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Neurotoxicity Associated with CD19-Targeted CAR-T Cell Therapies

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Abstract

Neurotoxicity is an important and common complication of chimeric antigen receptor-T cell therapies. Acute neurologic signs and/or symptoms occur in a significant proportion of patients treated with CD19-directed chimeric antigen receptor-T cells for B-cell malignancies. Clinical manifestations include headache, confusion, delirium, language disturbance, seizures and rarely, acute cerebral edema. Neurotoxicity is associated with cytokine release syndrome, which occurs in the setting of in-vivo chimeric antigen receptor-T cell activation and proliferation. The mechanisms that lead to neurotoxicity remain unknown, but data from patients and animal models suggest there is compromise of the blood–brain barrier, associated with high levels of cytokines in the blood and cerebrospinal fluid, as well as endothelial activation. Corticosteroids, interleukin-6-targeted therapies, and supportive care are frequently used to manage patients with neurotoxicity, but high-quality evidence of their efficacy is lacking.

1 Introduction

Chimeric antigen receptor (CAR)-modified T (CAR-T) cell immunotherapy has produced impressive results in clinical trials treating relapsed and/or refractory B-cell malignancies. T cells obtained from the patient, or less often from an allogeneic donor, are modified to express a CAR, which consists of an extracellular tumor-targeting moiety (usually a single-chain variable fragment derived from a tumor-reactive monoclonal antibody) fused to one or more intracellular T-cell signaling domains. On encounter with the antigen to which the

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Compliance with Ethical Standards

Conflict of interest Cameron J. Turtle receives research funding from Juno Therapeutics/Celgene and Nektar Therapeutics; has served on advisory boards for Juno Therapeutics/Celgene, Nektar Therapeutics, Precision Biosciences, Caribou Biosciences, Eureka Therapeutics, Gilead, and Aptevo; and has options in Precision Biosciences, Eureka Therapeutics and Caribou Biosciences. Juliane Gust and Agne Taraseviciute have no conflicts of interest that are directly relevant to the contents of this article.

single-chain variable fragment is directed, the CAR-T cell is activated, resulting in proliferation, cytokine secretion, and target cell lysis [1]. Lymphodepleting chemotherapy is usually administered to patients before CAR-T cell infusion to improve CAR-T cell in-vivo proliferation and potentially limit host T-cell-mediated CAR-T cell rejection. Minimal residual disease-negative complete response rates of 60–93% have been reported in relapsed and refractory acute lymphoblastic leukemia (ALL) [2–8]. Overall response rates of 63–82% in non-Hodgkin's lymphoma (NHL) [9–13] and 39–100% in chronic lymphocytic leukemia (CLL) [10, 14–16] have been noted (Table 1). These data have led to the US Food and Drug Administration (FDA) approval of tisagenlecleucel (Kymriah®; Novartis Pharmaceuticals Corporation, New Jersey, USA) for the treatment of relapsed/refractory B-cell precursor ALL in patients up to 25 years of age [6] and diffuse large B-cell lymphoma in adults [17]. Axicabtagene ciloleucel (Yescarta™; Kite Pharma, Santa Monica, CA, USA) is now approved for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma in adults [12]. New data are emerging in clinical trials of CAR-T cells targeting numerous other antigens [13, 18, 19].

Chimeric antigen receptor-T cell immunotherapy has the potential for significant, but generally reversible, adverse effects in a subset of patients. Chimeric antigen receptor-T cell proliferation after infusion can lead to hypercytokinemia and systemic cytokine release syndrome (CRS) [20–22]. Neurologic complications are common [23]. The broader application of CAR-T cell therapies in oncology will require a better understanding of the pathophysiology, prevention, and treatment of neurotoxicity.

2 Incidence of Neurotoxicity in Published Clinical Trials

The majority of CAR-T cell therapies target CD19 in patients with B-cell malignancies, and neurotoxicity has been reported in all studies that demonstrate robust anti-tumor efficacy (Table 1). The severity of neurotoxicity is graded using different systems in different trials; for the purpose of this overview, neurotoxicity is usually considered severe when it is grade 3 or greater by the Common Terminology Criteria for Adverse Events (v4). The reader should refer to Table 1 and published papers for the definitions of severe neurotoxicity in individual trials.

