BLOOD RESEARCH
VOLUME 58 · NUMBER S1
April 2023
REVIEW ARTICLE

Management of adverse events in young adults and children with acute B-cell lymphoblastic leukemia receiving anti-CD19 chimeric antigen receptor (CAR) T-cell therapy

Jae Won Yoo

Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2023.2023026
Blood Res 2023;58:S20-S28.

Received on January 27, 2023
Revised on February 17, 2023
Accepted on February 17, 2023

Correspondence to
Jae Won Yoo, M.D., Ph.D.
Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
E-mail: hoiring0209@gmail.com

Abstract

With impressive clinical advancements in immune effector cell therapies targeting CD19, chimeric antigen receptor (CAR) T-cell therapy has emerged as a new paradigm for treating relapsed/refractory B-cell malignancies. Currently, three second-generation CAR T-cell therapies have been approved, of which only tisagenlecleucel (tisa-cel) is approved for treating children and young adults with B-cell acute lymphoblastic leukemia (ALL) with durable remission rates of approximately 60–90%. Although CAR T-cell therapies are considered to treat refractory B-ALL, they are associated with unique toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The severity of CAR T-cell therapy toxicities can vary according to several clinical factors. In rare cases, severe CRS can progress to a fulminant hyperinflammatory syndrome known as hemophagocytic lymphohistiocytosis, which has a poor prognosis. The first-line treatments for CRS/ICANS include tocilizumab and corticosteroids. When severe CAR T-cell toxicity is resistant to first-line treatment, an additional approach is required to manage the persistent inflammation. In addition to CRS/ICANS, CAR T-cell therapy can cause early and delayed hematological toxicity, which can predispose patients to severe infections. The use of growth factors and anti-infective prophylaxis should follow institutional guidelines according to patient-specific risk factors. This review provides a thorough summary of updated practical recommendations for managing acute and delayed adverse effects following anti-CD19 CAR T-cell therapy in adults and children.

Key Words Chimeric antigen receptor T-cell, Cytokine release syndrome, Neurotoxicity syndromes, Prolonged cytopenia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with approximately 75% of cases occurring in patients aged <6 years [1]. During the past few decades, the application of classical multiagent chemotherapy in children with acute B-cell lymphoblastic leukemia/lymphoma has resulted in a marked improvement in survival rate, with the current 5-year overall survival (OS) exceeding 90% in high-income countries [2, 3]. However, survival rates in pediatric patients with relapsed B-cell ALL are significantly low, with a 5-year OS rate of 19–52% [4]. Immune effector cell therapies have significantly improved the survival of patients with relapsed/refractory (R/R) leukemia. Tisagenlecleucel (tisa-cel), a second-generation CD19-directed chimeric antigen receptor (CAR) T-cell product, is an effective and well-tolerated therapy approved by the Food and Drug Administration for use in pediatric and young adult patients with R/R B-cell ALL and in adults with R/R/diffuse large B-cell lymphoma and R/R follicular lymphoma [5]. The pivotal ELIANA clinical trials [6] along with the recently published data [7] demonstrated high long-term (median follow-up of 38.8 mo) relapse-free survival and OS rates of 52% and 63%, respectively, in children with B-cell ALL.

Despite the remarkable clinical success of CAR T-cell therapy, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and B-cell aplasia-associated hypogammaglobulinemia have been reported as fatal toxic side effects in pivotal trials [6, 8-10]. CRS and ICANS usually occur within the first eight weeks after infusion and are mostly manageable and reversible with

proper supportive care. Nevertheless, it is still imperative that clinicians identify and manage these common toxicities to avoid their life-threatening consequences [11, 12]. To date, numerous studies have addressed early and delayed adverse effects associated with CAR T-cell therapy, and protocols for diagnosing, grading, and managing CRS/ICANS and other toxicities have been developed [13-16]. The guidelines for first-line treatments to mitigate CRS/ICANS are well-established, while second-line treatments, which include anakinra (IL-1 receptor antagonist) [17, 18] and siltuximab (IL-6 receptor antagonist) [13] to treat persistent inflammatory processes, are still under active clinical investigation.

