not apply a formal systematic review methodology, predefined inclusion and exclusion criteria, or quantitative synthesis, and selection of the cited literature required a degree of author judgment. The available evidence is heterogeneous and is dominated by retrospective cohorts, single-center experiences, and small case series, with comparatively few prospective or randomized data, particularly for non-ICANS neurological toxicities and long-term outcomes. Variability in toxicity definitions, grading practices, CAR T-cell products, and follow-up duration across studies further limits direct comparisons and the generalizability of the findings. Finally, data specific to Latin America remain sparse, and several of the regional considerations discussed here are extrapolated from broader international experience. These limitations should be considered when interpreting the incidence estimates, biomarker associations, and management recommendations summarized above.

CONCLUSION

CAR T-cell therapies have substantially improved outcomes in hematologic malignancies but are associated with a broad spectrum of neurologic complications ranging from acute ICANS to delayed and atypical non-ICANS syndromes. Early recognition, standardized grading, and prompt multidisciplinary management involving hematology, neurology, and intensive care teams are essential to optimize patient safety while preserving treatment efficacy. As cellular therapies expand globally, particularly in resource-variable settings, institutional protocols adapted to local infrastructure and infectious epidemiology are increasingly important. Future priorities include validation of predictive biomarkers, prevention strategies for ICANS and non-ICANS toxicities, and prospective studies defining long-term neurologic outcomes.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

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