In studies using CAR constructs with a 4–1BB domain, neurologic adverse events were reported in 40–44% of children and young adults with ALL (13–21% severe) [4, 6], and 50% of adults with ALL (50% severe) [3]. In adults with NHL, neurotoxicity occurred in 28–39% (11–28% severe) [9, 11], and in adults with CLL the incidence was 6–33% (0–25% severe) [14, 16]. In a pediatric ALL trial using a CD19 CAR with a CD28 co-stimulatory domain, neurotoxicity was reported in 30% of children and young adults (5% severe) [5]. In an adult ALL trial using a CD28 co-stimulated CAR 44% of patients (42% severe) developed neurotoxicity [2]. Another adult trial, which used the same CAR construct but a different manufacturing approach, was closed because of a high incidence of fatal neurotoxicity [24]. Forty-five percent of adults with NHL treated with a CD28-containing CD19 CAR developed severe neurotoxicity [10, 25]. The reported prevalence and presentations of neurotoxicity vary widely between these studies and may be affected by

differences in disease, prior treatment history, patient age, CAR design, CAR-T cell manufacturing approach, lymphodepletion regimen, CAR-T cell dose and infusion regimen, product potency and efficacy, toxicity grading schemas, and treatment strategies in each study [22, 26].

Neurotoxicity has also been reported in clinical trials of CAR-T cells directed against targets other than CD19 [27–31]. Among patients treated with CD22-directed CAR-T cells for ALL, 25% developed neurotoxicity, but none had severe neurotoxicity or severe CRS [28]. Eighty-one percent of the patients in the study had previously received CD19 CAR-T cells, and the morphologic complete response rate was 57%. In a trial of CAR-T cells directed against B-cell maturation antigens expressed on multiple myeloma, 25% of patients experienced neurotoxicity (8% severe) [30]. Over-all, the rates of neurotoxicity, CRS, and clinical responses appear lower for non-CD19 CAR-T cells targeting hematologic malignancies (Table 2). Toxicity profiles may change with further development and optimization of these immunotherapies.

While CAR-T cell immunotherapies targeting solid tumors have not yet produced consistent clinical responses, a large number of trials are currently underway or in development [19, 32, 33]. Neurologic symptoms have not been reported in solid tumor CAR-T therapies [34–39] with the exception of brain tumor trials, where it is often difficult to distinguish between disease progression and treatment side effects. Transient focal neurologic symptoms or seizures were observed in 30% of patients treated for glioblastoma with intravenously infused CAR-T cells directed against epidermal growth factor receptor variant III [40], and in 25% of patients treated with intra-cranially delivered CAR-T cells targeting interleukin (IL)-13 receptor subunit alpha 2, with an additional 50% of patients in the IL-13 receptor subunit alpha 2 CAR trial developing severe headache [41, 42].

3 Clinical Presentation of Neurotoxicity Associated with CD19 Chimeric Antigen Receptor T Cells

3.1 Signs and Symptoms

Chimeric antigen receptor-T cell-associated neurotoxicity comprises a wide range of signs and symptoms, including delirium, headache, language disturbance, tremor, transient focal weakness, behavioral disturbances, ataxia, peripheral neuropathy, visual changes and generalized weakness, seizures, and acute cerebral edema [17, 23, 43, 44]. We recently reported a study of neurotoxicity in 133 adults with ALL, NHL or CLL who received T cells expressing a CD19-targeting CAR with a 4–1BB co-stimulatory domain. In this study, neurotoxicity onset occurred a median of 4 days after CAR-T cell infusion, with a peak on day 7, and a duration of 5 days [23]. The kinetics of presentation may differ between studies investigating different CAR-T cell therapies, and in studies in which dedicated assessment tools are employed to identify early signs of subtle neurotoxicity [6, 11, 23, 28, 44]. Most signs and symptoms of neurotoxicity resolve within 21 days of treatment—persistent abnormalities are uncommon [6, 23].

In our study, the most common sign, present in 66% of patients with neurotoxicity, was transient impairment of attention and cognitive processing, manifesting as delirium or confusion, which were also observed in other trials [6, 11, 23, 28, 44]. Language disturbance, such as word finding difficulty, is frequent and often associated with delirium, as are decreased arousability and somnolence. Headache is very common, and the temporal association with other neurologic signs suggests it is likely a manifestation of neurotoxicity. Seizures are reported with varying incidence. In our 133 adult patients treated with 4–1BB costimulated CAR-T cells seizures were infrequent and only occurred in patients with a prior history of seizures or life-threatening neurotoxicity [23]. In contrast, seizures were more common in pediatric trials [4, 6, 7] and in adults after treatment with CD28-costimulated CAR products, but were not usually associated with a poor long-term outcome [50].

