REVIEW

Immune Effector Cell–Associated Neurotoxicity Syndrome

A Practical Overview for the General Neurologist

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Abstract

Purpose of Review

The purpose of this review was to consolidate the clinical, radiographic, and laboratory findings of patients with immune effector cell–associated neurotoxicity syndrome (ICANS) to give physicians a comprehensive overview of its diagnosis and management.

Recent Findings

ICANS is a rare but potentially lethal complication of chimeric antigen receptor (CAR) T-cell therapy in patients with hematologic malignancies including leukemia, lymphoma, and multiple myeloma. They often have nonspecific neurologic symptoms, such as language difficulties, encephalopathy, and tremors. Workup may involve brain imaging, EEG, or lumbar puncture, but often, these are normal or nonspecific. Laboratory studies, particularly C-reactive protein and ferritin, can help physicians determine which patients are at risk of developing ICANS and how severe the symptoms may become. While most cases of ICANS resolve spontaneously with supportive measures, studies have shown that steroids play an integral role in treating patients who develop neurotoxicity secondary to CAR T-cell therapy.

Summary

By recognizing the signs and symptoms of ICANS, physicians can begin interventions early in the disease course and potentially mitigate any long-term effects. Although most patients recover without residual deficits, rapid progression to death has been reported in a minority of cases. Workup for other etiologies should be performed as clinically indicated, and abnormal findings should be treated according to standard-of-care practices.

Introduction

Chimeric antigen receptor (CAR) T-cell therapies have emerged as one of the newest innovations in the fight against cancer, particularly hematologic malignancies. These therapies have shown up to a 90% complete remission rate in pediatric patients with relapsed or refractory acute lymphoblastic leukemia[1,2] and a 54% complete remission rate in adult patients with lymphoma.[3] The development of these therapies first involves leukapheresis of a patient's blood and subsequent isolation of their T cells.[1] The extracted T cells are then introduced to a viral vector carrying RNA that codes for a CAR targeting tumor-identifying proteins, such as CD19 or B-cell maturation antigen (BCMA).[1,4,5] Exposure to this viral vector leads to permanent integration of the RNA into the T-cell genome, allowing continued expression of the CAR as the T cells replicate.[1] After replicating over a period of 9–11 days, these cells are then infused back into the patient. At the time of this publication, the FDA has approved 7 CAR T-cell therapies.[5]

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Therapies targeting CD19 are as follows:

- Tisagenlecleucel (Kymriah)
- Axicabtagene ciloleucel (Yescarta)
- Lisocabtagene maraleucel (Breyanzi)
- Brexucabtagene autoleucel (Tecartus)
- Obecabtagene autoleucel (Aucatzyl)

Therapies targeting BCMA are as follows:

- Idecabtagene vicleucel (Abecma)
- Ciltacabtagene autoleucel (Carvykti)

Shortly after encountering the patient's tumor cells, CAR T cells trigger a massive inflammatory response mediated by cytokine production from macrophages, although it seems that some CAR T-cell products have a greater propensity for causing severe inflammation in comparison with others.[6] This causes systemic inflammation and can lead to the development of cytokine release syndrome (CRS), a condition characterized by nonspecific flu-like symptoms including fever, headache, arthralgias, or rash.[7] In some cases, CRS can lead to rapid deterioration with multisystem organ failure, including pulmonary edema, renal failure, and cardiac instability.[7] The blood-brain barrier (BBB) is also permeable to these inflammation-inducing cytokines and allows them to diffuse into the CSF, along with the CAR T cells.[7] This effectively heralds the onset of immune effector cell–associated neurotoxicity syndrome (ICANS), although the exact pathophysiology is currently under investigation.[6,8] As many as 70% of patients receiving CAR T-cell therapies have been shown to develop ICANS.[9] It is, therefore, important that neurologists be aware of the presenting signs and symptoms and the evidence-based approach to their management.

In this narrative review, we provide an overview of ICANS for the practicing clinician, discussing (1) the spectrum of clinical presentations, (2) commonly used methodology for grading severity, (3) proposed risk factors, (4) complications, (5) diagnostic evaluation, (6) management considerations, and (7) prognosis.

