Journal of the Neurological Sciences 424 (2021) 117405

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Neurological complications of cancer immunotherapy (CAR T cells)

Daniel B. Rubin [a,*], Henrikas Vaitkevicius [b]

[a] Division of Neurocritical Care, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States of America
[b] Marinus Pharmaceuticals, Inc., Radnor, PA, United States of America

ARTICLE INFO

Keywords:
Neuroimmunology
Neuro-oncology
CAR T cells

ABSTRACT

Chimeric antigen receptor (CAR) T cell therapy has become an indispensable tool in the treatment of advanced malignancy, however, it is associated with significant neurologic toxicity. The pathophysiology of CAR T-cell associated neurotoxicity is incompletely understood, and the specific risk factors have only recently begun to be characterized. Despite a growing clinical experience with CAR T cell therapy, the unpredictability of neurologic symptoms remains a source of great anxiety for patients and practitioners alike, and a major limitation for more widespread adoption of this important treatment modality. The purpose of this review is to familiarize clinicians with the typical clinical manifestations and salient features of CAR T cell associated neurotoxicity. We place an emphasis on highlighting the clinical and laboratory markers that may be helpful for predicting clinical course, allowing teams to anticipate necessary supportive measures. We will also review the appropriate diagnostic workup for CAR T cell neurotoxicity and current treatment recommendations.

1. Introduction

Chimeric antigen receptor (CAR) T cell therapy has, in recent years, transformed the care of patients with relapsed and refractory hematologic malignancy. Clinical trials enrolling patients with historically poor prognoses are now boasting sustained rates of remission well above 50% [1–14]. However, this impressive efficacy is accompanied by significant toxicity that limits more widespread adoption. There are two main forms of toxicity that accompany CAR T cell therapy: cytokine release syndrome (CRS) and a syndrome of neurotoxicity, also known as the Immune Effector Cell (IEC) Associated Neurologic Syndrome (ICANS) [15–20]. CRS is a syndrome of multi-organ dysfunction characterized by fever, hypotension, and hypoxia caused by the widespread release of pro-inflammatory cytokines after CAR T cell infusion [1,19,20]. If left untreated, CRS can progress to multi-organ failure and death [21]. However in most cases it is effectively mitigated by treatment with appropriate immunotherapy, namely the anti-IL-6R antibody tocilizumab [11,17,21]. In contrast, the neurotoxicity associated with CAR T cell therapy is more idiosyncratic, and its clinical features are diverse and can at times be difficult to treat. Despite a growing clinical experience with CAR T cell therapy, the unpredictability of neurotoxicity remains a source of great anxiety for patients and practitioners alike. And unlike CRS, which often precedes neurotoxicity, the pathophysiology of CAR T cell-associated neurotoxicity is incompletely understood [16,18,19,22,23]. The goal of this review is to introduce clinicians to the scope and expected course of neurologic symptoms encountered after CAR T cell infusion. An emphasis is placed on highlighting certain clinical and laboratory markers that may be helpful for predicting clinical course, allowing teams to anticipate necessary supportive measures. We will also review the appropriate diagnostic workup for CAR T cell neurotoxicity and current treatment recommendations.

2. Clinical syndrome

Patients undergoing CAR T cell therapy may experience a wide range of neurologic symptoms, including encephalopathy, agitated or hypokinetic delirium, aphasia, ataxia, tremor, apraxia, focal motor weakness, seizures, and in rare cases, fatal cerebral edema [5,9,10,19,22,24–28]. Table 1 details the relative frequency of different neurologic symptoms encountered in one of the largest cohorts of 100 patients undergoing CAR T cell therapy [26].

For most patients undergoing CAR T cell therapy, there is a relatively stereotyped progression of clinical and laboratory findings that follow cell infusion. Fig. 1 demonstrates the mean fever curves and laboratory values in a cohort of consecutive 209 patients undergoing CAR T cell therapy at our institution. The earliest clinical sign of toxicity is typically

* Corresponding author at: Division of Neurocritical Care, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 175 Cambridge St. Suite 300, Boston, MA 02114, United States of America.
E-mail address: drubin4@mgh.harvard.edu (D.B. Rubin).

https://doi.org/10.1016/j.jns.2021.117405
Received 9 February 2021; Received in revised form 10 March 2021; Accepted 16 March 2021
Available online 18 March 2021
0022-510X/

Table 1
Neurologic symptoms encountered in a 100-patient cohort after CAR T infusion.

Symptoms:	Number of Patients
Encephalopathy	57
Headache	42
Tremor	38
Aphasia	35
Somnolence	21
Agitated delirium	15
Focal Weakness	11
Rigors	11
Asterixis	8
Scotoma	5
Abulia	4
Allodynia	3
Apraxia	3
Scintillation	3
Stroke	2
Intracranial hemorrhage	2
Autonomic instability	2
Seizure	1
Death	5

fever, which most commonly begins on treatment day 2 but may emerge as early as the day of cell infusion. Serum C-reactive protein (CRP) tends to rise during this period as well and has been correlated with the severity of both CRS and subsequent neurotoxicity. Patients at this time may develop hypoxia and hypotension, the hallmark clinical features of CRS [20], and treatment for CRS is often indicated. Importantly, symptoms may resemble sepsis, and as patients are often neutropenic early in the course of treatment, concomitant workup and management of infection is generally indicated. CRS usually resolves by day 5, or sooner if treated. Simultaneously the CAR T cells undergo expansion, which can be observed in rising absolute lymphocyte counts. Laboratory monitoring demonstrates rising levels of serum procalcitonin and ferritin and dropping serum fibrinogen levels. Though neurotoxicity can occur at any time post-treatment, in most cases, neurotoxicity onset occurs following this initial cell expansion phase, approximately one week after the date of infusion [24–26]. In a large cohort study, the median date of onset of neurologic symptoms was post-treatment day 6 and median date of peak neurologic symptom severity was post-treatment day 8 (Fig. 2) [26]. Symptoms then usually persist for several days, depending on the course of treatment. Within 1–2 weeks most patients recover completely [22]. More persistent symptoms are rare [18], with the exception of tremor, which may take many weeks to resolve [7,16]. A small proportion of patients suffer from a more prolonged course of encephalopathy that, while usually mild, can prove frustratingly refractory to treatment and lead to prolonged hospitalization.

In terms of absolute frequency, the most common neurologic symptom encountered during CAR T cell therapy is encephalopathy, which is seen in more than half of all patients [5,9,10,18,22,24,26,28,29]. Encephalopathy is often described as "altered mental status" or "confusional state" [5,6]; in the setting of CAR T cell therapy these terms all refer to the same general clinical syndrome, characterized as a state of waxing and waning inattentiveness with or without accompanying confusion, disorientation, impulsivity, and emotional lability. A depressed level of arousal, ranging from mild somnolence to significant lethargy, stupor and even coma is commonly described [29]. Patients with milder symptoms may have only slight memory impairment, disorientation, attentional deficits, or difficulty following multi-step commands [5,22], whereas in more severe cases patients experience periods of frank agitated delirium requiring the use of neuroleptics and ICU level care or obtundation requiring intubation for airway protection [2,22,24,26,28,29]. When present, these severe symptoms tend to evolve from milder syndromes over the course of days. In some instances, however, severe encephalopathy presents abruptly [25]. During early periods of encephalopathy, patients often have symptoms of frontal lobe dysfunction including positive frontal release signs on neurologic exam, such as palmomental, snout, and grasp reflexes [22,26]. While global symptoms are frequently observed, it is important to recognize that CAR T related neurotoxicity frequently leads to focal neurologic deficits out of proportion to the degree of encephalopathy.

Another commonly encountered neurologic symptom is aphasia, which is seen in up to a third of patients [24,26,28]. Aphasic patients are commonly described clinically as having "decreased fluency", "diminished fluency", or "word-finding difficulty". As described above, in more severe cases patients may experience broken speech limited to 1–2 word phrases or even complete muteness [13,25]. Like encephalopathy, the onset and progression of aphasia is typically insidious over hours to days, however in some instances symptom onset can be abrupt, mimicking acute ischemic stroke [25]. Encephalopathy and aphasia can occur together, and when they do symptoms often take on a predictable, stepwise progression. Mild dysfluency, difficulty with handwriting, and/or word finding difficulty appears first, accompanied by confusion or disorientation [11]; in the subset of patients that develop more severe language deficits, symptoms then progress towards more dense aphasias and in extreme cases mutism [22,26], accompanied by an abulic or catatonic-like mental state. Interestingly, in cases of even mild aphasia, following the resolution of language symptoms patients are amnestic to the entire experience [26].