Acute cerebral edema is a life-threatening complication that has only been described after treatment with CD19-directed CAR-T cells. The occurrence of fatal cerebral edema in five patients led to the termination of a clinical trial in adults with ALL [24]. Deaths due to cerebral edema have been reported in clinical trials using CAR constructs containing either 4–1BB or CD28 co-stimulatory domains, in children and adults with ALL, and in adults with NHL and CLL [11, 23, 24, 45]. Cerebral edema can develop in a matter of hours, often while CRS is abating, and patients progress from mild confusion or somnolence to coma and brain death. Other fatal neurologic events after CD19 CAR-T cell therapy have included cortical necrosis, acute cerebral hemorrhage during resolving CRS, edema and hemorrhage of the brainstem and deep brain structures, multifocal thrombotic microangiopathy, and subacute encephalomalacia [6, 11, 23, 24]. Neuropathologic studies at autopsy after fatal neurotoxicity have demonstrated perivascular infiltration of $CD8^+$ T cells [11, 23], and CAR-T cells in brain tissue and CSF [23]. Widespread neuronal and white matter injury with macrophage infiltration and microglial activation have also been reported [11, 24].

3.2 Findings on Cerebrospinal Fluid Examination

Neurotoxicity is associated with increased CSF protein and white blood cell counts [23, 46], consistent with increased trafficking of cells and serum proteins across the blood–CSF barrier. Although CAR-T cells are detected in the CSF of most patients who undergo sampling during neurotoxicity, they can also be detected in the CSF of patients without neurotoxicity [23, 46, 47], suggesting that their presence in the CSF alone is not sufficient to induce neurologic dys-function. We found that in patients with severe neurotoxicity, $CD4^+$ CAR-T cells were slightly enriched in CSF compared with blood, suggesting that central nervous system (CNS) migration may differ between CAR-T cell subsets. In a non-human primate model of CD20-directed CAR-T cells, neurotoxicity was associated with the accumulation of both CAR-and non-CAR-T cells in the CSF and in the brain parenchyma [48]. We observed high CSF levels of interferon-γ, IL-6, tumor necrosis factor (TNF)-α and TNFRp55/p75 in patients with neurotoxicity, suggesting that the blood–brain barrier (BBB) may not prevent transit into the CSF of cytokines that circulate at high levels in the blood during CRS. Some studies have shown that some cytokines are present at higher levels in CSF compared with blood, suggesting increased production within the CNS [49].

3.3 Central Nervous System Imaging

Head imaging reveals several characteristic patterns associated with neurotoxicity. During mild neurotoxicity, imaging is frequently normal [5, 7, 23]. Common magnetic resonance imaging findings during neurotoxicity include reversible patchy T2 hyperintensities in the white matter, and symmetric T2 hyperintensities in the thalami and other deep gray matter structures [23, 44, 46]. These findings are indicative of interstitial edema and may be associated with microhe-morrhages. Diffusion restriction in regions of cortical gray matter has also been observed, and can evolve into cortical laminar necrosis [23, 44]. Finally, global cerebral edema can be identified on imaging and is associated with devastating neurologic injury [23]. The heterogeneity of imaging findings suggests that different underlying mechanisms may be responsible for neurotoxicity.

3.4 Electroencephalography

The role of electroencephalography (EEG) monitoring in neurotoxicity is not yet well defined, although its routine use for risk assessment has been advocated [50]. In patients who underwent EEG, the most common finding was diffuse slowing, a non-specific indicator of encephalopathy that is common in critically ill patients. Causes can include medication effects, toxic metabolites, or hypoxia/ischemia [23, 50, 51]. In our clinical experience with children and adults, seizures were only detected on EEG in CAR-T cell-treated patients who also had clinically apparent seizures, while others have noted non-convulsive status epilepticus [50].

3.5 Grading of Neurotoxicity

Neurotoxicity signs and symptoms are typically graded using systems based on the Common Terminology Criteria for Adverse Events, with grades 1 through 5 representing mild, moderate, severe, life-threatening, and fatal toxicity, respectively. Some investigators have proposed modified grading systems. In our report of neurotoxicity in 133 adults treated with CD19 CAR-T cells incorporating 4–1BB co-stimulation, the presence of delirium or seizures resulted in a designation of grade ≥ 3 neurotoxicity because of the requirement for hospitalization. Gardner et al. used Common Terminology Criteria for Adverse Events grading, with the exception that seizures were designated as grade ≥ 3 neurotoxicity [4]. Neelapu et al. also assigned grade ≥ 3 neurotoxicity for any seizures, and added grade ≥ 4 for any motor weakness [50]. No grading systems have yet been shown to correlate with long-term clinical outcomes in prospectively validated studies.