Clinical Presentation

While CRS can occur as early as the day of CAR T-cell administration, ICANS typically develops a few days later.[6] Several studies reported a median onset of mild neurotoxicity 4–9 days after the first CAR T-cell administration, although severe neurotoxicity may present after 10 or more days.[10-14] ICANS may develop with or without a preceding CRS,[7] but data suggest that the development of CRS is itself a risk factor for developing neurotoxicity, as evidenced by 2 retrospective studies in which all patients with ICANS were found to have a preceding CRS.[14,15]

Neurologic symptoms range from mild word-finding difficulty, anomia, acalculia, handwriting changes, or tremor to more severe neurologic dysfunction characterized by aphasia, seizures, cerebral edema, and coma.[8,11] These symptoms may wax and wane, but virtually, all patients experience complete resolution, with only a few rare fatalities reported.[7,8] One study involving patients with ICANS (n = 53) reported a median time of 1 day from the onset of neurologic symptoms to the highest neurotoxicity grade (range 0–19 days).[10] Although the presentation of ICANS is variable, most of the patients present with some combination of encephalopathy, aphasia, and tremor.[11] Other symptoms have been reported and will be described briefly.

Encephalopathy

Most patients with ICANS will develop encephalopathy.[11,15] This typically presents as fluctuating attention deficits and is rarely fulminant at onset, although it may rapidly progress to coma and other minimally conscious states.[11] One study found that 92% of patients with low-grade neurotoxicity were classified as having mild encephalopathy, such as confusion or decreased arousal.[11] Patients may also experience more subtle deficits in mentation, such as difficulty following complex commands or naming objects, even if they are not disoriented.[8,15] Others may exhibit apraxia or executive dysfunction that can be difficult to distinguish from encephalopathy, manifesting as difficulty with learned tasks such as using a telephone or writing a sentence.[12] It is, therefore, important to evaluate multiple aspects of a patient's mental status beyond orientation.

Aphasia

Expressive aphasia is also common and is considered to be one of the most sensitive indicators of ICANS onset.[8] Symptoms may begin as subtle word-finding difficulties and progress over hours to global aphasia.[12] In one phase I clinical trial, expressive aphasia was the first neurologic symptom seen in 19 of 22 patients with severe neurotoxicity.[12] Another study found that 35 of 44 patients developed aphasia, with 6 patients experiencing global aphasia; all patients had resolution of their language difficulties before discharge, however, and some even had no recollection of their symptoms.[15]

Tremor

Although tremor is one of the most common presenting symptoms, it is not used to grade the severity of neurotoxicity because of its nonspecific nature and treatment is often not required.[8] In one study of 39 patients who developed movement-related symptoms, enhanced physiologic tremor was the most common concern (28 patients) and all cases self-resolved.[15] Other reported movement symptoms include asterixis and myoclonus,[15] but the frequency of these is uncertain.

Headache

As with tremor, headache is not used to determine the severity of neurotoxicity because it can occur as part of CRS or even as a response to chemotherapy itself.[7,8] Often, headache

is characterized by nonspecific features.[15] In one study, headache was the only neurologic symptom in 9 of 53 patients with neurotoxicity.[10] Unless there is suspicion for increased intracranial pressure (e.g., positional characteristics, vomiting, abducens palsy, and papilledema), headache can be managed symptomatically with analgesics as appropriate based on the patient's medical history.[8]

Seizures

Seizures occur less frequently than the previously described symptoms, but when present, they are indicative of severe neurotoxicity.[8] In 3 studies, seizures were only seen in 20% or fewer of patients with neurotoxicity.[10,15,16] Another study suggested that seizures tend to occur after global aphasia and may represent peak neurotoxicity.[8] ICANS does not seem to significantly exacerbate seizures in patients with a history of seizures, however, as evidenced by the fact that, of 6 patients reported in the literature with previous seizures, only 2 experienced seizures in the setting of neurotoxicity.[10] Most researchers who started seizure prophylaxis before the onset of clinical seizures found that it did not prevent seizures or ictal-interictal activity on EEG.[11] Initiation of antiseizure medications (ASMs) such as levetiracetam 750 mg twice daily may be considered in patients with epileptiform or ictal-interictal features on EEG (such as epileptiform discharges, generalized periodic discharges [GPDs], or lateralized periodic discharges) as these patterns indicate increased risk of clinical seizures and may contribute to encephalopathy.[7,11,12]