Headache is another commonly encountered symptom [6,7,18,26,28,29]. Patients typically describe the headaches associated with CAR T cell therapy as "tension-like" or "pressure-like"; they are usually mild and rarely debilitating. Migraine headache is less common, although migrainous symptoms like scintillating visual obscurations and migratory sensory changes have all been described and may relate to a common pathophysiologic mechanism involving blood-brain barrier dysfunction and foci of cortical spreading depression [26].

Hyperkinetic movement symptoms (including tremor, myoclonus, and asterixis) are another common class of neurologic symptoms encountered [9,24,26,29]. The most common of these is a heightened physiologic tremor or new high frequency tremor with movement. These symptoms are often subtle but can progress to impair function. Significantly, tremor is often the first symptom of neurotoxicity to develop, and so daily physical exam should always include tests of both resting and intention tremor. Myoclonus, asterixis, and other movement symptoms are also quite common but rarely severe [24–26].

Several other focal neurologic symptoms have all been seen in smaller numbers of CAR T cell patients. Weakness in an arm, leg, or part of the face have been described in up to 10% of patients, and when abrupt in onset may raise concern for acute ischemic stroke [7,18,26,29]. Other symptoms, including ataxia, apraxia, allodynia, vision changes, and autonomic instability manifesting as postural orthostasis have also all been observed in smaller numbers of patients [18,26,29]. Seizures, including non-convulsive seizures, have been reported in many clinical trials [2,14,18,24,25,28–30], and should remain on the differential diagnosis for prolonged alteration in level of arousal, in particular in cases that are not following the expected course of recovery. Fortunately, recurrent seizures following the resolution of neurotoxicity are uncommon, and most patients do not require long-term anti-epileptic drug (AED) therapy. Rare cases of fulminant cerebral edema, in which patients progress clinically from mild confusion to obtundation and ultimately to brain death over the course of hours, have been reported as well [27,28,31,32].

As has already been discussed, the symptoms of neurotoxicity, when focal in nature and abrupt in onset, often resemble the clinical syndrome of acute ischemic stroke. Significantly, patients undergoing CAR T cell therapy are often at increased risk of thromboembolic events due to elevated levels of pro-inflammatory cytokines and other coagulopathies [19,22,24,28]. As a result, patients that develop abrupt-onset focal neurologic symptoms should undergo an appropriate evaluation for

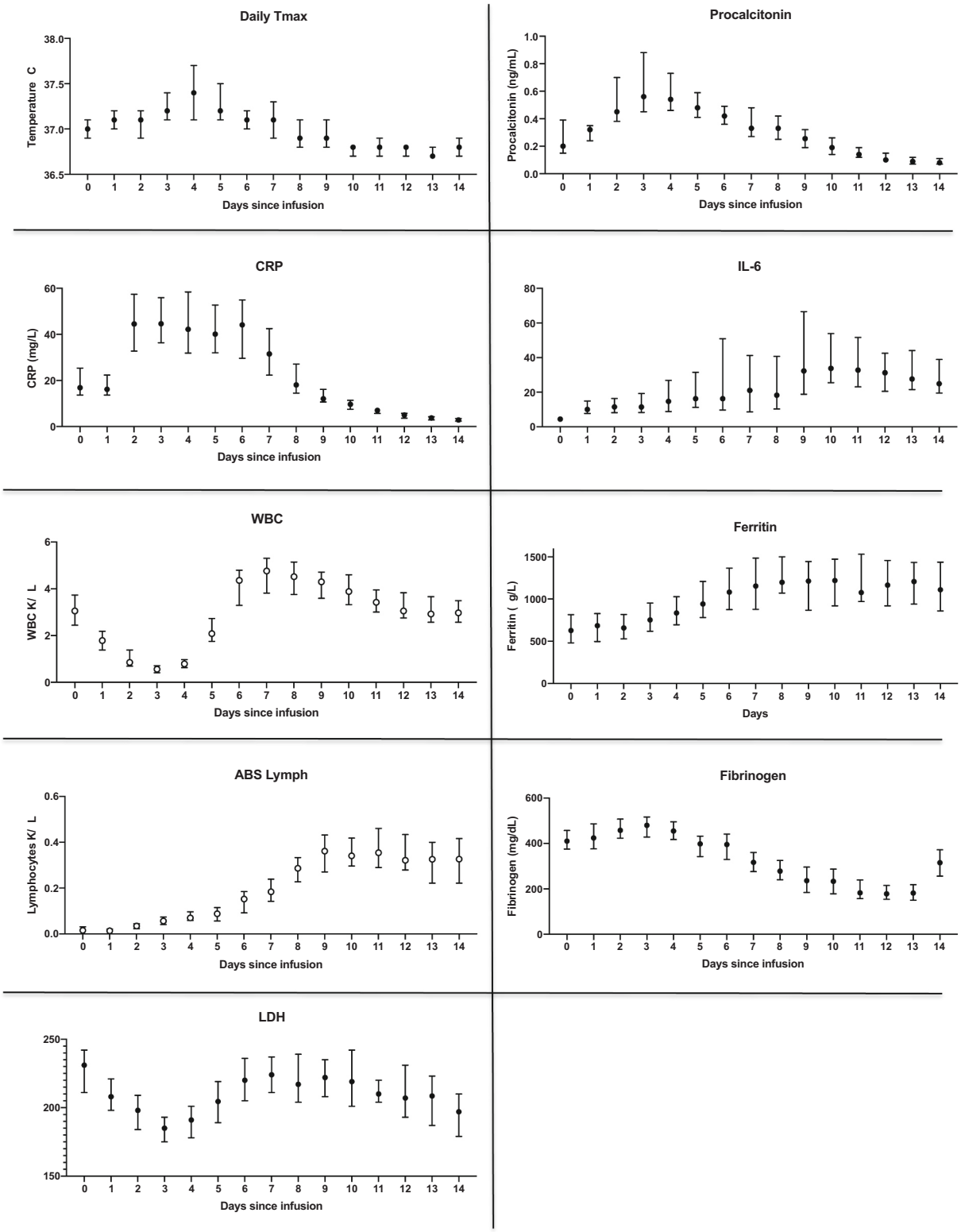

Fig. 1. Average maximum daily temperature and average daily laboratory values in consecutive 209 patients treated with CAR T cell therapy at our institution. Day 0 indicates the day of cell infusion. Temperature commonly begins rising on treatment day 1–2 and peaks on day 4, accompanied by a rise in serum CRP and procalcitonin. Patients are initially lymphopenic as result of the induction chemotherapy, but as the CAR T cell population expands, serum white blood cell and absolute lymphocyte counts rise; this is followed by a more gradual rise in LDH, IL-6, and ferritin and a decline in serum fibrinogen. CRP = C-reactive protein, WBC = white blood cell count, LDH = lactate dehydrogenase.

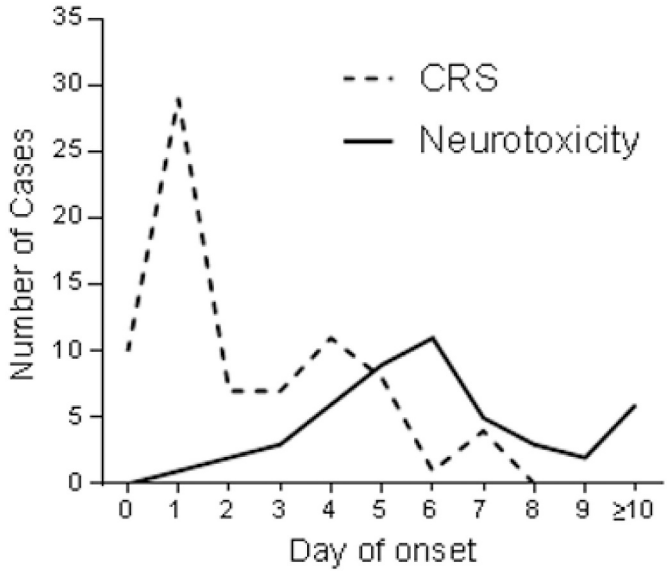

Fig. 2. Onset of CRS precedes neurotoxicity. In a cohort of 100 patients treated with CAR T cell therapy, the most common day of onset of CRS was day 1. Neurotoxicity began later, most commonly on treatment day 6.