4 Clinical Factors Associated with the Development of Neurotoxicity

The association of neurotoxicity with CRS is well recognized. Severe neurotoxicity is mainly seen in patients with concurrent or preceding CRS, and is uncommon in the absence of significant CRS [4, 6, 12, 21, 23, 46]. Neurotoxicity appears to present later than CRS, may take longer to resolve, and is less responsive to IL-6-targeted therapies than CRS. Most investigators consider neurotoxicity to be a related, but distinct, entity from CRS. The use of diverse CRS grading schemes [22, 26] makes it difficult to compare the impact of CRS on neurotoxicity between studies (Table 1). In a multivariate analysis of 133 adults treated with CD19 CAR-T cells at the Fred Hutchinson Cancer Research Center, we found that factors

leading to more severe CRS, such as higher in-vivo CAR-T cell numbers, higher CAR-T cell dose, higher tumor burden, and use of fludarabine in lymphodepletion resulted in a higher risk of neurotoxicity. Other investigators have also reported an association of neurotoxicity with higher pre-infusion tumor burden in ALL [23, 46] and greater peak CAR-T cell counts in vivo after infusion [12, 23, 46]. We also observed that pre-existing neurologic comorbidities were associated with an increased risk of neurotoxicity, although it is unknown which of these heterogenous conditions confers the greatest risk [23]. The design of the CAR (for example, incorporation of a CD28 or a 4–1BB co-stimulatory domain) and CAR-T cell manufacturing processes may also contribute to differences in the risk of neurotoxicity [52].

5 Biomarkers Associated with Neurotoxicity

5.1 Biomarkers During Acute Neurotoxicity

In patients with severe neurotoxicity, serum levels of several inflammatory mediators are higher after CAR-T cell infusion than in patients with grade ≤ 2 neurotoxicity. Consistently identified cytokines include IL-6 [12, 23, 44, 46], IL-10 [12, 44, 46], and interferon-γ [23, 44, 46]. Associations of neurotoxicity with higher serum levels of C-reactive protein, ferritin, granulocyte-macrophage colony-stimulating factor, granzyme B, IL-15, IL-2, IL-2 receptor-α, IL-5, and TNFα [12, 23, 44, 46] have also been reported. None of these cytokines appear to be specific for neurotoxicity as they are also observed in elevated levels during severe CRS. Numerous cytokines are elevated in the CSF during acute neurotoxicity, likely owing to both increased BBB permeability and local production within the CNS [23, 44, 46]. In a non-human primate model of B cell-directed, CD20-targeted CAR-T cells, animals developed CRS and neurotoxicity associated with elevated serum levels of IL-6, IL-8, IL-1 receptor antagonist, MIG (CXCL9), and I-TAC (CXCL11); and disproportionately high levels of IL-6, IL-2, granulocyte-macrophage colony-stimulating factor, vascular endothelial growth factor, IL-1β, IL-1 receptor antagonist, monocyte chemoattractant protein-1 (MCP-1) [CCL2], and IP-10 (CXCL10) in the CSF compared with serum during in-vivo CAR-T cell expansion [48]. In a mouse model, monocyte-derived IL-1 but not IL-6 was identified as a targetable mediator of neurotoxicity [53]. Possible loss of microglia was seen in a mouse model of CAR-T cell-induced neurotoxicity [54].

Cytokine production by cell types other than infused CAR-T cells is not well understood. Autopsy studies in a patient with fatal CRS that was accompanied by mental status changes showed IL-6 expression by endothelial cells but not T cells [55], similar to endothelial responses seen with other inflammatory stimuli such as lipopolysaccharide challenge [56, 57]. Additionally, new insights from a xenogeneic model of CD19 CAR-T cell therapy have identified monocyte-derived IL-1 and IL-6 as key mediators of CRS [53]. In a different model, CRS was associated with down-regulation of macrophage inducible nitric oxide synthase [58]. In some patients with severe CRS and neurotoxicity, serum ferritin levels are markedly elevated, similar to those in macrophage activation syndrome and hemophagocytic lymphohistiocytosis, suggesting a role for macrophage activation in the pathophysiology [59].