Focal Weakness

The presence of hemiparesis or quadriparesis is also indicative of severe neurotoxicity.[8] One study found that 10 of 48 patients with neurotoxicity developed transient focal weakness, with one additional case due to acute embolic stroke.[15] By contrast, gait instability is more nonspecific and may be a complication of chemotherapy or deconditioning rather than neurotoxicity.

Grading ICANS Severity

The severity of neurologic symptoms is determined based on the integration of 2 scoring systems: the Immune Effector Cell-Associated Encephalopathy (ICE) score for patients aged 12 years or older (or the Cornell Assessment for Pediatric Delirium [CAPD] score for patients younger than 12 years and for older patients with developmental delay [for example, those with Down syndrome]) and 4 other neurologic domains as determined by the American Society for Transplantation and Cellular Therapy (ASTCT).[8] For patients aged 12 years or older, providers should first calculate the patient's ICE score (Table 1).

The total number of points is then used to partially determine the severity of neurotoxicity, with grade 1 or 2 representing mild neurotoxicity and grade 3 or 4 representing severe neurotoxicity[8]:

- Grade 0 (no ICANS): 10 points
- Grade 1: 7–9 points
- Grade 2: 3–6 points
- Grade 3: 0–2 points
- Grade 4: 0 points

Of note, a patient with a score of 0 points can be classified as having either grade 3 or grade 4 ICANS. This is due to the possibility of a patient being awake but globally aphasic, which would be classified as grade 3 ICANS. Patients who are unarousable score 0 points and should be classified as grade 4. The CAPD scoring system, which is used in the evaluation of patients younger than 12 years (or ≥12 years of age with developmental delay), is distinct from the ICE score and is not detailed in this review.[8]

The second scoring system used to determine neurotoxicity grade involves 4 neurologic domains outlined in the ASTCT consensus criteria (Table 2). These criteria are the same for both adult and pediatric patients and include level of consciousness, seizures, motor findings, and cerebral edema/elevated intracranial pressure (ICP).

After determining the ICE/CAPD score and applying the ASTCT consensus criteria, providers should grade neurotoxicity based on the most severe component. For example, a patient with an ICE score of 8 (grade 1) who developed a clinical seizure lasting <5 minutes would be considered grade 3 ICANS according to the ASTCT consensus criteria. Alternatively, a patient who is spontaneously awake and does not meet any ASTCT consensus criteria for severe neurotoxicity but has an ICE score of 2 points would also be considered grade 3 ICANS, based on the ICE score.

Predicting ICANS/Risk Factors

Predicting who is at risk of developing neurotoxicity and the degree of severity remains a challenge. There is no unifying algorithm to make such determinations, but several potential risk factors have been examined.

Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a significant risk factor for developing neurotoxicity, as evidenced by multiple studies showing a high rate of concurrence between CRS and ICANS, including one study in which all 48 patients with neurotoxicity had preceding CRS.[11,15] Multiple studies showed that early-onset fever was associated with higher grade neurotoxicity.[10,11] In one study, a measured temperature ≥38.9°C and IL-6 serum concentration of >16 pg/mL within 36 hours of the first CAR T-cell infusion were shown to have 100% sensitivity for later development of grade 4 neurotoxicity.[10] In this same study, all patients who developed severe neurotoxicity had a temperature ≥38°C.[10] Severe CRS is highly associated with severe neurotoxicity, particularly if CRS onset is within 3 days of CAR T-cell infusion.[14,15,17]

Table 1 Encephalopathy Assessment for Grading ICANS in Patients Aged 12 Years or Older