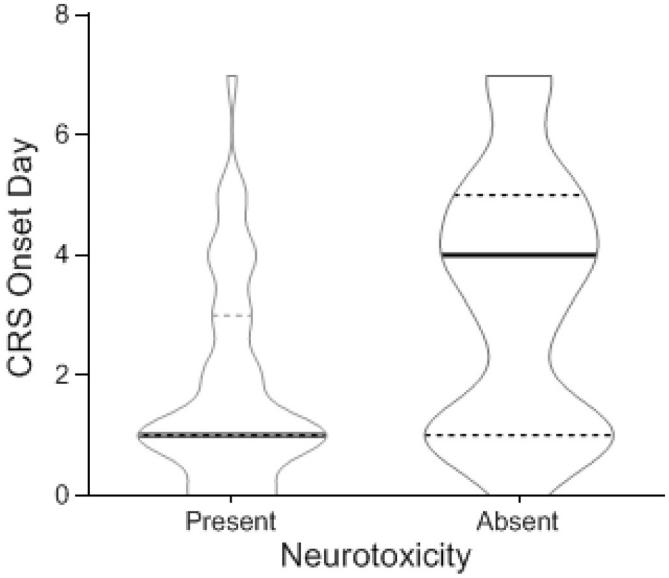

Fig. 3. Earlier onset of CRS is associated with increased risk of neurotoxicity. Violin plot showing the relative frequency (plot width) of CRS onset day in patients with and without neurotoxicity. Thick solid line indicated the median; thin dashed lines demarcate the IQR. In patients that subsequently developed neurotoxicity, the median day of onset of CRS was on day 1; in patients that did not develop neurotoxicity the median day of CRS onset was day 4.

acute ischemic stroke (see Approach to Management below) until proven otherwise, and symptoms should not simply be assumed to be due to CAR T cell toxicity.

3. Risk factors for neurotoxicity

The incidence of neurotoxicity after CAR T cell treatment ranges from 27%–67% [4–6,9,10,14,22,25,26,29], however, the risk of neurotoxicity and the specific symptoms encountered depends on several different factors. The CAR T cell target antigen, specific co-stimulatory domains, CAR T cell dose, conditioning chemotherapy regimen, the primary malignancy being treated, prior therapies, and the underlying disease burden all have an impact on the risk and presentation of neurotoxicity [17,21,22,28,33]. For example, fatal cerebral edema, the most feared neurologic complication of CAR T cell therapy, has primarily been observed in patients being treated for acute lymphoblastic leukemia (ALL) [17,27,28,31]. Similarly, seizures, which have been reported in a high proportion of patients treated for ALL [14,25,28–30,34], appear less common in patients treated for lymphoma [5,9,24,26,35]. Among patients with lymphoma, there is a higher incidence of neurologic symptoms among patients with more aggressive subtypes and relatively fewer symptoms observed in patients being treated for indolent subtypes like follicular lymphoma and marginal zone lymphoma [4,7,36]. Patients treated with CAR T cells targeting B-cell maturation antigen (BCMA) for multiple myeloma are overall less likely to experience significant neurotoxicity [17,22,37–39], despite often impressive rates of CRS.

In addition to these pre-treatment clinical factors, there are a number of variables that can be followed during the course of treatment that can be helpful in predicting the likelihood and severity of neurotoxicity. As mentioned above, neurotoxicity onset typically occurs between treatment days 5–8, and earlier onset of neurologic symptoms (i.e. before day 5) generally portends a more severe clinical course [26]. More aggressive treatment in these cases is recommended. Similarly, earlier onset of CRS and more severe CRS is associated with increased risk for neurotoxicity and for more severe neurotoxicity (Fig. 3) [14,24,26,28,36].

Certain laboratory values can also be helpful in predicting the course of neurotoxicity. Serum C-reactive protein (CRP) is a non-specific marker of systemic inflammation, and is usually elevated in patients undergoing CAR T cell therapy [30,40]. Patients that experience neurotoxicity have significantly higher baseline and peak CRP levels than those that do not experience neurotoxicity and have CRP levels that peak earlier than those patients that do not experience neurotoxicity (Fig. 4) [8,17,22,24,26,30,36,40]. The serum level of the inflammatory cytokine IL-6 is probably the most specific biomarker for CRS and neurotoxicity [17,28,30], however, the ability to check levels is not routinely available in most facilities and the commercial assays are not reliable after exposure to tocilizumab [41], limiting the clinical utility of this assay.

Additionally, treatment of CRS with tociluzimab may also increase the risk for and severity of subsequent neurotoxicity [36]. Tocilizumab is a monoclonal anti-IL6R antibody that does not cross the blood brain barrier. By antagonizing peripheral activation of IL-6R, it may actually potentiate the effects of IL-6 centrally [19,20,29], and so patients treated aggressively with tocilizumab early for CRS should be monitored closely for signs of neurotoxicity, and earlier treatment of neurologic symptoms

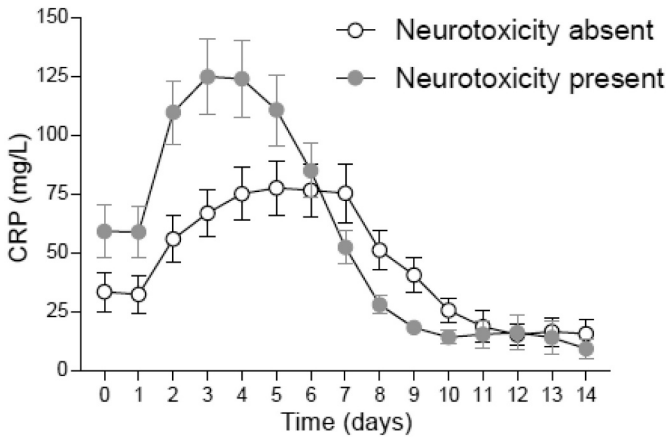

Fig. 4. Baseline and peak serum CRP levels are higher and peak earlier in patients that develop neurotoxicity. The mean (+/− standard deviation) serum CRP level on each day of treatment of all patients that did (filled circles) or did not (empty circles) develop neurotoxicity.

is recommended in these cases.

4. Pathophysiology

The pathophysiology of CAR T cell neurotoxicity is incompletely understood, but a number of lines of evidence suggest that it may be due to endothelial activation resulting from high levels of pro-inflammatory cytokines, with subsequent increased permeability of the blood brain barrier (BBB) and secondary cortical dysfunction [28]. This provides a potential mechanism for the cases of diffuse and often fatal cerebral edema that have been reported [26–28,31], and is supported by findings of widespread endothethial activation and disruption from pathologic specimens in humans that died from CAR T associated neurotoxicity [26,28,31] (Fig. 5) as well as findings of meningeal inflammation and blood brain barrier breakdown in animal models of CAR T cell neurotoxicity [23,42]. This mechanism of cytokine-promoted endothelial dysfunction is also supported by clinical trials demonstrating elevated levels of pro-inflammatory cytokines in patients that experience neurotoxicity [22,25], and the finding that neurotoxicity often occurs several days after the peak of CRS [26,28]. CSF from patients experiencing neurotoxicity has been shown to contain elevated levels of a number of inflammatory cytokines, including IL1α, IL-6, IL-10, GzB, G-CSF, TNFα, IFNγ, IFNα2, FLT3L, eotaxin, fractalkine, and GRO [25,28,29], as well as activated levels of GFAP and S100b, which are specific markers of astroglial injury and activation [29]. Cytokine-induced activation of glial cells resulting in increased BBB permeability may disrupt the local homeostasis of extracellular contents resulting in cortical circuit dysfunction, such as cortical spreading depression. Such a mechanism could account for periods of both focal and generalized symptoms, the lack of structural findings on imaging, the absence of impressive signs of CNS inflammation, the non-specific but abnormal EEG patterns observed [24,26,28,35], cortical hypometabolism seen on FDG-PET [26], and the reversibility of symptoms. More recent work has demonstrated elevated levels of the excitatory neurotransmitters glutamate and quinolinic acid within the CSF of patients with neurotoxicity, suggesting that increased CNS cytokine levels leading to endogenous production of these substances may underlie some of the symptomatology observed [25].

