La terapia e il rapporto con i neurologi

Matilde Inglese MD, PhD

DiNOGMI, Università di Genova
AOM, Plesso San Martino

Major Adverse Syndromes

Cytokine Release Syndrome (CRS)

Most common toxicity. Incidence **>50%** (higher in pediatrics). Onset days 1–14, median day 3. Fever, hypotension, hypoxia.

Immune effector cell associated syndrome (ICANS)

Immune effector cell–associated neurotoxicity. Incidence **20–40%**; severe in ~10%. Onset median day 4, up to 14 days.

Delayed-onset neurological syndromes

Neurological syndromes specific to single CAR T-cell types, such as movement and cerebellar toxicities reported with BCMA and GPRC5D-targeted therapies

Tumor inflammation-associated neurotoxicity

TIAN is a focal neurotoxicity arising in patients with CNS tumors treated with CAR T-cells Unlike ICANS, it is driven by local inflammation. TIAN is thus related to on-target on-tumor effects.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	**Timing**: Early onset **Mechanism**: Likely *off-target/off-tumour effect* **Outcome**: Reversible
Antigen-Specific Neurotoxicity Syndromes ***BCMA-targeted:*** MNTs & cranial nerfs palsies ***GPRC5D-targeted:*** Cerebellar syndromes	**Timing**: Delayed onset **Mechanism**: Possible *on-target/off-tumor effects* **Outcome**: Irreversible
Tumor Inflammation-Associated Neurotoxicity (TIAN)	**Timing**: Early onset, can overlap with ICANS. **Mechanism**: Possible *on-target/on-tumor effects* **Outcome**: Reversible

- **Neurotoxicity affects 37.5–77% of anti CD19 CAR-T cell** patients, with high-grade (grade 3–4) events occurring **in 31%** and very rare deaths reported.
- ICANS appears more frequently with CAR constructs incorporating the CD28 costimulatory domain, such as axi-cel or brexu-cel, compared to those with a 4-1BB domain, such as tisa-cel or liso-cel
- Neurotoxicity associated with **BCMA-targeted CAR T-cell therapies** in multiple myeloma is less frequent, occurring in approximately **21% of** patients treated with app roved products

Neurological symptoms and signs

- **Cognitive impairments**, observed in nearly all affected individuals, and nonpyramidal motor symptoms, which occur in roughly 40% of cases.

- Cognitive disturbances are often severe (36%) and may include aphasia, agraphia, executive dysfunction, cognitive slowing, apraxia, disorientation, agitation, dyscalculia, hemineglect, hallucinations, and confusional states, either in isolation or in various combinations .

- **Nonpyramidal motor signs** such as tremor, myoclonus,or dyskinesia are commonly observed and can help support the diagnosis

- **Seizures** are reported in 1–4% of patients,but might sometimes be related to alternative causes, such as disease relapse, central nervous system infections, or the use of high-dose antibiotics.