ICE
Orientation: orientation to year, month, city, hospital = 4 points
Naming: ability to name 3 objects (e.g., point to clock, pen, and button) = 3 points
Following commands: ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue") = 1 point
Writing: ability to write a standard sentence (e.g., "Our national bird is the bald eagle") = 1 point
Attention: ability to count backward from 100 by 10 = 1 point

Abbreviations: ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy score. Reprinted from *Biology of Blood and Marrow Transplantation*, 25(4), Lee DW, Santomasso BD, Locke FL, et al., ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells, 625–638, Copyright 2019, with permission from Elsevier.[8]

C-Reactive Protein

C-reactive protein (CRP) levels have been found to correlate with development of neurotoxicity but do not predict severity.[11,15] In one study, patients who developed neurotoxicity had a median peak CRP level of 163.9 mg/dL and a median baseline CRP level of 36.7 mg/dL.[15] These levels were higher than those in patients who did not develop neurotoxicity, but neither the peak nor baseline CRP levels correlated with disease severity.[15] CRP also peaked before the onset of neurotoxicity, but its role in ICANS development, if any, is unclear.[11,18]

Ferritin

In contrast to CRP, elevated ferritin levels may be useful as a biomarker for both impending and peak neurotoxicity.[11] One study found that higher levels of ferritin on day 3 after infusion (with day 0 as the day of infusion) correlated with a greater probability of severe neurotoxicity; specifically, a ferritin level of 2,000 ng/mL was associated with a 51% probability, whereas a level of 4,000 ng/mL was associated with a 98% probability.[19] Baseline ferritin level on the day of CAR T-cell infusion, however, does not seem to influence the severity of neurotoxicity.[11]

Tocilizumab and IL-6

The association between tocilizumab and neurotoxicity may be related to its primary mechanism of action as an IL-6 receptor antagonist, resulting in increased circulating levels of IL-6.[7] One study found that all patients with a serum IL-6 concentration ≥501 pg/mL within the first 6 days after CAR T-cell infusion developed grade 4 neurotoxicity, whereas the same concentration after 6 days was associated with a much lower rate of similar neurotoxicity (18%).[10] Three studies described elevated IL-6 levels in the CSF of patients with ICANS,[20] but the exact role of IL-6 in the development of neurotoxicity remains unclear. The extent to which tocilizumab contributes to neurotoxicity is debated, but more recent studies suggest that tocilizumab use for CRS prophylaxis may not affect the incidence or severity of ICANS at all.[21-23]

One proposed risk stratification tool is the modified Endothelial Activation and Stress Index (m-EASIX), which incorporates

Table 2 ASTCT ICANS Consensus Grading for Adult and Pediatric Populations

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (the patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	The patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse
Seizure	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 events
Motor findings	N/A	N/A	N/A	Hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; abducens palsy; papilledema; or Cushing triad

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy score; ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy score.
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LDH, CRP, and platelet levels to predict disease severity when calculated on days +1 and +3 after CAR T-cell infusion.[24] Other notable factors that have been associated with neurotoxicity include older age,[12,17,46] though evidence is somewhat conflicting, and poor performance status.[46]

Complications of ICANS

Thus far, we have discussed the symptoms that may alert the provider to the development of neurotoxicity. Although most patients recover completely, several significant complications, some of which are irreversible, have been reported in the literature.

Cerebral Edema

Cerebral edema is arguably the most feared complication of ICANS as it can occur without warning and rapidly progress to coma or death.[8,10,15] The presence of edema on imaging or the suspicion of edema based on examination findings should lead to an automatic designation of grade 3 or 4 neurotoxicity, unless this edema is secondary to intracranial hemorrhage.[8,26] In 1 study of patients who received axicabtagene (n = 46), one patient who had previously only shown signs of CRS developed aphasia with progression to cerebral edema and death over a period of 12 hours.[27] Death occurred within 5 days of infusion, despite the use of standard interventions for cerebral edema, including hypertonic solutions, ventriculostomy, and hyperventilation.