There exists ongoing debate as to whether elevated levels of pro-inflammatory cytokines observed within the CSF in patients with neurotoxicity are due to active infiltration of CAR T cells into the CNS [8,19,23,28,43] or simply passive movement of the cytokines through the disrupted BBB [16]. However, several studies have shown no difference in the frequency or cell counts of CAR T cells in the CSF of patients with or without neurologic symptoms [10,29,44]; cases of patients with CAR T cell associated neurotoxicity have been reported in which no CAR T cells are present in CSF [2]; and the magnitude of CSF pleocytosis, when observed, is not correlated with the severity of neurologic symptoms [25,26]. Furthermore, in spite of the findings of widespread endothelial activation, pathologic specimens from patients that died from CAR T associated neurotoxicity did not show evidence of an inflammatory process (Fig. 5) [26]. The ongoing uncertainty regarding the underlying etiology highlights the importance of ongoing research focused on further elucidating the mechanisms on CAR T cell associated

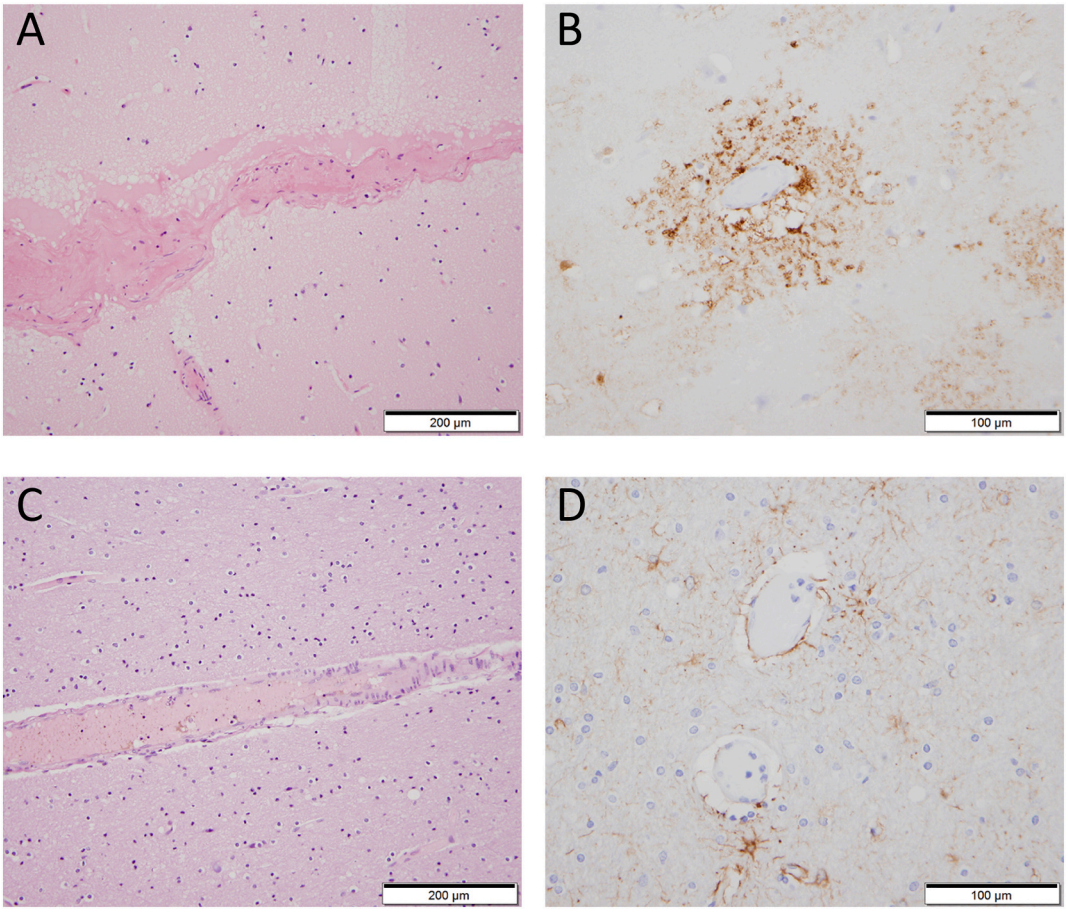

Fig. 5. Pathologic specimen from the brain of a patient that died from grade 5 neurotoxicity. A. H&E staining reveals perivascular extravasation of acellular proteinaceous material but is notably absent an inflammatory cellular infiltrate. B. GFAP immunohistochemistry demonstrates astrocytic clasmatodendrosis (retraction of astrocyte foot processes), indicating breakdown of the blood brain barrier. C, D. These findings are not observed in a pathologic specimen of the brain obtained from a patient who received CAR T cells and subsequently died in the setting of severe CRS but that did not develop neurotoxicity. (Modified from [26]).

neurotoxicity.

5. Clinical evaluation

One of the most interesting features of CAR T cell neurotoxicity is that, even in the setting significant neurologic dysfunction, there are rarely any major positive findings on most diagnostic studies. However, in most cases, neurologic symptoms begin quite subtly, and early signs of neurologic dysfunction are easily missed. Thus it is imperative that all patients receiving CAR T cells undergo a thorough daily neurologic exam that specifically includes tests of attention, memory, motor function, visual fields and coordination [11,15]. When detected, neurologic dysfunction is assigned a grade, which is important not only for reporting purposes but also as a helpful adjunct to guide management and aid communication among providers.

There are several different scales that have been developed to assess the severity of neurotoxicity. One commonly used clinical tool is the Common Terminology Criteria for Adverse Events (CTCAE) score, which grades neurotoxicity based on the severity of a number of different neurologic symptoms, including encephalopathy, seizure, aphasia, tremor, headache, confusion, and level of consciousness (Table 2) [45]. One shortcoming of the CTCAE grading tool is that it primarily relies on an assessment of the ability to complete ADLs and iADLS to evaluate encephalopathy and confusion, which may be difficult to objectively and reproducibly assess in hospitalized patients. Additionally, this grading scale may underestimate the clinical significance on new onset seizures, which in practice are considered a sign of more severe toxicity. A more recently developed grading scale relies on the Immune Effector Cell-Associated Encephalopathy (ICE) score (which is an adaptation of another commonly used clinical tool, the CARTOX-10 score), in which a total of 10 possible points are assigned for completing 10 basic cognitive tasks (Table 3A) [15]. The Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) grade is then determined by ICE score, level of arousal, seizure severity, and clinical evidence of motor deficits and elevated intracranial pressure (Table 3B) [15]. This tool does not evaluate tremor or headache, however, and so may miss the earliest signs of neurotoxicity, though the clinical relevance of these symptoms is debatable as they are rarely treated. One shortcoming of both of these scales is that they are largely determined by level of consciousness, and so may underemphasize severe focal neurologic deficits that do not impair cognition or arousal.

In most major centers treating patients with CAR T cells, diagnostic and treatment decisions are guided by neurotoxicity grade. Although the thresholds for specific interventions (both diagnostic and therapeutic) are often institution-specific, there are certain basic steps that are broadly applicable. All patients with new onset neurologic symptoms, in particular encephalopathy, should undergo a laboratory workup to evaluate for reversible metabolic derangements that may be contributing to symptoms (Table 4). A basic metabolic panel with extended electrolyte panel, blood glucose level, liver function tests, thyroid function tests, serum ammonia level, and urinalysis with urine sediment should all be sent [11,17]. Patients with fever should have blood, urine, and sputum cultures sent and a chest X-ray performed [11,17]. Lumbar puncture may be considered as well, in particular in patients with meningismus. In patients with a history of prolonged corticosteroid use, a serum cortisol should be measured to evaluate for adrenal insufficiency. From a prognostic standpoint, trending CRP, IL-6, procalcitonin, ferritin, and fibrinogen levels (Fig. 1) may be very helpful in determining the expected clinical course [24,26,30,36,40].

Most patients with new neurologic symptoms, and in particular any patient with grade $\geq$ 2 neurotoxicity, should also undergo a neuroimaging study to rule out an acute structural injury [11,17,19]. The most convenient and accessible study in most instances is a non-contrast CT of the brain, and in general this is sufficient to rule out major structural neurologic injury. Though CT of the brain is almost always normal in CAR T neurotoxicity [26], both stroke and intracranial hemorrhage (including both intracerebral and subarachnoid hemorrhage) have been reported in patients undergoing CAR T cell therapy [26,28,29,40]. Given the relatively low sensitivity of non-contrast CT for acute ischemic stroke, in patients with focal neurologic deficits (e.g. focal weakness, numbness, aphasia, visual field deficits), it is worthwhile to obtain a CT angiogram of the head and neck as well. If focal symptoms persist and CT/CTA is negative, an MRI of the brain should be obtained [17]. In some case series MRI of the brain has revealed regions of T2/FLAIR hyperintensity of uncertain etiology [8,22,24,28,29], which may be a marker of an inflammatory CNS process and would certainly warrant treatment. Patients with paraparesis or other clinical signs suggesting a myelopathic process should undergo MRI of the spine, as spinal cord edema has been observed in a small number of cases as well (Fig. 6). Importantly, any abrupt change in neurologic exam or level of arousal or other clinical signs of elevated intracranial pressure (such as nausea/vomiting, severe headache, 3rd or 6th nerve palsy, Cushing's triad) should prompt repeat imaging with a stat CT scan of the brain, as cerebral edema can develop rapidly and requires prompt recognition and

Table 2
The CTCAE v5.0 Grading Criteria for CAR T cell associated neurotoxicity.

