Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

27

Jeremy H. Rees

A common and challenging side effect associated with CAR-T cell therapy is immune cell-associated neurotoxicity syndrome (ICANS), which occurs in 20–60% of patients, of whom 12–30% have severe ($\geq$ grade 3) symptoms.

The underlying mechanism driving the syndrome is not fully understood, but there is evidence for the release of inflammatory cytokines secreted by macrophages and monocytes, increasing vascular permeability and endothelial activation and leading to blood–brain barrier breakdown. ICANS is not thought to be directly mediated by CAR-T cells themselves.

Risk factors for ICANS include high disease burden, older age, and the specific CAR-T product.

The onset of ICANS occurs (on average) approximately 5 days following CAR-T cell infusion and sometimes occurs concurrently with or shortly after cytokine release syndrome (CRS). However, in approximately 10% of patients, ICANS presents more than 3 weeks after CAR-T cell infusion.

Symptoms of ICANS are variable and can initially be vague. Patients experience mild tremor and confusion, which can then proceed to agitation, seizures, and cerebral oedema. A prominent and early feature of ICANS is hesitancy of speech and deterioration in handwriting, which can progress to aphasia with both expressive and receptive components, whereby the patient is alert but mute. The most devastating consequence of ICANS is the occurrence of status epilepticus, fatal cerebral oedema and occasionally intracerebral haemorrhage.

ICANS is a clinical diagnosis—brain MRI and CSF evaluation are rarely helpful but can be used to rule out alternative diagnoses, e.g., CNS infection. The EEG

J. H. Rees (✉)

National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, London, UK

UCL Institute of Neurology, London, UK

e-mail: jeremy.rees@ucl.ac.uk

Table 27.1 Immune Effector Cell Encephalopathy (ICE) Score

Immune Effector Cell Encephalopathy (ICE) Score
<ul style="list-style-type: none"> • <i>Orientation</i>: Orientation to year, month, city, hospital: 4 points • <i>Naming</i>: Ability to name 3 objects (e.g., point to clock, pen, button): 3 points • <i>Following commands</i>: Ability to follow simple commands (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue”): 1 point • <i>Writing</i>: Ability to write a standard sentence (e.g., “our national bird is the bald eagle”): 1 point • <i>Attention</i>: Ability to count backwards from 100 by 10: 1 point

recording can be normal but can also demonstrate a pattern of variable abnormalities, including nonconvulsive status epilepticus.

Most cases spontaneously resolve, often with supportive care and early intervention with corticosteroid therapy.

All patients should be proactively monitored for ICANS twice daily to assess subtle changes in cognition using the 10-point Immune Effector Cell Encephalopathy (ICE) score (Table 27.1), which evaluates orientation, attention, writing, and language. This score is then integrated into an overall assessment of neurological function incorporating seizure activity, change in consciousness level, motor findings, and elevation in intracerebral pressure/cerebral oedema to obtain an ICANS grade. The higher the ICE score is, the lower the ICANS grade. Any patient with an ICE score less than 2 or with seizures is classified as severe (grade 3 or 4) and should be transferred to intensive care. Factors associated with a higher risk of $\geq$ grade 3 ICANS include a higher disease burden, low platelet count, and the development of early and severe CRS.

Management of ICANS is based on the severity of the score and the concurrence of CRS. Management is supportive for grade 1 ICANS, and dexamethasone with rapid taper is given for grade ≥ 2 ICANS. Suggested doses include 10–20 mg intravenous dexamethasone every 6 h for grades 2–3 and 1 g IV methylprednisolone for at least 3 days for grade 4 until symptoms improve. Seizures are treated with levetiracetam and status epilepticus with benzodiazepines. We do not recommend the use of prophylactic anti-epileptic drugs.

Other experimental approaches to the management of ICANS have been directed at controlling the potency of the CAR itself. Several CAR constructs have been designed with “suicide switches” or as “tunable CARs” by incorporating mechanisms designed to turn off or downgrade the CAR in the event of severe toxicity. In severe unresponsive cases, anakinra (IL-1 receptor antagonist) or chemotherapy to kill the CAR-T cells have been used. However, most cases resolve and do not result in residual neurocognitive damage (Tables 27.2 and 27.3).