Since the clinical use of CAR T-cell therapy progressed rapidly since its approval in 2017, other delayed toxicities beyond CRS and ICANS have emerged. Among these, hematologic toxicities such as toxicity, anemia, neutropenia, and thrombocytopenia are frequently observed in clinical practice. These common and poorly understood toxicities have been under-reported. Uniform reporting across clinical trials and data collection worldwide is required to understand the mechanisms of hematologic toxicities and associated risk factors. Although CAR T-cell therapy enhances long-term survival, it can also be accompanied by long-term adverse effects that can affect the patient's chronic health condition.

In this review, the most recent updated data regarding the common toxicities associated with the use of commercially available CAR T-cell products, including CRS, ICANS, and hematologic toxicities, mostly in children and young adults with B-cell ALL.

CRS

CRS is a clinical syndrome caused by the rapid release of cytokines from immune effector cells after immunotherapy such as CAR T-cell therapy. The timing of CRS onset differs across clinical trials; tisa-cel contains 4-1BB costimulatory subunits and has a median onset of three days after infusing patients with B-ALL [6]. The clinical features of CRS include fever, hypoxia, tachycardia, capillary leak, and hypotension [12, 19]. In cases of severe CRS, multi-organ failure, including cardiac arrhythmia, acute renal injury, liver dysfunction, and coagulopathy, can occur and prove fatal. The incidence and severity of CRS vary according to CAR T-cell products, CAR T-cell doses, different malignancies, and disease status at the time of infusion [20]. A prevalence of 70% has been reported in clinical trials of CAR T-cell therapy in children and adults [6]. Although frequent, the

Table 1. Grading and management of CRS. Adapted from the ASTCT consensus [16], EBMT/JACIE/EHA recommendation [13], and PALISI-CARTOX network [15].

		Grade 1	Grade 2	Grade 3	Grade 4
Grade	Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
	Hypotension	X	O (not requiring vasopressors)	O (requiring vasopressor)	O (requiring multiple vasopressors)
	Hypoxia	X	O (requiring low-flow nasal cannula)	O (requiring high-flow nasal cannula)	O (requiring positive pressure)
Management	Supportive care	- Intravenous fluid therapy - Antipyretics - After blood cultures and other infection tests, start preemptive broad-spectrum antibiotics			
	Transfer to ICU	X	Alert your ICU	Transfer to ICU	
	Tocilizumab	(consider if patient's fever persists for 3 days)	Tocilizumab i.v. 8 mg/kg (In children <30 kg→12 mg/kg), max=800 mg Start in the hematology unit before transfer to ICU Repeat tocilizumab if patients did not improve after 12 hours		
	Corticosteroids	X	(consider if patient's symptoms deterioration **or** no response after two doses of tocilizumab) ① Dexamethasone i.v. 10 mg/6 h (In children <30 kg, 0.5 mg/kg/6 h, max 10 mg) **or** mPD i.v. 1–2 mg/kg/day divided every 6–12 h	① Dexamethasone i.v. 10 mg/6 h (in children <30 kg, 0.5 mg/kg/6 h, max 10 mg) **or** mPD i.v. 1–2 mg/kg/day divided every 6–12 h ② Increase dexamethasone dose to 20 mg/6 h, if absence of improvement	① Dexamethasone i.v. 20 mg/6 h ② Switch to mPD i.v. 1,000 mg/day for 3 days followed by a rapid taper ③ Consider repeat tocilizumab

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, MD Anderson Cancer Center CAR T-cell Therapy-Associated Toxicity; CRS, cytokine-releasing syndrome; EBMT, European Society for Blood and Marrow Transplantation; ICU, intensive care unit; IV, intravenous; JACIE, Joint Accreditation Committee of ISCT and EBMT, European Hematology Association; mPD, methylprednisolone; PALISI, Pediatric Acute Lung Injury and Sepsis Investigators.

symptoms were usually mild-to-moderate and resolved within a few days without requiring intervention. Previous data showed that only 16–48% of children with B-ALL exhibited ≥grade 3 CRS, whereas life-threatening CRS was uncommon (~7.5%) [11, 21-24].