Features	Grade 1	Grade 2	Grade 3	Grade 4
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Seizure	Brief partial seizures and no loss of consciousness	Brief generalized seizure	New-onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated
Cerebral edema			New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated

Table 3
The ASTCT ICANS consensus grading for adults.

A: The immune effector cell-associated encephalopathy (ICE) score				
Feature	Task			Points
Orientation	Orientation to year, month, city, hospital			4
Naming	Ability to name 3 objects (e.g., point to clock, pen, button)			3
Commands	Ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")			1
Writing	Ability to write a standard sentence (e.g., "Our national bird is the bald eagle")			1
Attention	Ability to count backwards from 100 by 10			1
B. The Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading Scale				
Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	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
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
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as 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; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Table 4
Approach to encephalopathy.

4A: Diagnostic Workup
Review medications
Comprehensive metabolic panel
Glucose, Ammonia, ESR, CRP
B12, TSH, cortisol
Urinalysis and urine culture
Chest X-ray
Lumbar puncture
Neuroimaging (as per Table 5)
4B: Management
Delirium precautions
Address constipation
Treat infections
Thiamine
Dexamethasone trial

intervention to prevent death.

In patients with persistent encephalopathy, and in particular those with an altered level of arousal, an EEG should be obtained to evaluate for non-convulsive seizure and better characterize encephalopathy [18,35]. If the technical capabilities exist for 24-h continuous EEG, this is preferable to a routine (30-min) study as it has higher yield for both seizures and other pathologic patterns of cortical activity [46]. Though seizures are relatively uncommon with most modern CAR T constructs, EEG often reveals focal patterns of abnormal cortical activity, such as focal slowing or lateralized periodic discharges (Fig. 7), which are likely indicative of underlying cortical dysfunction [18,24,26,35]. Indeed, often these focal EEG abnormalities are the only positive findings on diagnostic workup [26].

Most other diagnostic studies can be considered on a case-by-case basis. Importantly, patients undergoing CAR T cell therapy are often considerably immunosuppressed [17,19], and so in the setting of neurologic symptoms and fever, lumbar puncture should be considered to rule out central nervous system (CNS) infection. While opening pressure and protein levels are often mildly elevated [16], other routine CSF studies are typically normal or only mildly inflammatory in the setting of neurotoxicity [26,28]. Specialized CSF cytokine profiles may provide a more specific marker for neurotoxicity but are not routinely available outside of the research setting at this time [25,28,29]. Transcranial Doppler (TCD) ultrasound has demonstrated elevated flow velocities in patients with focal neurologic symptoms, and has been used in our institution as an adjunct to EEG to confirm focal areas of dysfunction in patients with persistent symptoms and normal imaging [26]. TCDs have the advantage over EEG of being easily repeatable on a daily basis, and so may be of value in monitoring, with elevated flow velocities serving as a biomarker for cortical dysfunction. Velocity measurements by TCD ultrasound may be operator dependent, and it is standard practice to have the same ultrasonographer perform serial studies when feasible. [18]FDG-PET has also been used to demonstrate cortical hypometabolism in patients with neurotoxicity [26], and may be a useful marker, though data on this modality are limited (Fig. 8).

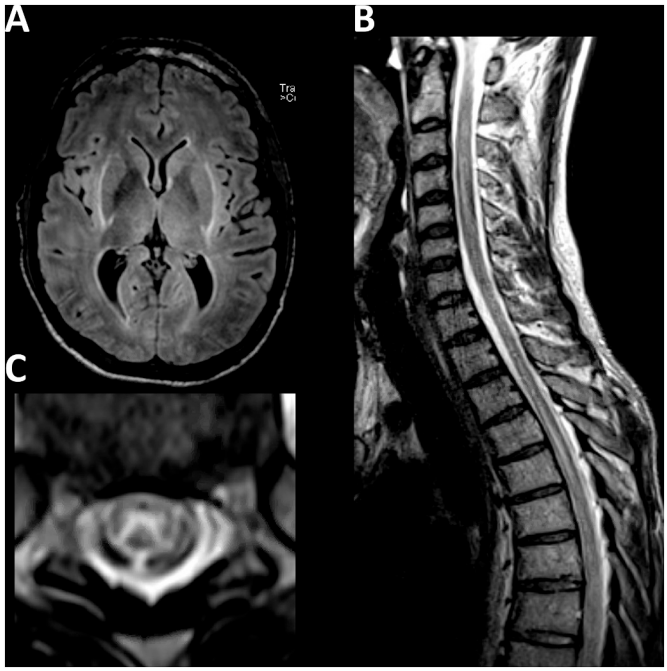

Fig. 6. MRI from a patient with CAR T cell neurotoxicity manifesting as myelopathy. A. MRI brain demonstrates T2/FLAIR signal hyperintensities in the bilateral external capsules and thalami. B. C. MRI of the spinal cord demonstrates non-enhancing longitudinally-extensive lesions in the cervical, thoracic, and lumbar regions selectively affecting the gray matter.

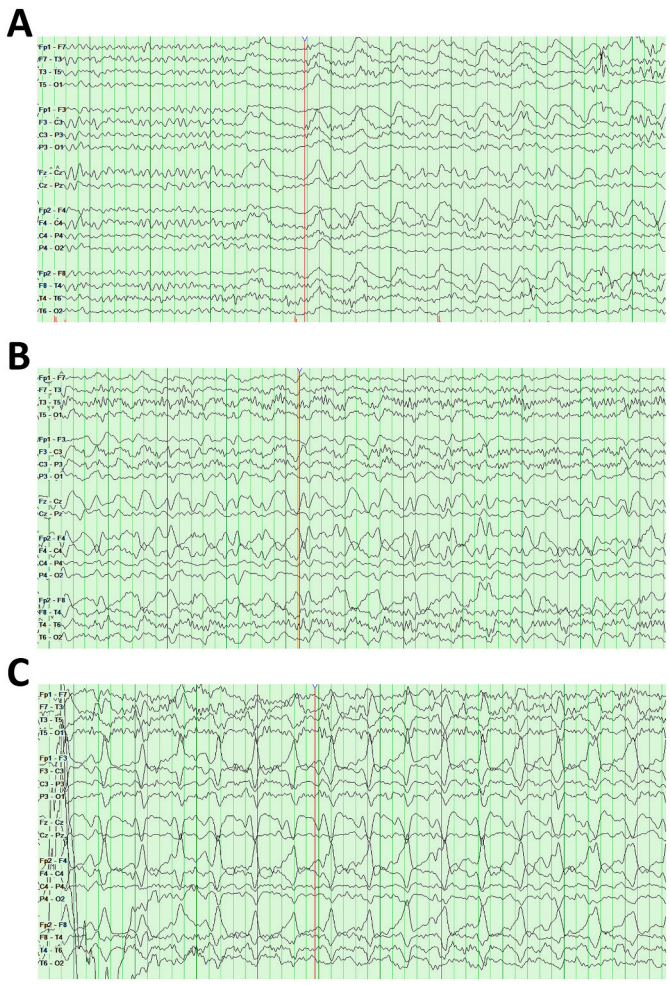

Fig. 7. EEG reveals non-specific patterns on the ictal-interictal spectrum, including (A) generalized rhythmic delta activity (GRDA), (B) lateralized rhythmic delta activity (LRDA)., and (C) generalized periodic discharges.

6. Approach to management

The decision of when and how to treat neurotoxicity is an area of active investigation, and there exists considerable variation in practice when it comes to determining the threshold for treatment. In early trials, there was concern that using corticosteroids to treat neurotoxicity might impair the anti-tumor effect of the CAR T cells [2,10,16,34], and so there was initially a high threshold to treat. Following the occurrence of a number of high profile cases of fatal cerebral edema [27,31], and with more recent data suggesting that the judicious use of corticosteroids probably does not impact the therapeutic effect of the CAR T cells [5,14,18,24], the threshold to treat neurotoxicity has lowered considerably. The main consideration that typically has to be considered is risk/benefit profile of corticosteroids. Many patients receiving CAR T cell therapy are elderly and at risk for hospital-associated delirium, and high-dose corticosteroids are potently deliriogenic. Given that the most commonly encountered symptom is delirium, caution should be exercised against overly treating encephalopathy that does not respond to initial doses of steroids. In contrast, focal neurologic symptoms, such as aphasia and focal weakness, do likely warrant prompt and repeated treatment. Importantly, there should be a lower threshold to treat patients that develop earlier neurologic symptoms than those that occur later in the hospital course, as it is specifically these patients that develop severe neurotoxicity. A summary of management guidelines by grade is provided in Table 5 and a summary of suggested treatments is provided in Table 6.