We observed profound monocytopenia during severe neurotoxicity and CRS, which could be consistent with monocyte activation and extravasation into tissues. We and others have noted that consumptive coagulopathy was most pronounced in patients with severe neurotoxicity [23, 60]. The presence of elevated D-dimer, prothrombin, and activated partial thromboplastin times decreased fibrinogen and platelet counts, and high red cell and platelet transfusion requirements in the setting of hypotension and capillary leak suggested that vascular dysfunction and endothelial activation might be present during neurotoxicity [23]. A contribution from endothelial activation to neurotoxicity was supported by the observation that patients with grade ≥ 4 neurotoxicity had higher angiopoietin-2 and von Willebrand factor serum levels compared with patients with grade ≤ 3 neurotoxicity [23, 61]. In association with endothelial activation after CAR-T cell infusion, increased transit of interferon-γ and TNFα across the BBB could induce stress and apoptosis of vascular supporting pericytes and potentially amplify increased endothelial permeability and BBB dysfunction [62, 63]. In support of this, pathologic examination of the brain of a patient with fatal neurotoxicity demonstrated endothelial activation with von Willebrand aggregation and a thrombotic microangiopathy with multifocal vascular disruption [23].

5.2 Candidate Predictive Biomarkers to Guide Early Intervention

Early recognition of patients at the highest risk of neurotoxicity might provide an opportunity for early intervention before severe neurotoxicity develops. In our study of neurotoxicity after 4–1BB co-stimulated CAR-T cell therapy, we found that in the first 36 h after CAR-T cell infusion, patients who subsequently developed the most severe neurotoxicity (grade ≥ 4) had higher serum MCP-1, IL-15, IL-10, and IL-2 in the first 36 h, as well as an earlier peak of IL-6 compared with those with grade ≤ 3 neurotoxicity [23]. We also found an increased angiopoietin-2:angiopoietin-1 ratio prior to lymphodepleting chemotherapy in patients who subsequently developed grade ≥4 neurotoxicity, indicating that pre-existing dysregulation of endothelial activation may increase neurotoxicity risk [23]. Algorithms based on levels of multiple cytokines within the first 24–36 h after CAR-T cell infusion predicted the development of neurotoxicity with high sensitivity and specificity, but may be impractical in the clinical setting where there is limited ability to perform such laboratory assays in real time [23, 64]. In our study, fever ≥ 38.9 °C alone within 36 h of CAR-T cell infusion had 100% sensitivity and 82% specificity for the development of life-threatening neurotoxicity, allowing the potential use of this simple clinical marker for risk stratification. The specificity was improved (94%) by the addition of a single serum assay for MCP-1 that was only performed on patients with fever ≥ 38.9 °C in the first 36 h after CAR-T cell infusion [23].

Others have proposed similar algorithms to predict the development of severe CRS [21, 65]. In a trial of CD28 costimulated CD19 CAR-T cells for patients with NHL, development of grade ≥ 3 neurotoxicity was associated with increased C-reactive protein, ferritin, IL-15, IL-16, IL-2 receptor-α, IL-6, and MCP-1 levels on the day immediately preceding CAR-T cell infusion [64]. Clearly, different approaches will likely be required for CAR-T cell products with distinct kinetics and presentations of neurotoxicity. Early intervention strategies using these biomarkers will require prospective validation in future clinical trials.

6 Management of Chimeric Antigen Receptor-T Cell-Associated Neurotoxicity

The role of disease-modifying interventions for neurotoxicity is debated, with some investigators using supportive care only, arguing that the vast majority of neurologic symptoms and signs resolve within 21 days after CAR-T cell infusion [6, 23]. Others advocate aggressive and early treatment with immunomodulators [50, 66]. Most patients with neurotoxicity also experience CRS, which may be treated with tocilizumab, an IL-6 receptor antibody, and/or corticosteroids to modulate T-cell activity [22, 67, 68], but the subsequent effect of these interventions on neurotoxicity is not well understood.

6.1 Tocilizumab

Tocilizumab is a humanized monoclonal antibody that targets cell-associated and soluble IL-6 receptor, blocking the binding of IL-6, a proinflammatory cytokine [69–71]. It was developed for the treatment of rheumatologic disorders [72] and approved by the FDA for use in rheumatoid arthritis [73], systemic juvenile idiopathic arthritis [74], and giant cell arteritis [75]. Its potential for treating CRS was considered in light of the high levels of IL-6 observed during CRS and the similarities with macrophage activation syndrome seen in systemic juvenile idiopathic arthritis [22, 76]. Retrospective analyses showed a sufficient likelihood of efficacy and safety in treating CAR-T cell-associated CRS, and it was approved by the FDA for this indication in 2017 [77]. Use of tocilizumab in patients with CRS as a result of robust CAR-T cell proliferation does not appear to affect anti-tumor response [4]; however, it is uncertain whether tocilizumab could affect efficacy when used prophylactically in patients with moderate or low levels of in-vivo CAR-T cell proliferation. No randomized controlled clinical trials of tocilizumab for CRS treatment have been conducted to date; nevertheless, its observed clinical efficacy has made it a mainstay for the treatment of severe CRS.