When CAR T-cells associate with their target (CD19) on lymphoblasts and normal B cells, signaling through this receptor induces marked *in vivo* activation and proliferation of CAR T-cells, resulting in a cascade of immune stimulation of several cell types, such as macrophages, monocytes, and dendritic cells [25, 26]. This process leads to high serum concentrations of pro-inflammatory cytokines. Notably, interleukin (IL)-6, IL-8, IL-10, IL-15, interferon gamma (IFN-γ), monocyte chemoattractant protein-1, C-reactive protein, and ferritin have been associated with severe CRS [20, 25, 27-32]. However, there is no validated model to predict CRS severity. For patients with a high pre-infusion disease burden (≥5% BM lymphoblasts, CNS3, or non-CNS extramedullary disease), the intensity of lymphodepletion chemotherapy, CAR T-cell doses, pre-existing thrombocytopenia, and comorbidities showed inferior survival and increased toxicities [33].

The first sign of CRS is fever, and mild CRS (grade 1) can be treated. In contrast, treated patients with high CRS grades should be transferred to the local intensive care unit (ICU) (Table 1). Early detection and management of CRS are important to mitigate the risk of fatal adverse events. Once the diagnosis and grading of CRS are made, treatment is initiated with antipyretics, fluid therapy, and vasopressor therapy in cases of hypotension [12]. CRS symptoms and laboratory findings may be misdiagnosed as infection; therefore, all febrile patients should undergo comprehensive infection evaluation and empirical broad-spectrum antibiotics should be initiated [34]. Other differential diagnoses include tumor lysis syndrome and disease progression. When fever persists for ≥3 days with no signs of other illnesses, anti-cytokine therapy should be considered to reduce the exaggerated immune response [13].

Recent studies have shown that IL-1 and IL-6 released by monocytes and macrophages are the major reasons for CAR T-cell-related CRS and ICANS, with monocytes contributing more than macrophages [28, 30]. The use of tocilizumab, a recombinant monoclonal IL-6 receptor antagonist approved for treating CRS in children undergoing CAR T-cell therapy [23, 35], can result in a rapid improvement of CRS symptoms. If the patient's symptoms did not improve after two doses of tocilizumab, dexamethasone was administered. Corticosteroids are recommended for severe CRS, particularly when associated with neurotoxicity [13]. Furthermore, recent studies have suggested that both tocilizumab and dexamethasone can be used early [36, 37] and do not affect the clinical outcomes of CAR T-cell therapy [8, 15]. Two study groups have reported their experiences with early or prophylactic tocilizumab administration in pediatric patients. The Seattle Children's Research Institution published the results of tocilizumab use for mild CRS in their PLAT-02 (NCT02028455) trial. Only 15% of patients who received tocilizumab early exhibited severe CRS compared with the control group (30%) [38]. In the ELIANA study (CTL019), 47% of patients required ICU admission to manage severe CRS. Notably, the principal risk factor identified for severe CRS is a high tumor burden (≥40% lymphoblasts) in the bone marrow [23, 24]. Preemptive tocilizumab administration based on disease burden, in which patients with a high tumor burden received a single dose of tocilizumab after developing a high/persistent fever, led to a reduction in the expected incidence of grade 4 CRS [39]. These studies demonstrated that the early and prophylactic use of tocilizumab did not negatively impact the antitumor efficacy of CAR T-cell therapy. However, there is insufficient clinical data for children to support formal recommendations.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE TOXICITY