As stated above, the mainstay of treatment for neurotoxicity is with corticosteroids [18,19,21]. The most commonly used approach is to administer dexamethasone 10 mg IV every six hours until symptom improvement is noted [16,18]. In patients with worsening neurotoxicity unresponsive to dexamethasone, treatment may be escalated to high-dose methylprednisolone (1000 mg IV QD x 3 days)) [16,18,21]. Although the IL-6 receptor inhibitor tocilizumab is highly efficacious in the treatment of CRS, it has little to no effect on neurotoxicity (and in fact may even worsen neurotoxicity by potentiating the effects of IL-6 on the CNS) [17,19,20,29] and should not be used for the treatment of neurologic symptoms alone [16,21,22]. If patients receive tocilizumab for CRS while experiencing neurotoxicity, there should be a low threshold to treat neurologic symptoms simultaneously with corticosteroids [21].

Unlike tocilizumab, the direct IL-6 antagonist siltuximab likely does not exacerbate neurotoxicity; however, unlike tocilizumab it is not currently approved for the treatment of CRS [21,28]. Anecdotal reports of its use for severe neurotoxicity have been promising and more study of siltuximab in CAR T cell therapy is warranted [11,16,21,22,47]. Another biological agent being considered for the treatment of neurotoxicity is the IL-1 receptor antagonist anakinra, which has been effective in animal models of CAR T cell associated neurotoxicity [42,48] and is being trialed in some institutions. In cases of severe refractory neurologic toxicity and widespread cerebral edema, anti-thymocyte globulin (ATG) can be used to effectively wipe out all CAR T cells, however, this very likely will result in therapeutic failure. Similarly, certain CAR T cell products have been engineered with “suicide” gene constructs that allow for rapid ablation of the cells in the setting of impending death due to toxicity, albeit at the cost of abrogation of the therapeutic effect [1,16,17,49,50]. Importantly, neither siltuximab, anakinra, or ATG are currently FDA approved for the treatment of CAR T cell associated neurotoxicity and so their use is considered “off-label”. Before initiating treatment with any of these agents, their relative risks and benefits should be discussed with the treating oncologist.

Because of the small but significant associated risk of seizure, many patients receiving CAR T cell therapy also receive a prophylactic anti-epileptic drug (AED) [16,18,21,26]. At present it is uncertain which patients should receive AED prophylaxis. Some centers treat all patients with up to 30 days of seizure prophylaxis, whereas others reserve prophylaxis for patients with either a history of seizures, prior neurologic injury, or symptoms of neurotoxicity [51,52]. The most commonly used AED used is levetiracetam, which is preferred for its relatively mild side-effect profile and minimal drug-drug interactions [11]. Patients that are found to have seizures either clinically or on EEG should of course be treated with additional AEDs as needed to control seizures, as well as corticosteroids [21]. The optimal duration of AED therapy after seizure has not been defined but patients rarely require long-term treatment. Patients that develop agitated delirium may require symptomatic treatment with neuroleptics for safety. Patients with autonomic instability manifesting as severe postural hypotension and/or syncope [6,26] may require treatment with midodrine, fludrocortisone, and an abdominal binder to support blood pressure and prevent orthostatic syncope.

If cerebral edema is observed or even highly suspected, high dose corticosteroids (methylprednisolone 1000 mg IV QD x 3 days) [11,16] and hyperosmolar therapy (hypertonic saline and/or mannitol) should be initiated immediately [11,18,21], and treatment with ATG or activation of a construct’s “suicide switch” should be strongly considered [1,16]. Urgent neurosurgical consultation should be obtained for placement of a ventriculostomy catheter for intracranial pressure measurement and cerebrospinal fluid (CSF) diversion. Depending on the response to initial treatments, more aggressive therapy for intracranial hypertension, including anesthetic-induced coma, pharmacological paralysis, or therapeutic hypothermia may be necessary. A point of controversy surrounds the management of patients with severe CRS or neurotoxicity that require intubation and deep sedation or paralysis for

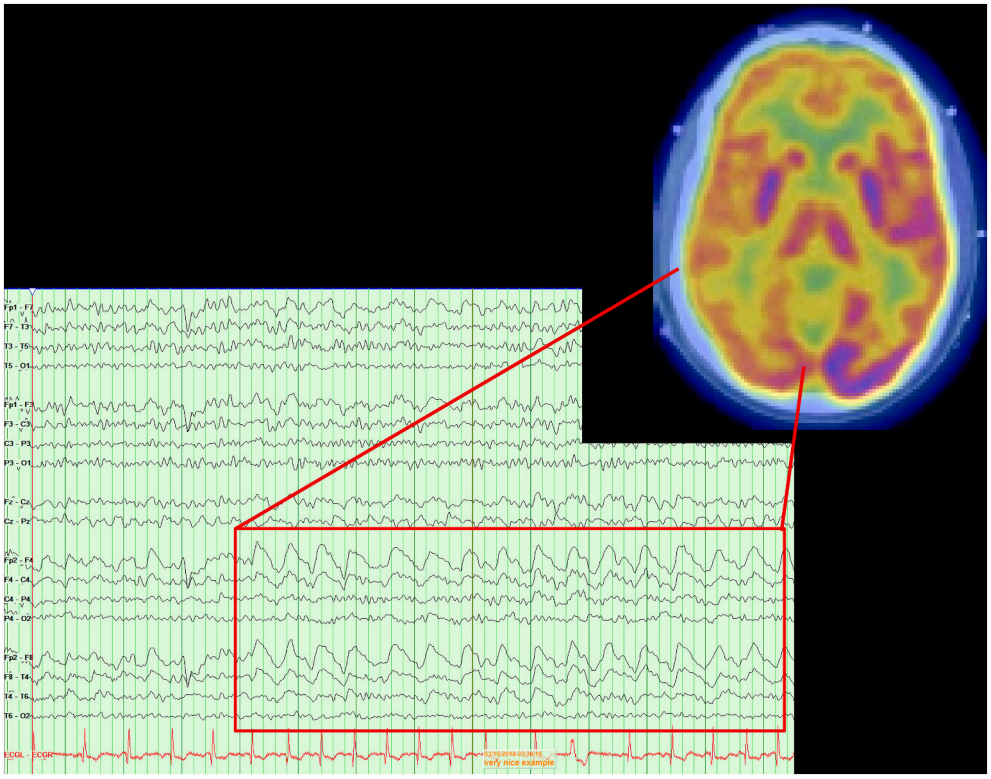

Fig. 8. Brain regions corresponding to EEG abnormalities are typically hypometabolic in neurotoxicity. EEG demonstrates focal slowing in a patient with intermittent left visual field deficit and left arm numbness with corresponding cortical hypometabolism on FDG-PET scan.

Table 5
Approach to management of CAR T cell associated neurotoxicity.

	All Patients	Grade 1	Grade 2	**Grade 3**	**Grade 4**
Diagnostics	Daily neuro exam	Neurology consult Laboratory workup Consider head CT if high risk*	Neurology consult ICU Consult Head CT EEG Consider TCD ultrasound	Neurology consult ICU Consult CT/CTA or MRI/MRA EEG (24 h) Consider TCD ultrasound Consider LP	Neurology consult ICU Consult CT/CTA or MRI/MRA EEG (24 h) Consider TCD ultrasound LP if not contraindicated Consider ICP monitor (if intubated)
Treatment	Consider seizure prophylaxis (levetiracetam 750 mg BID)	Consider seizure prophylaxis (if not already started) Consider dexamethasone (esp. if high risk*)	Consider dexamethasone (esp. if high risk)	ICU transfer Dexamethasone	ICU transfer Methylprednisolone Hyperosmolar therapy Consider siltuximab† Consider anakinra† Consider ATG†

* Risk factors for severe neurotoxicity include: high burden of disease, early onset of neurologic symptoms, early CRS, high grade CRS, treatment of CRS with multiple doses of tocilizumab, markedly elevated serum CRP/IL-6.

† These agents are not FDA approved for the treatment of CAR T cell associated neurotoxicity and their use is considered "off-label"; consideration of relative risks and benefits should occur in consultation with the treating oncologist.

control of symptoms; in some of these patients who are at risk for cerebral edema and in whom frequent neurologic exams are not possible, it may be reasonable to consider the prophylactic placement of a ventriculostomy catheter or subdural bolt for intracranial pressure monitoring [21].

In patients that develop the abrupt onset of focal neurologic symptoms (e.g. aphasia, hemiparesis), the decision of whether to treat for stroke with systemic thrombolysis is somewhat more complicated, although in reality, IV-tPA is contraindicated in the majority of patients undergoing CAR T cell therapy due to thrombocytopenia or decreased fibrinogen. In these cases, if an acute vessel occlusion is confirmed on CTA or MRA, mechanical thrombectomy should be considered. If stroke occurs in the presence of new or worsening coagulopathy, steroids are often administered as this may represent a variant of disseminated intravascular coagulopathy (DIC) driven by cytokine-induced endothelial dysfunction [17,19,21,22,28]. Table 7 presents an approach to the management of acute stroke in CAR T cell patients.