Key Points

- ICANS is a common and usually reversible toxicity of CAR-T cell therapy, occurring within a week of infusion, often after cytokine release syndrome.
- ICANS is a clinical diagnosis—common early symptoms include word finding difficulties, confusion, and impaired fine motor skills. Investigations are rarely helpful except to rule out an alternative diagnosis, such as CNS infection.
- Severe ICANS consists of seizures, coma, and cerebral oedema and requires ITU care.
- Management of ICANS is largely supportive and depends on severity. Corticosteroids are the mainstay of care for all but Grade I ICANS and should be prescribed at high doses with a rapid taper.
- The prognosis is good, and the majority of patients fully recover without any long-term sequelae.

Table 27.2 American Society for Transplantation and Cellular Therapy (ASTCT) ICANS Consensus Grading for Adults

<i>Overall ICANS Grade</i>
Grade 1
Grade 2
Grade 3
Grade 4
<i>ICE score^a</i>
7–9
3–6
0–2
0 (patient is unarousable and unable to perform the ICE assessment)
<i>Depressed level of consciousness^b</i>
Awakens spontaneously
Awakens to voice
Awakens only to tactile stimulus
Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
<i>Seizure</i>
N/A
N/A
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

(continued)

Table 27.2 (continued)

<i>Motor findings^c</i>
N/A
N/A
N/A
Deep focal motor weakness, such as hemiparesis or paraparesis
<i>Elevated ICP/cerebral oedema</i>
N/A
N/A
Focal/local oedema on neuroimaging ^d
Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; Sixth nerve palsy; papilloedema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS

N/A indicates not applicable

^aA patient with an ICE score of 0 may be classified as having grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as having grade 4 ICANS if unarousable

^b Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication)

^c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading

^d Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0

Table 27.3 Approach to management of ICANS

ICANS Grade	Management
Grade 1	<p>Consider levetiracetam seizure prophylaxis (750 mg BD)</p> <p>Avoid medications that cause central nervous system depression</p> <p>Seek neurology specialist consultation</p> <p>Supportive care</p> <p>Fundoscopy examination to assess for papilloedema</p> <p>Brain MRI with contrast (brain CT if brain MRI is not feasible)</p> <p>Consider diagnostic lumbar puncture with measurement of opening pressure where possible, sending samples for culture and sensitivity, cytology, biochemistry, and virology as a minimum</p> <p>Consider spine MRI if the patient has focal peripheral neurological deficits</p> <p>Consider electroencephalogram (EEG)</p> <p>Consider tocilizumab 8 mg/kg but only if concurrent CRS</p> <p>Twice daily neurocognitive assessment using the ICE score and ICANS grading</p>
Grade 2	<p>Investigations and supportive care as per grade 1</p> <p>Consider dexamethasone at a high dose with rapid weaning</p> <p>Consider transferring the patient to the intensive care unit (ICU)</p>

Table 27.3 (continued)

ICANS Grade	Management
Grade 3	Investigations and supportive care as per grade 1 Administer dexamethasone 10–20 mg IV every 6 h or methylprednisolone equivalent until improvement to grade 1 and then taper Management of seizures with lorazepam 0.5 mg IV or other benzodiazepines as needed, followed by loading with levetiracetam or other anticonvulsants as required If fundoscopy reveals stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure > 20 mmHg, seek urgent advice from neurologist Consider repeat neuroimaging (CT or MRI) every 2–3 days if the patient has persistent grade ≥ 3 ICANS
Grade 4	Investigations and supportive care as per grade 1 Transfer patient to intensive care unit (ICU); consider mechanical ventilation for airway protection Seizure management as per grade 3 For convulsive status epilepticus, seek urgent advice from neurologist Administer methylprednisolone 1000 mg/day for 3 days, then taper at 250 mg every 12 hrs for 2 days, then 125 mg every 12 hrs for 2 days, then 60 mg every 12 hrs for 2 days For management of raised intracranial pressure, consider acetazolamide 1000 mg IV, followed by 250–1000 mg IV every 12 h; elevating the head of the bed; hyperventilation; and hyperosmolar therapy with mannitol

Further Reading

- Neill L, Rees J, Roddie C. Neurotoxicity – CAR-T cell therapy: what the neurologist needs to know. *Pract Neurol*. 2020;20:287–95. <https://doi.org/10.1136/practneurol-2020-002550>.
- Rubin DB, Danish HH, Ali AB, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. *Brain*. 2019;142:1334–48. <https://doi.org/10.1093/brain/awz053>.
- Tallantyre EC, Evans NA, Parry-Jones J, et al. Neurological updates: neurological complications of CAR-T therapy. *J Neurol*. 2021;268:1544–54. <https://doi.org/10.1007/s00415-020-10237-3>.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.