Evidence for the efficacy of tocilizumab in neurotoxicity is limited to published data from phase I and II clinical trials, although additional studies are underway [20, 23, 78]. In these trials, tocilizumab was used to treat CRS and/ or neurotoxicity in 23–48% of affected patients with ALL [2–7], 6–43% with NHL [9–12], and 0–25% with CLL [10, 14] (Table 1), but the indication for treatment (CRS vs. neurotoxicity) and outcomes of the intervention have not been consistently reported. Some clinical centers employtocilizumab as a first-line therapy for neurotoxicity [50], whereas others do not use it at all for this indication [52].

A temporal association between the resolution of CRS symptoms and the development of neurotoxicity has been noted. Some investigators have considered that IL-6 receptor blockade with tocilizumab may lead to increased circulating IL-6 in the CNS, and possibly exacerbate neurotoxicity [79, 80]. Observational studies found that while early treatment with tocilizumab decreased the incidence of severe CRS, it was not associated with a decreased incidence or severity of neurotoxicity [45, 81].

6.2 Corticosteroids

Dexamethasone and other corticosteroids are used as first-line therapy for neurotoxicity by many groups [67, 81]. Dexamethasone has excellent CNS penetration and is a standard of care in the treatment of cerebral edema and inflammation in the setting of brain tumors and neurotrauma [82, 83]. High-dose methylprednisolone is generally reserved for more severe cases of CAR-T cell associated neurotoxicity, and is employed based on its well-studied effectiveness and safety in neuroinflammatory disorders [84, 85]. Because glucocorticoids can affect T-cell function [86], there has been concern that their use may decrease the efficacy of CAR-T cell immunotherapy. However, short courses of low-to moderate-dose corticosteroids (e.g. dexamethasone 10 mg twice daily for two to four doses or equivalent) administered to patients with toxicity due to robust CAR-T cell expansion do not appear to ablate CAR-T cell expansion or persistence, and do not have an obvious detrimental effect on anti-tumor efficacy [81]. High-dose corticosteroids (e.g., methylprednisolone 1 g/day) may result in profound lymphopenia and reduced circulating CAR-T cell counts; however, effects on anti-tumor efficacy have not been formally determined.

6.3 Other Biologics

Siltuximab is a chimeric monoclonal antibody that directly binds IL-6, preventing it from binding with soluble and membrane-bound IL-6 receptors [79, 87]. It has been used to manage CRS and/or neurotoxicity [88], and to manage neurologic adverse events during CAR-T cell treatment of glioblastoma [40]. Anakinra is a recombinant IL-1 receptor antagonist, which is FDA approved for the treatment of adult RA and neonatal-onset multisystem inflammatory disease. Anakinra is also effective in systemic juvenile idiopathic arthritis and has been used to manage life-threatening macrophage activation syndrome [89]. In a murine model of CAR-T cell-associated CRS and neurotoxicity, administration of anakinra at the time of CAR-T-cell infusion abrogated both CRS and neurotoxicity [53]. Other therapeutic approaches, such as plasma exchange, angiopoietin-1 augmentation, platelet hypertransfusion or small-molecule inhibition of cytokine signaling pathways, might be useful to treat CRS and neurotoxicity, but there are no data in humans to support their efficacy [90].

6.4 Anti-Seizure Prophylaxis

The role of anti-seizure prophylaxis for patients receiving CAR-T cell immunotherapy has not definitively been determined. Some CAR-T cell investigators start all patients on anti-seizure prophylaxis, some use it only for patients with CRS, and others do not use seizure prophylaxis at all [23, 50, 66]. Levetiracetam is frequently used for seizure prophylaxis, but the ideal timing, dose, and overall utility of this strategy are unknown. The adverse-event profile is favorable, and it does not have the marked effects on drug metabolism observed with some other anti-seizure medications.

6.5 Acute Management of Life−Threatening Neurotoxicity

Given the limited clinical experience with fulminant CAR-T cell-related neurotoxicity, it is not known what neurocritical care strategies are indicated in patients with cerebral edema or other rapidly progressive neurologic symptoms. Management may include standard

neuroprotective interventions for patients with suspected increased intracranial pressure, including treatment of fever, normocarbia or short-term mild hyperventilation, and optimizing cerebral perfusion by preventing hypotension, treating hypertension with caution, and keeping the head of bed midline position [91, 92]. Continuous EEG monitoring can be used to rule out subclinical seizures and monitor for changes in background electrical patterns, especially in critically ill patients with limited ability to participate in the exam [51]. Imaging findings of cerebral edema can be subtle even when clinical symptoms are well established, and should not be used alone for reassurance. Hyperosmolar therapy with mannitol or hypertonic saline, high-dose corticosteroids, sedation, and aggressive management of seizures are reasonable interventions for patients who have progressive and severe neurologic symptoms. There is no evidence that invasive neuromonitoring is helpful, and it is associated with significant risk as patients are frequently coagulopathic. Early detection of risk for deterioration is most likely the best method of preventing fulminant cerebral edema, as once established, it progresses rapidly and may not be reversible.