All patients with grade 2 toxicity (CRS or neurotoxicity) should be evaluated by an intensivist, and ICU transfer should be considered for any patient with grade 3 or rapidly worsening grade 2 toxicity. It is our practice to transfer all patients with severe toxicity (both CRS and neurotoxicity) preferentially to the neuro ICU rather than the medical

Table 6
Treatment of CAR T cell associated neurotoxicity.

Prophylactic Levetiracetam	750 mg BID day −1 to day 30
Dexamethasone	10 mg IV q6hr, reassess prior to each dose
Methylprednisolone	1 g IV QD x3 days, followed by taper of 250 mg BID x 2 days, 125 mg BID x 2 days, 60 mg BID x 2 days
Tocilizumab (IL6R)*	8 mg/kg (max 800 mg) q8hr as needed, reassess before each dose, max of 4 doses
Siltuximab (IL6)†	11 mg/kg IV x1
Anakinra (IL1R)†	100 mg SQ QD x 7
Anti-thymocyte globulin (rabbit)†	1–2 mg/kg IV x3, reassess
Hyperosmolar therapy	Mannitol 1 g/kg IV Q6h 23% NaCl 30 cc IV Q6h 3% NaCl 250 cc IV Q6h
Isolated seizures	Lorazepam 2 mg IV Q5 min Levetiracetam 60 mg/kg (Max 3000 mg) IV bolus Levetiracetam 1500 Q12h maintenance
Status epilepticus	Intubate Propofol IV 0-83μg/kg/min; titrate to seizure control Midazolam 0-30 mg/h; titrate to seizure control Lacosamide 200 mg Q12h Transfer to neuro ICU

* Tocilizumab may be used for the treatment of CRS and neurotoxicity occurring concurrently but has no role in the treatment of (and may potentially worsen) isolated neurotoxicity.

† These agents are not FDA approved for the treatment of CAR T cell associated neurotoxicity and their use is considered "off-label"; consideration of relative risks and benefits should occur in consultation with the treating oncologist.

Table 7
Management of acute ischemic stroke in patients undergoing CAR T cell therapy.

Diagnostics	
Vascular imaging of the head and neck (CTA or MRA)	
Echocardiogram	
Fibrinogen	
D-dimer	
HgA1c	
Lipid panel	
Treatment	
Platelets >100 k/uL Fibrinogen >200 mg/dL	Consider IV tPA if no contraindications, aspirin 81 mg, consider anticoagulation if embolic
Platelets >50 k/uL	Aspirin 81 mg, consider anticoagulation if embolic
Large vessel occlusion on CTA/MRA	Mechanical thrombectomy
Fibrinogen <150 mg/dL D-dimer >500 ng/mL	Consider dexamethasone for DIC

ICU, as patients with severe CRS are the most likely to subsequently develop significant neurotoxicity. For this same reason, recognizing that not all centers have neuro ICU capabilities, we recommend that all patients being evaluated for ICU transfer should also be evaluated by a neurologist. Institutional practices vary considerably, but it is important to ensure that regardless of disposition, patients have access to specialists comfortable with the neurocritical care tools required for the management of high grade neurotoxicity (e.g. continuous EEG monitoring, seizure management, and hyperosmolar therapy).

7. Conclusion

CAR T cell therapy is an extraordinarily efficacious immunologic therapy for relapsed and refractory hematologic malignancy. However, treatment-associated neurotoxicity remains a significant challenge to clinicians, and often defines the length of hospitalization for patients undergoing these treatments. The mechanism of neurotoxicity is poorly understood but appears to be driven by neurovascular bundle dysfunction triggered not by direct cellular autoimmunity but by dramatic fluctuations in the levels of inflammatory cytokines systemically and within the CNS. In the coming years, basic and translational research aimed at elucidating the underlying mechanisms of CAR T cell associated neurotoxicity will undoubtedly bring more advanced diagnostic and treatment approaches. It is thus imperative that neurologists be familiar with the risk factors, symptomatology, and management of CAR T cell neurotoxicity, so that we may be able to adequately care for this vulnerable patient population.

Declaration of Competing Interest

Dr. Rubin has received consultancy fees from Celgene/Bristol Myers Squibb. Dr. Vaitkevicius is an employee of Marinus Pharmaeuticals, Inc.

References

[1] J.N. Brudno, J.N. Kochenderfer, Chimeric antigen receptor T-cell therapies for lymphoma, Nat. Rev. Clin. Oncol. 15 (1) (2018) 31–46, https://doi.org/10.1038/nrclinonc.2017.128.
[2] M.L. Davila, I. Riviere, X. Wang, et al., Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia, Sci Transl Med 6 (224) (2014), https://doi.org/10.1126/scitranslmed.3008226, 224ra25-224ra25.
[3] S.A. Grupp, M. Kalos, D. Barrett, et al., Chimeric antigen receptor-modified T cells for acute lymphoid leukemia, N. Engl. J. Med. 368 (16) (2013) 1509–1518, https://doi.org/10.1056/NEJMoa1215134.
[4] A.V. Hirayama, J. Gauthier, K.A. Hay, et al., High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy, Blood. 134 (7) (2019) 636–640, https://doi.org/10.1182/blood.2019000905.
[5] S.S. Neelapu, F.L. Locke, N.L. Bartlett, et al., Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma, N. Engl. J. Med. 377 (26) (2017) 2531–2544, https://doi.org/10.1056/NEJMoa1707447.
[6] S.J. Schuster, J. Svoboda, E.A. Chong, et al., Chimeric antigen receptor T cells in refractory B-cell lymphomas, N. Engl. J. Med. 377 (26) (2017) 2545–2554, https://doi.org/10.1056/NEJMoa1708566.
[7] J.N. Kochenderfer, M.E. Dudley, S.H. Kassim, et al., Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor, J. Clin. Oncol. 33 (6) (2015) 540–549, https://doi.org/10.1200/JCO.2014.56.2025.
[8] D.W. Lee, J.N. Kochenderfer, M. Stetler-Stevenson, et al., T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial, Lancet. 385 (9967) (2015) 517–528, https://doi.org/10.1016/s0140-6736(14)61403-3.
[9] F.L. Locke, S.S. Neelapu, N.L. Bartlett, et al., Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma, Mol. Ther. 25 (1) (2017) 285–295, https://doi.org/10.1016/j.ymthe.2016.10.020.
[10] S.L. Maude, N. Frey, P.A. Shaw, et al., Chimeric antigen receptor T cells for sustained remissions in leukemia, N. Engl. J. Med. 371 (16) (2014) 1507–1517, https://doi.org/10.1056/NEJMoa1407222.
[11] S.S. Neelapu, S. Tummala, P. Kebriaei, et al., Chimeric antigen receptor T-cell therapy — assessment and management of toxicities, Nat. Rev. Clin. Oncol. 15 (1) (2018) 47–62, https://doi.org/10.1038/nrclinonc.2017.148.
[12] H. Hiramatsu, S. Adachi, K. Umeda, et al., Efficacy and safety of tisagenlecleucel in Japanese pediatric and young adult patients with relapsed/refractory B cell acute lymphoblastic leukemia, Int. J. Hematol. (2019), https://doi.org/10.1007/s12185-019-02771-2.
[13] S.L. Maude, T.W. Laetsch, J. Buechner, et al., Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia, N. Engl. J. Med. 378 (5) (2018) 439–448, https://doi.org/10.1056/nejmoa1709866.
[14] R.A. Gardner, O. Finney, C. Annesley, et al., Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults, Blood. 129 (25) (2017) 3322–3331, https://doi.org/10.1182/blood-2017-02-769208.
[15] D.W. Lee, B.D. Santomasso, F.L. Locke, et al., ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells, Biol Blood Marrow Transplant. 25 (4) (2019) 625–638, https://doi.org/10.1016/j.bbmt.2018.12.758.
[16] B.R. Dholaria, C.A. Bachmeier, F. Locke, Mechanisms and management of chimeric antigen receptor T-cell therapy-related toxicities, BioDrugs. 33 (1) (2019) 45–60, https://doi.org/10.1007/s40259-018-0324-z.
[17] J.N. Brudno, J.N. Kochenderfer, Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management, Blood Rev. 34 (2019) 45–55, https://doi.org/10.1016/j.blre.2018.11.002.
[18] J. Gust, A. Taraseviciute, C.J. Turtle, Neurotoxicity associated with CD19-targeted CAR-T cell therapies, CNS Drugs. 32 (12) (2018) 1091–1101, https://doi.org/10.1007/s40263-018-0582-9.
[19] J.N. Brudno, J.N. Kochenderfer, Toxicities of chimeric antigen receptor T cells: recognition and management, Blood. 127 (26) (2016) 3321–3330, https://doi.org/10.1182/blood-2016-04-703751.