Vascular Complications

Patients with ICANS have been infrequently reported to experience both ischemic and hemorrhagic strokes. One prospective study of 100 patients who received CAR T-cell infusion reported 2 patients with ischemic stroke; however, both patients had vascular risk factors that predisposed them to this complication.[15] This same study reported that 2 patients developed nonfatal spontaneous subarachnoid hemorrhage without associated aneurysm or vascular malformation.[15] In at least 2 patients with vascular complications, a platelet count less than 25,000/mL at the time of the event was documented.[15] Evidence of thrombocytopenia and disseminated intravascular coagulation (DIC) in ICANS has been reported elsewhere in the literature, with one study noting transient DIC in 5 of 15 patients with severe neurotoxicity.[16] The available data thus suggest that stroke is rarely associated with ICANS, as further supported by 1 study that reported no evidence of acute ischemia in any of 53 patients,[12] and that stroke may be related to vascular risk factors or hematopoietic insufficiency rather than neurotoxicity.

Status Epilepticus

Nonconvulsive status epilepticus (NCSE) has been reported in ICANS with variable frequency, which ranges from 10% to 33% of patients in studies.[11,12,28] In one study of patients receiving axicabtagene (n = 33), 3 of 9 patients with severe ICANS developed NCSE.[28] This finding has been described predominantly in case series of patients with severe neurotoxicity.[11,12]

The frequency of generalized convulsive status epilepticus (GCSE), in contrast to NCSE, is less defined. One study reported that, in 4 of 13 patients who developed seizures, only one was found to have GCSE, whereas 2 patients developed NCSE.[29] In all reported cases of status epilepticus attributed to neurotoxicity, both clinical and electrographic seizure activity resolved following standard status epilepticus protocols.[12] It is also worth noting that no studies thus far have reported any cases of focal seizures secondary to neurotoxicity, although generalized seizures were clinically suspected to be of focal onset in some cases.[12]

Workup and Differentials

ICANS should be suspected in any patient who develops neurologic signs or symptoms after receiving CAR T-cell therapies, but it is important that other etiologies also be considered. In patients with aphasia or hemiparesis, for example, stroke should be excluded before attributing such deficits to a nonemergent process. Infection should be high on the differential diagnosis of ICANS because patients who receive CAR T-cell therapies are usually heavily pretreated with chemotherapy and other modalities that can result in a profound immunocompromised status. Dangerous electrolyte abnormalities are not uncommon in this patient population, whether due to life-threatening tumor lysis syndrome or systemic injuries such as acute kidney injury, and may produce a clinical picture similar to ICANS. The workup for other etiologies should be pursued according to the clinical picture but is expected to be largely normal in ICANS, although several nonspecific positive findings have been described.

Neuroimaging

Owing to its nonspecific nature, ICANS may present similarly to stroke, encephalitis, tumor progression, or even posterior reversible encephalopathy syndrome. CT and MRI can help distinguish among these etiologies. Any patient presenting with acute-onset focal neurologic deficits should undergo ischemic workup if there is a possibility they could receive interventions such as intravenous thrombolysis or thrombectomy. However, most patients with ICANS who undergo neuroimaging have normal or nonspecific findings.

In one study, 21 of 25 patients received CT scans at the onset of neurologic symptoms, which were normal in 20 of the 21 patients.[11] In this same study, 8 of 10 patients who underwent MRI had unremarkable results; one patient developed T2 hyperintensities in the periventricular region and fluid-attenuated inversion recovery (FLAIR) abnormalities associated with restricted diffusion anterior to the splenium of the corpus callosum, while another developed a recurrent leukoencephalopathy that was attributed to fludarabine

use.[11] Another study of 33 patients with neurotoxicity found T2/FLAIR hyperintensities involving the bilateral thalami, basal ganglia, or extreme capsule, extending as far caudally as the medulla, although this was only seen in 4 of 14 patients with severe neurotoxicity; all 5 patients with low-grade neurotoxicity who underwent MRI brain had normal scans.[12] Contrast enhancement may also be present.[10] Abnormal MRI findings are generally reversible, with resolution occurring after clinical improvement.[12] MRI of the spine or orbits can be considered as clinically indicated, and emergent CT head imaging should be obtained for signs of increased intracranial pressure.