7 Conclusions

To further increase our understanding of neurotoxicity associated with CAR-T cell therapy, numerous lines of further investigation are needed. Ongoing characterization of the clinical features of neurotoxicity, particularly in patients who have received CAR-T cell immunotherapy targeting antigens other than CD19, and identification of long-term impacts of CAR-T cell immunotherapy on cognitive outcomes will be critical. Consensus criteria for grading of short-and long-term toxicities will be invaluable. Development of sensitive and specific methods for the prediction of severe neurotoxicity and testing of early intervention or prophylactic strategies will help improve the therapeutic index of CAR-T cells while maintaining anti-tumor efficacy. Finally, robust animal models will be invaluable for improving our understanding of the pathophysiology of neurotoxicity and the development of candidate treatments and prevention strategies as CAR-T cell therapy enters the mainstream of oncology.

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Key Points

Neurotoxicity is a common complication of chimeric antigen receptor-T cell therapy for hematologic malignancies, which is typically self-limited but can be life threatening or fatal.

Neurotoxicity is associated with an elevation of serum and cerebrospinal fluid cytokines, including interleukin-6 and interferon-γ, and systemic cytokine release syndrome is strongly associated with the development of neurotoxicity.

Commonly used therapeutic approaches, including corticosteroids and interleukin-6 blockade, require further study, and there is a need for standardized grading, monitoring, prevention, and treatment of neurologic complications of chimeric antigen receptor-T cell therapy.

Table 1

Neurotoxicity in CD19-directed chimeric antigen receptor (CAR) T cell clinical trials

References (first author. year)	NCT	*N*	Age range (Years)	CAR construct	Lympho-depletion *(N)*	CRR (%)	ORR (%)	NT (%)	sNT (%)	CRS[a] (%)	sag[a] (%)	Loci (%)	steroids (%)
ALL													
Lee. 2015 [5]	NCT01593696	20	5–27	28z	Flu/Cy	70[g] 60[h]	n/a	30	5	75[c*]	30	27	13
Gardner. 2017 [4]	NCT02028455	43	1–25	4–1BB	Cy (27) or Flu/Cy (14)	93[h] 93[h]	n/a	44	21[b]	93[c*]	23	42	25
Maude. 2018 [6]	NCT02435849	75	3–23	4–1BB(tisagenle-ckucel)	Flu/Cy (71) orCy/Etop (1)	81[g] 81[h]	n/a	40	13	77[p]	46	48	0
Maude. 2014[7]	NCT01626495 NCT01029366	30	5–60	4-IBB(CT1.019, tisafpnlecleucel)	Cy/VP (5). Ara-CJEtop (I). Flu/Cy (15). Cy (3). Clo (1). CVAD-A (1).orCVAD-B (1)	90[g] 79[h]	n/a	43	NR	88[*]	27	30	20
Turtle. 2016 [3][c]	NCT01865617	30	20–73	4–1BB	Cy/Etop (2). Cy (I I), or Flu/Cy (17)	100[g] 93[h]	n/a	50	50	83[c]	23	27	37
Park. 2018 [2]	NCT01044069	53	23–74	28z (19–28z)	Cy (43) or Flu/cy (10)	83[g] 67[h]	n/a	44	42	85[M]	26	42	38
NHL													
Kochenderfer. 2015 [10]	NCT00924326	11	30–68	28z	Flu/Cy (15)	36	80	NR	45	NR[c]	36	25	0
Turtle. 2016 [9]	NCT01865617	32	36–70	4-IBB	Cy or Cy/Etop (12) or Flu/Cy (20)	33	63	28	28[d]	63[c*]	13	9	13
Schuster. 2017 [11]	NCT02030834	28	25–77	4-IBB (CTL019)	Cy (11), modEPOCH (3). bend (8). Cy/T81 (4). Cy/Etop (I). Flu/Cy (1). Carbo/Gem (10)	57	64	39	11	57[p]	18	20	6
Neelapu, 2017 [12]	NCT07248216	101	23–76	28z (axicabtagene cibaleucel)	Flu/Cy (101)	54	82	64	28	93[L]	13	43	27
CLL													
Turtle. 2017 [14][c]	NCT01865617	24	40–73	4–188	Cy (1). Flu (2) Flu/Cy (21)	29	71	33	25[d]	83[L]	8	25	25