[20] D.W. Lee, R. Gardner, D.L. Porter, et al., Current concepts in the diagnosis and management of cytokine release syndrome, Blood. 124 (2) (2014) 188–195, https://doi.org/10.1182/blood-2014-05-552729.
[21] C. Gutierrez, C. McEvoy, E. Mead, et al., Management of the critically ill adult chimeric antigen receptor-t cell therapy patient: a critical care perspective, Crit. Care Med. 46 (9) (2018) 1402–1410, https://doi.org/10.1097/CCM.0000000000003258.
[22] B. Santomasso, C. Bachier, J. Westin, K. Rezvani, E.J. Shpall, The other side of CAR T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden, Am Soc Clin Oncol Educ B. 39 (39) (2019) 433–444, https://doi.org/10.1200/EDBK_238691.
[23] A. Taraseviciute, V. Tkachev, R. Ponce, et al., Chimeric antigen receptor T cell–mediated neurotoxicity in nonhuman primates, Cancer Discov. 8 (6) (2018) 750–763, https://doi.org/10.1158/2159-8290.CD-17-1368.
[24] P. Karschnia, J.T. Jordan, D.A. Forst, et al., Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells, Blood. 133 (20) (2019) 2212–2221, https://doi.org/10.1182/blood-2018-12-893396.
[25] B.D. Santomasso, J.H. Park, D. Salloum, et al., Clinical and biological correlates of neurotoxicity associated with car t-cell therapy in patients with B-cell acute lymphoblastic leukemia, Cancer Discov. 8 (8) (2018) 958–971, https://doi.org/10.1158/2159-8290.CD-17-1319.
[26] D.B. Rubin, H.H. Danish, A.B. Ali, et al., Neurological toxicities associated with chimeric antigen receptor T-cell therapy, Brain. 142 (5) (2019) 1334–1348, https://doi.org/10.1093/brain/awz053.
[27] DeAngelo DJ, A. Ghobadi, J.H. Park, et al., Clinical outcomes for the phase 2, single-arm, multicenter trial of JCAR015 in adult B-ALL (ROCKET Study). 32nd Annual Meeting and Pre-Conference Programs of the Society for Immunotherapy of Cancer (SITC 2017): part one, J Immunother Cancer 5 (S2) (2017), https://doi.org/10.1186/s40425-017-0289-3.
[28] J. Gust, K.A. Hay, L.-A. Hanafi, et al., Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells, Cancer Discov. 7 (12) (2017) 1404–1419, https://doi.org/10.1158/2159-8290.CD-17-0698.
[29] J. Gust, O.C. Finney, D. Li, et al., Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy, Ann. Neurol. 86 (1) (2019) 42–54, https://doi.org/10.1002/ana.25502.
[30] C.J. Turtle, L.-A. Hanafi, C. Berger, et al., CD19 CAR–T cells of defined CD4+:CD8 + composition in adult B cell ALL patients, J. Clin. Invest. 126 (6) (2016) 2123–2138, https://doi.org/10.1172/JCI85309.
[31] M. Torre, I.H. Solomon, C.L. Sutherland, et al., Neuropathology of a case with fatal CAR T-cell-associated cerebral edema, J. Neuropathol. Exp. Neurol. 77 (10) (2018) 877–882, https://doi.org/10.1093/jnen/nly064.
[32] C.J. Turtle, K.A. Hay, L.A. Hanafi, et al., Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib, J. Clin. Oncol. 35 (26) (2017) 3010–3020, https://doi.org/10.1200/JCO.2017.72.8519.
[33] J.H. Park, I. Rivière, M. Gonen, et al., Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia, N. Engl. J. Med. 378 (5) (2018) 449–459, https://doi.org/10.1056/NEJMoa1709919.
[34] M.L. Davila, C. Sauter, R. Brentjens, CD19-targeted T cells for hematologic malignancies, Cancer J. 21 (6) (2015) 470–474, https://doi.org/10.1097/PPO.0000000000000153.
[35] A. Herlopian, J. Dietrich, J.S. Abramson, A.J. Cole, M.B. Westover, EEG findings in CAR T-cell therapy-related encephalopathy, Neurology. 91 (5) (2018) 227–229, https://doi.org/10.1212/WNL.0000000000005910.
[36] D.B. Rubin, A. Al Jarrah, K. Li, et al., Clinical predictors of neurotoxicity after chimeric antigen receptor T-cell therapy, JAMA Neurol. 02114 (2020) 4–10, https://doi.org/10.1001/jamaneurol.2020.2703.
[37] N. Raje, J. Berdeja, Y. Lin, et al., Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma, N. Engl. J. Med. 380 (18) (2019) 1726–1737, https://doi.org/10.1056/NEJMoa1817226.
[38] J.N. Brudno, I. Maric, S.D. Hartman, et al., T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma, J. Clin. Oncol. 36 (22) (2018) 2267–2280, https://doi.org/10.1200/JCO.2018.77.8084.
[39] S.A. Ali, V. Shi, I. Maric, et al., T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma, Blood. 128 (13) (2016) 1688–1700, https://doi.org/10.1182/blood-2016-04-711903.
[40] C.J. Turtle, L.A. Hanafi, C. Berger, et al., Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells, Sci Transl Med 8 (355) (2016), https://doi.org/10.1126/scitranslmed.aaf8621, 355ra116.
[41] F. Chen, D.T. Teachey, E. Pequignot, et al., Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy, J. Immunol. Methods 434 (2016) 1–8, https://doi.org/10.1016/j.jim.2016.03.005.
[42] M. Norelli, B. Camisa, G. Barbiera, et al., Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells, Nat. Med. 24 (6) (2018) 739–748, https://doi.org/10.1038/s41591-018-0036-4.
[43] Y. Hu, J. Sun, Z. Wu, et al., Predominant cerebral cytokine release syndrome in CD19-directed chimeric antigen receptor-modified T cell therapy, J. Hematol. Oncol. 9 (1) (2016) 70, https://doi.org/10.1186/s13045-016-0299-5.
[44] A.V. Hirayama, C.J. Turtle, Toxicities of CD19 CAR-T cell immunotherapy, Am. J. Hematol. 94 (S1) (2019) S42–S49, https://doi.org/10.1002/ajh.25445.
[45] National Cancer Institute, Common terminology criteria for adverse events (CTCAE). Version 4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
[46] A.F. Struck, G. Osman, N. Rampal, et al., Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram, Ann. Neurol. 82 (2) (2017) 177–185, https://doi.org/10.1002/ana.24985.
[47] B. Shah, V. Huynh, L.S. Sender, et al., High rates of minimal residual disease-negative (MRD−) complete responses (CR) in adult and pediatric and patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) treated with KTE-C19 (anti-CD19 chimeric antigen receptor [CAR] T cells): Pr, Blood. 128 (22) (2016) 2803, https://doi.org/10.1182/blood.V128.22.2803.2803.
[48] T. Giavridis, S.J.C. van der Stegen, J. Eyquem, M. Hamieh, A. Piersigilli, M. Sadelain, CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade, Nat. Med. 24 (6) (2018) 731–738, https://doi.org/10.1038/s41591-018-0041-7.
[49] X. Zhou, G. Dotti, R.A. Krance, et al., Inducible caspase-9 suicide gene controls adverse effects from alloreplete T cells after haploidentical stem cell transplantation, Blood. 125 (26) (2015) 4103–4113, https://doi.org/10.1182/blood-2015-02-628354.
[50] T. Gargett, M.P. Brown, The inducible caspase-9 suicide gene system as a "safety switch" to limit on-target, off-tumor toxicities of chimeric antigen receptor T cells, Front. Pharmacol. 5 (2014) 235, https://doi.org/10.3389/fphar.2014.00235.
[51] A.J. Kansagra, N.V. Frey, M. Bar, et al., Clinical utilization of Chimeric Antigen Receptor T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL)–an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplant, Bone Marrow Transplant. 54 (11) (2019) 1868–1880, https://doi.org/10.1038/s41409-019-0451-2.
[52] I. Yakoub-Agha, C. Chabannon, P. Bader, et al., Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE), Haematologica. 105 (2) (2020) 297–316, https://doi.org/10.3324/haematol.2019.229781.