EEG

EEG is one of the most sensitive tools for seizure risk stratification. Encephalopathic patients should be monitored at least initially with a routine EEG. If epileptiform abnormalities or electrographic seizures are present, switching to continuous EEG monitoring is recommended, particularly if there is concern for NCSE. In one study of 18 patients with neurotoxicity, all patients were found to have delta-range or theta-range slowing either diffusely or in the frontal regions.[11] Generalized slowing seems to be the most common EEG finding in other studies as well, along with frontal or generalized rhythmic delta activity.[8,12,15] GPDs may also be seen, and clinical deterioration may correlate with peak GPD intensity.[11,12] Although EEG abnormalities are common, most are nonspecific findings that should not be used to classify patients as having severe neurotoxicity. It is important to remember that the only EEG findings that characterize severe ICANS are electrographic or electroclinical seizures.[8]

Lumbar Puncture

As with the other diagnostic studies previously discussed, lumbar puncture often yields normal or nonspecific findings. In addition, many patients cannot safely undergo lumbar puncture because of coagulopathy. In one prospective study of 48 patients with neurotoxicity, 5 of 13 who underwent lumbar puncture had white blood cell counts >5 cells per microliter (median 3, range 0–35) and 3 patients had protein >60 mg/dL (median 51, range 27–234), but culture and cytology were negative.[15]

The extent to which the presence of CAR T cells in the CSF influences neurotoxicity and its severity is debated. CAR T cells have been found in the CSF of patients both with and without neurotoxicity, and higher quantities do not seem to correlate with more severe neurotoxicity.[12] Two studies showed that CAR T cells persist in the CSF even after resolution of neurologic symptoms.[10,12]

In summary, workup of ICANS may include neuroimaging, EEG, or lumbar puncture, but these often yield nonspecific findings and thus should be used primarily to rule out secondary etiologies.

Management

Steroids

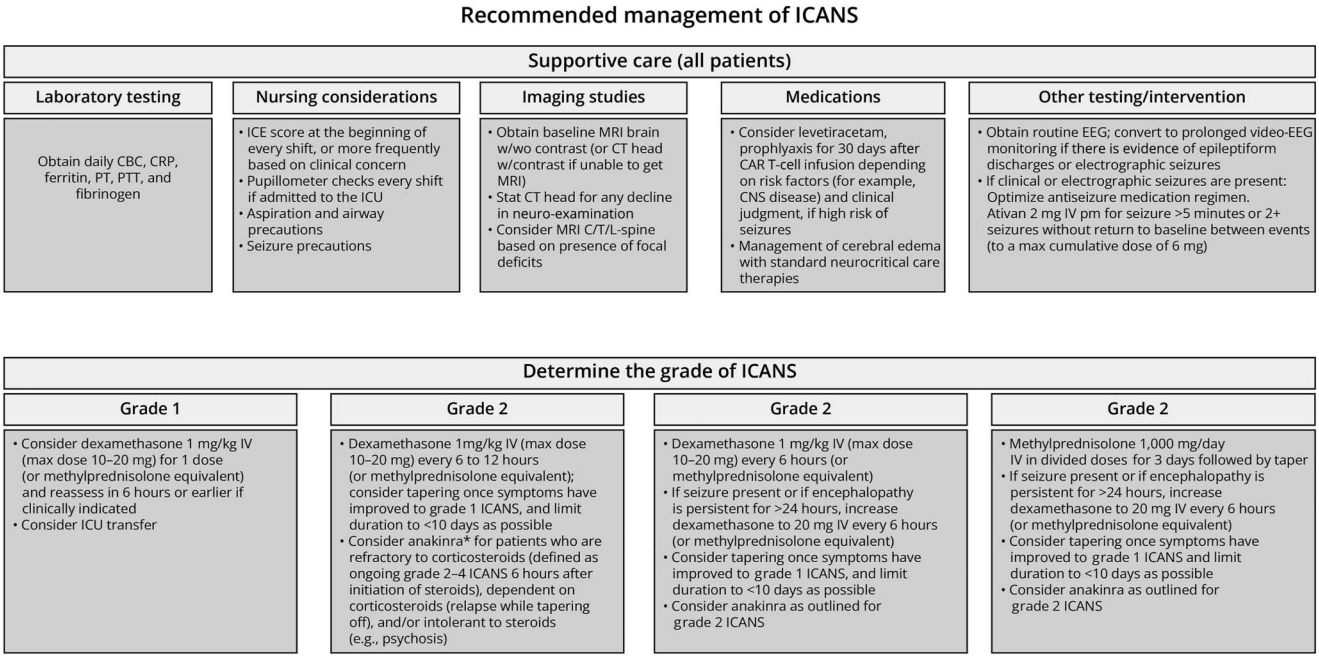
Owing to their wide range of anti-inflammatory effects and their ability to cross the BBB, steroids are considered first-line treatment for ICANS.[18,20] However, there is no established therapeutic dose, duration, or taper for such therapy. For patients with grade ≤3 neurotoxicity, several authors suggest the use of dexamethasone 1 mg/kg every 6 hours (Figure).[7,22,30] For patients with grade 4 neurotoxicity or who are refractory to dexamethasone, methylprednisolone 1,000 mg/d should be considered.[7,22,30] As of yet, there is no evidence to suggest that methylprednisolone is superior to dexamethasone, but methylprednisolone may exert more suppressive effects on T cells compared with dexamethasone and, therefore, could decrease the efficacy of CAR T-cell therapies.[20,31,32]