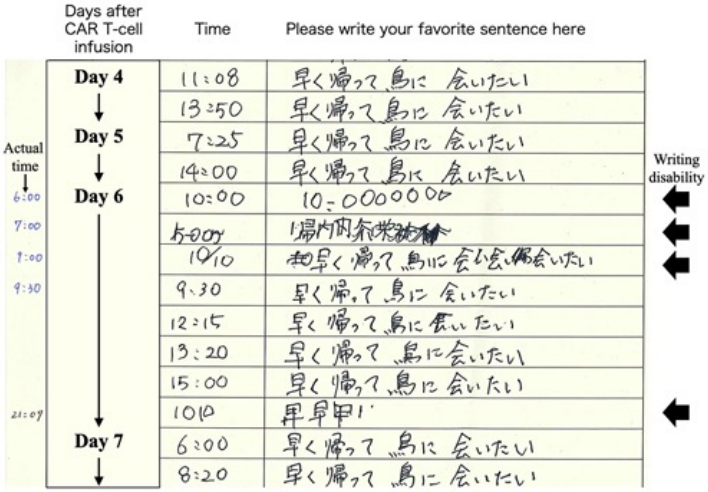
Delayed-onset neurological syndroms

B cell maturation antigen (BCMA)-targeted CAR-T cell therapies, used in multiple myeloma patients. It usually occurs after CRS and ICANS, with a median onset of 36 days postinfusion (range 14–914 days).
Patients may develop irreversible movement disorders, cognitive deficits, personality changes, or combinations of them. Neurological examination can find tremor, cogwheel rigidity, micrographia, apathy, impaired attention and memory, hypophonia, gait disturbances, and reduced facial expressivity
As BCMA is expressed in the basal ganglia, the pathogenesis of this complication might be related to an **off- tumor on-target effect**

GPRC5D-directed CAR-T cell therapies: cerebellar toxicity including dysarthria, ataxia, nystagmus and vertigo, with symptoms appearing at a median of 93days (range 15–170 days) after treatment. As GPRC5D expression has been reported in the inferior olivary nucleus an on-target **off-tumor effect is likely.**

Immune effector cell-associated encephalopathy (ICE) scoring

Evaluation	Question	Point
Orientation	1. Year	1
	2. Month	1
	3. City	1
	4. Hospital	1
Naming (Ability to name 3 objects)	5. Clock	1
	6. Pen	1
	7. Button etc.	1
Following commands	8. Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1
Writing	9. Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1
Attention	10. Ability to count backwards from 100 by 10	1



Hideki G,
Journal of clinical and experimental hematopathology, 2025

ICANS Grading

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (unarousable patient and unable to perform ICE scoring)
Level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable patient, or vigorous or repetitive tactile stimuli required to arouse; stupor or coma
Seizure	None	None	Any clinical seizure, focal or generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure or cerebral edema	None	None	Focal or local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Table 1. Neurological monitoring

Timing	Neurological evaluation[a]	MRI/CT	EEG	CSF study	Brain [^{18}F] FDG-PET
Before infusion	Yes – baseline neuroological exam (incl. MoCA, history)	Yes	No	No	Consider – for baseline
During therapy (Day 1–15)	Yes – daily ICE score, tremor, cognition	If neuro symptoms	If seizures	If safe; for ICANS	Consider – may detect early changes
After infusion	Consider – if symptoms persist	Yes – for late symptoms	Yes – if mental status changes	Yes – to exclude other causes	Consider – for cortical monitoring

Ursu R. et al. Cur<r Opin Neurol 2025, 38:688–6942025

Table 2. Management of ICANS by Grade

Grade	Location	Steroids	Additional treatment	Supportive care
1	Hematology unit	Dexamethasone i.v. q24h in case of high-risk patients[a] or co-occurring CRS	–	
2	Hematology or ICU	Dexamethasone 10 mg i.v. q12h	—	Antiepileptics if needed
3	ICU	Dexamethasone 10 mg i.v. q6h	± Anakinra 100 mg q12h if >24 h symptoms	Antiepileptics if needed
4	ICU	Methylprednisolone 1000 mg i.v. q12–24h	± Anakinra q6–12h, ± siltuximab or chemotherapy	Antiepileptics if needed

Key Take home messages

1 High index of suspicion

Any patient with hematologic malignancy and recent CAR-T history presenting with fever, hypotension, or altered mental status.

2 Diagnoses of exclusion

Rule out sepsis and meningitis first. CRS/ICANS symptoms overlap significantly with infection.

3 Grade to guide treatment

Grading determines intervention level. Delayed tocilizumab or steroids can be detrimental.

4 Collaborate early

Involve hematology/oncology immediately. Transfer to CAR-T–certified center if needed.

CRS: Grading & Incidence

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring a low-flow nasal cannula or blow-by oxygen	Requiring a high-flow nasal cannula, face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation)

CRS incidence varies by product: tisagenlecleucel (B-ALL) 77% any grade; axicabtagene ciloleucel (DLBCL) 93%. Higher disease burden at infusion increases CRS risk. Early management prevents high-grade progression.