References (first author. year)	NCT	*N*	Age range (Years)	CAR construct	Lympho-depletion *(N)*	CRR (%)	ORR (%)	NT (%)	sNT (%)	CRS[a] (%)	sag[a] (%)	Loci (%)	steroids (%)
Fraietta. 2018 [16]	NCT01029366 NCT01747486 NCT02640209	41	61–66[e]	4–188	n/a	20	39	6[f]	0[f]	69[f]	38[f]	NR	NR

4–1BB 4–1BB costimulatory domain, *28z* CD28-CD3zeta costimulatory domain, *ALL* acute lymphoblastic leukemia, *Ara-C* cytarabine, *Bend* bendamustine, *Carbo* carboplatin, *CHOP* Children's Hospital of Philadelphia, *CLL* chronic lymphocytic leukemia, *clo* clofarabine, *CRR* complete remission rate, *CRS* cytokine release syndrome, *CTCAE* Common Terminology Criteria for Adverse Events, *CVAD-A* cyclophosphamide + vincristine + adriamycin, *CVAD-B* methotrexate + cytarabine, *Cy* cyclophosphamide, *Etop* etoposide, *Flu* fludarabine, *Gem* gemcitabine, *mod-EPOCH* modified EPOCH (doxorubicin, etoposide, cyclophosphamide), *MSKCC* Memorial Sloan Kettering Cancer Center, *n/a* not available, *NCT* national clinical trial, *NHL* non-Hodgkin's lymphoma, *NR* reported, *NT* neurotoxicity, *ORR* overall response rate, *sCRS* severe CRS (CTCAE grade 3 or greater, or as defined in the publication), *sNT* severe neurotoxicity (CTCAE grade 3 or greater), *steroids* corticosteroids, *TBI* total body irradiation, *toci* tocilizumab, *VP* etoposide

[a]The CRS grading system is indicated by the following superscripts: C = CTCAE criteria; L = Lee criteria [22]; P = Penn/CHOP criteria [26]; M = MSKCC criteria [2];

[*] indicates modified crite-ria, please refer to the individual publication for details

[b]CTCAE grade 3 or greater, and/or any seizures

[c]Data on expanded cohort available in [23]

[d]CTCAE grade 3 or greater, and/or any seizures, and/or grade 2 delirium

[e]Only median age reported

[f]Toxicities only reported for the 16 patients who responded to CAR T cells

[g]Morphologic remission

[h]Minimal residual disease-negative remission

Table 2

Neurotoxicity in selected non-CD I9-directed chimeric antigen receptor (CAR) T cells for hematologic malignancies

References (first author, year)	NCI	*N*	Age group	CAR target	CAR construct	Disease	CRR (%)	sNT (%)	NT (%)	CRS (%)	sCRS (%)	toci (%)	steroids (%)
Fry. 2018 [28]	NCT02315612	21	Peds. adult	CD22	4-IBB	ALL (majority CD19 CAR pretreated)	57[a] 43[b]	0	25	76	0	0	0
Ramos, 2017 [27]	NCT01316146	9	Adult	CD30	28z	HL, ALCL	33	0	0	0	0	n/a	n/a
Wang. 2017 [29]	NCT02259556	18	Peds, adult	CD30	4-IBB	HL	0	0	0	0	0	n/a	n/a
Ali. 2016 [30]	NCT02215967	12	Adult	BCMA	28z	MM	8	8	25	50	25	33	0
Ritchie. 2013 [3 1]	CTX 08-0002	4	Adult	LeY	28z	AML	25	0	0	25	0	0	0

4–1BB 4–1BB co-stimulatory domain, *28z* CD28 co-stimulatory domain. *ALCL* anaplastic large cell lymphoma. *ALL* acute lymphoblastic leukemia. *AML* acute myelogenous leukemia, *BCMA* B-cell maturation antigen. *CRR* complete remission rate. *CRS* cytokine release syndrome. *HL* Hodgkin's lymphoma, *MM* multiple myeloma. *n/a* not available. *NCI'* national clinical trial. *NT* neurotoxicity. *peds* pediatrics, *sCRS* severe CRS, *sNT* severe neurotoxicity (Common Terminology Criteria for Adverse Events grade 3 or higher), *steroids* corticosteroids. *foci* tocilizumab

[a] Morphologic remission

[b] Minimal residual disease-negative remission

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