The duration of steroid therapy is not well defined but should be limited because prolonged steroid use (≥10 days) is associated with decreased overall survival[11,33] and is also a strong risk factor of CMV reactivation, particularly in patients who received BCMA-targeted CAR T-cell therapy.[34,35] Owing to the side-effect profile and the self-limited nature of neurotoxicity, steroid therapy may be tapered before complete resolution of symptoms, but there is no generally recommended taper course.[22] Another concern is that corticosteroids may alter CAR T-cell therapy, although the evidence is currently mixed.[11,32,33] Authors who reported no effect on CAR T-cell efficacy are quick to observe that most patients receive steroids after T-cell expansion has already occurred, raising the possibility that patients who receive them before sufficient T-cell expansion may experience a decreased tumor response to their CAR T-cell infusion.[32]

Tocilizumab

Primarily used for the management of CRS, tocilizumab has not been found to be effective in treating ICANS and may actually be a risk factor of severe ICANS.[6] Currently, in the setting of isolated CRS or ICANS with concurrent CRS, tocilizumab can be administered as a one-time dose at 12 mg/kg for patients <30 kg or at 8 mg/kg for patients ≥30 kg (not to exceed 800 mg) and repeated once after 24–48 hours if there is no clinical improvement.[31] As an IL-6 receptor antagonist, tocilizumab blocks IL-6 from binding to its receptor, thus promoting systemic inflammation, but this results in increased serum IL-6 levels, potentially allowing more IL-6 to translocate across the BBB and cause neurotoxicity.[7,20,31] Because it cannot cross the BBB, tocilizumab cannot exert its anti-inflammatory effects in the CNS.[31] Therefore, providers should be aware that neurotoxicity may develop or worsen if already present. For this reason, tocilizumab is generally reserved for patients with severe CRS.[18] For patients with CRS who do not respond to 2 doses of tocilizumab, further administration is generally not recommended.[22] Data suggest that tocilizumab does not alter the efficacy of CAR T-cell therapies.[36,37]

Figure Flowchart for the Management of ICANS



*Anakinra: Up to 12 mg/kg/day (100 mg subcutaneously or IV twice daily for 7 days). In case of high-grade ICANS or not responsive to initial dose, consider increasing to 200 mg every 8 hours for up to 10 days