Secondary hemophagocytic lymphohistiocytosis (HLH) is a cytokine-driven fulminant hyperinflammatory syndrome associated with immune-induced multiorgan failure [40]. Secondary HLH can occur in patients with severe infection, malignancy, or autoimmune disease, and is rarely associated with allogeneic hematopoietic stem cell transplantation and CAR T-cell therapy. Reports on HLH-like toxicity following CAR T-cell therapy (carHLH) are increasing, with fever, organomegaly, jaundice, gastrointestinal problems, and pulmonary complications being the major clinical features [18, 41-43]. Although the incidence of carHLH is relatively rare (3–4%) [44], it has a high mortality rate. Moreover, it is difficult to distinguish carHLH from severe CRS because of overlapping symptoms and the tendency of CRS to progress into fulminant HLH. Serum ferritin is a suitable and reliable biomarker of HLH and can be used to monitor treatment responses [44]. Neelapu *et al.* [19] proposed diagnostic criteria for carHLH, which include a peak serum ferritin level of >10,000 μg/L and concomitant organ failure (Table 2).

There is no approved protocol for grading carHLH; its management is independent of grading [14]. Aggressive immunosuppression is required to effectively manage carHLH, and tocilizumab and corticosteroids remain the recommended first-line treatment [13, 44]. Given the fatal nature of fulminant HLH, alternative approaches to control hyperinflammation should be considered in patients resistant to first-line treatment. Anakinra, a recombinant IL-1 receptor blocker, has been approved for treating autoinflammatory disorders in children [45]. Data regarding the clinical use of anakinra in children with carHLH are limited, and treatment guidelines for it have not yet been established. Anakinra is typically added to advanced CRS as a second-line treatment, and studies have shown that it may be effective in controlling CAR T-cell therapy-associated toxicities by suppressing inflammatory pathways [17, 41, 43, 46]. Although the optimal dose and treatment duration has not been determined, a starting dose of 2 mg/kg subcutaneously or intravenously every 6 h (8 mg/kg/day, maximum daily dose of 400 mg)

Table 2. Diagnosis, assessment, and management of suspected CAR T-cell associated HLH. Adapted from Neelapu *et al.* [19].

Diagnostic criteria	1. Peak serum ferritin level of >10,000 ng/dL during cytokine-release phase (typically after post-infusion day+5) 2. Subsequent development of any 2 of the following (grading as per CTCAE, version 5.0) ① Hepatic toxicity: increase in serum bilirubin, AST, or ALT (hepatic toxicity) ② Renal toxicity: oliguria or increase in serum creatinine levels ③ Pulmonary toxicity: pulmonary edema ④ Hemophagocytosis: presence in BM or other organs
Assessment	Grade organ toxicity as per CTCAE, version 5.0
Management	1. All grades ① Supportive care - replacement of fibrinogen if patient's fibrinogen <150 mg/dL ② Start corticosteroids if the patient is unstable 2. Presence of ≥grade 3 organ toxicities ① Start anti-IL-6 therapy (tocilizumab) concurrent with corticosteroid ② If there is a suboptimal response or the patient is refractory to response after 48 hours of starting treatment, consider adding anakinra (suggested second-line treatment), etoposide (there is a concern for the effect on CAR T-cells), and intrathecal chemotherapy (if there is a presence of HLH-related neurotoxicity)

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; CAR, chimeric antigen receptor; CTCAE, Common Terminology Criteria for Adverse Events; HLH, hemophagocytic lymphohistiocytosis; IL-6, interleukin-6.

Table 3. The scoring system of ICANS: ICE (for patients ≥12 yr) and CAPD (for patients <12 yr) scores.