Anakinra

In patients with life-threatening or refractory ICANS, anakinra along with steroids can be considered, although high-quality evidence for this approach is lacking.[38] Anakinra prevents IL-6–mediated inflammation by blocking IL-1, which normally triggers monocytes to produce IL-6.[7,22] One retrospective study evaluating the use of anakinra in the setting of steroid-refractory ICANS found that high-dose anakinra (8 mg/kg/d) was associated with a lower mortality rate compared with low-dose anakinra (100–200 mg/d) and did not negatively affect CAR T-cell efficacy, while another study suggested that anakinra may be safe up to 12 mg/kg/d.[39,40] One preclinical study of patients who received anakinra before CAR T-cell infusion (n = 20) and for 7 days after infusion found lower rates of ICANS (but not CRS) of any grade and no effect on the efficacy of T-cell expansion.[41] This suggests a potential role for anakinra to prevent neurotoxicity, although currently there are no widely accepted strategies for its use.

Pharmacologic management of ICANS is also complicated by the fact that there are many biochemical mediators at play and blocking only one inflammatory pathway is unlikely to fully prevent or improve symptoms.[20] Other therapies that continue to be studied include siltuximab,[42] lenzilumab,[43] and dasatinib.[44]

Seizure Management

The utility of prophylactic ASMs before any seizure activity is debatable. One study found that all patients who had been started on levetiracetam therapy eventually developed rhythmic or periodic EEG patterns,[11] but others have reported that treatment with ASMs and dexamethasone resulted in transient electroclinical improvement.[12] Providers can thus expect that EEG will be abnormal but nonspecific in patients with ICANS, and any evidence of electrographic or clinical seizures should be treated accordingly.

Cerebral Edema

Although the role of craniotomy is uncertain, standard neurocritical care practices for lowering intracranial pressure may be adequate in patients who do not progress to herniation.[38] Owing to the possibility for rapid progression of neurologic symptoms, clinicians often admit patients with grade >2 neurotoxicity to an intermediate care floor or intensive care unit for close monitoring.[7]

Prognosis

Most of the patients who experience neurotoxicity are expected to have complete resolution of symptoms before being discharged from the hospital. At least 5 studies noted a median duration of 5–9 days for neurologic symptoms.[10,12,44-46] Median duration of symptoms was found to be similar in both mild and severe neurotoxicity (11 days), with 2 studies noting the possibility of duration >60 days for severe neurotoxicity.[10,12]

At least 2 studies have found that prolonged steroid use (≥10 days) is associated with lower rates of overall survival.[11,33] Higher cumulative dose and early steroid use (within 7 days of CAR T-cell infusion) have also been associated with both lower progression-free survival (PFS) and overall survival (OS).[33] By contrast, tocilizumab use does not seem to affect either PFS or OS.[33,36,37]

Conclusion

While CAR T-cell therapies are a promising new advancement in the fight against cancer, their use is certainly not without limitations because severe and life-threatening inflammatory responses may occur after infusion. Neurologists should be aware that, with the exception of rare cases of fulminant and fatal cerebral edema, most patients with neurotoxicity secondary to CAR T-cell therapy present with signs of nonspecific neurologic dysfunction. Early clinical findings may be subtle but can rapidly progress to aphasia, coma, and, rarely, brain death. Workup may include MRI, EEG, and CSF studies, but results may be negative or only yield nonspecific findings; thus, the primary role of these diagnostic modalities is to exclude other etiologies. Patients with severe CRS should be monitored carefully because they are at higher risk of severe neurotoxicity, which may or may not occur concurrently. While serum ferritin may correlate with impending and peak neurotoxicity, other serum and CSF biomarkers are generally not helpful in predicting severity of disease. Tocilizumab should be reserved for the management of CRS because of its inability to diffuse across the BBB and its potential to exacerbate ICANS. In addition to supportive care, corticosteroids are the mainstay of treatment in all patients with ICANS. The use of other cytokine inhibitors (for example, anakinra or siltuximab) is a potential option but remains under investigation.

Author Contributions

C.K. Cevering: drafting/revision of the manuscript for content, including medical writing for content. H. Abdel-Azim: drafting/revision of the manuscript for content, including medical writing for content. S.J. Khazal: drafting/revision of the manuscript for content, including medical writing for content. C. Casassa: drafting/revision of the manuscript for content, including medical writing for content.

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