ICE score definitions (adapted from Lee *et al.* [16])					Total score
Orientation	Orientation to year, month, city, hospital			4	
Naming	Ability to name three objects (e.g., table, television, pen)			3	
Following commands	Ability to follow simple commands (e.g., 'smile' or 'open your month')			1	
Writing	Ability to write a standard sentence (e.g., 'happy to have my family around')			1	
Attention	Ability to count backwards from 100 to 0 by 10s			1	
CAPD encephalopathy assessment (adapted from Traube *et al.* [55])					Total score
	Always	Often	Sometimes	Rarely	Never
Eye contact with caregiver	0	1	2	3	4
Purposeful actions	0	1	2	3	4
Aware of their surroundings	0	1	2	3	4
Being restless	4	3	2	1	0
Being inconsolable	4	3	2	1	0
Being underactive	4	3	2	1	0
Slow response to interactions	4	3	2	1	0
Communicating needs and wants	4	3	2	1	0

Abbreviations: CAPD, Cornell Assessment of Pediatric Delirium; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune effector Cell Encephalopathy.

is administered from days to weeks, based on protocols used in autoimmune or rheumatic diseases [47, 48]. Anakinra was suggested to serve as a steroid-sparing agent and the last medication to be weaned off without affecting CAR T-cell efficacy; however, this should be validated in future prospective trials. In addition to anakinra, etoposide can be used to selectively remove activated T-cells, resulting in therapeutic benefits. However, it may also eliminate the patient's CAR T-cells, thus reducing their clinical efficacy [19, 49].

ICANS

ICANS is a common and challenging adverse effect of CAR T-cell therapy, which occurs in 25–44% of children with hematologic malignancies [11, 22, 23]. The incidence rate of severe ICANS observed in pivotal studies on tisa-cel was 12–13% [6, 50]. ICANS usually occurs within 7–10 days and sometimes up to 3 weeks after CAR T-cell infusion and can occur concurrently or shortly after CRS [25]. The underlying pathophysiology of ICANS is not fully understood, but it appears to be associated with the release of inflammatory cytokines by macrophages/monocytes, increased vascular permeability, and endothelial activation, resulting in the disruption of the blood-brain barrier (BBB)

[51]. Common clinical symptoms of ICANS include depressed consciousness, language disturbances, seizures, motor weakness, and cerebral edema. Dysgraphia has been noted as an early indicator of ICANS [19]. Although most ICANS cases are reversible and manageable, severe presentations, such as rapidly progressive cerebral edema, can be fatal. The clinical risk factors associated with an increased risk of severe ICANS include young age, high disease burden, severe CRS with high ferritin and/or cytokine levels, neurological comorbidities, and high CAR T-cell doses [52-54].

To grade ICANS, the 10-point immune effector cell-associated encephalopathy (ICE) score was used in adult patients. However, this tool is inappropriate for pediatric patients, particularly those aged <12 years or patients with developmental delays [15]. The Cornell Assessment of Pediatric Delirium (CAPD), adapted by Traube *et al.* [55], is a validated screening tool for recognizing delirium in pediatric patients, and its sensitivity and specificity are highest in patients aged <12 years. The guidelines recommend that delirium assessment should be performed at least twice per day during the high-risk period of ICANS, after 4 weeks of CAR T-cell infusion [13, 15]. Assessing patterns in ICE/CAPD scores within an individual patient is crucial for early intervention. The ICANS grading integrates the ICE (for children aged ≥12 yr) and CAPD (for children aged <12 yr) scores into an overall assessment of neurological function (Table 3, 4).

Neuroimaging findings during ICANS in children with ALL are still lacking; therefore, there are no pathognomonic imaging findings related to ICANS [56]. Brain magnetic resonance imaging, electroencephalography, and cerebrospinal fluid (CSF) examination can aid in the differential diagnosis of stroke, hemorrhage, infection, and malignancy. Gaining a clear understanding of the various imaging phenotypes and cytokine levels in CSF will improve timely diagnosis and therapeutic interventions.

Although there is no well-established recommendation to guide the management of ICANS in children with B-ALL [57], supportive care with or without short-term cortico-

Table 4. Overall gradingand management of ICANS. Adapted from ASTCT consensus [16], EBMT/JACIE/EHA recommendation [13], and PALISI-CARTOX Network [15].

		Grade 1	Grade 2	Grade 3	Grade 4
Grade	ICE score (≥12 yr)	7–9	3–6	0–2	Impossible
	CAPD score (<12 yr)	1–8	1–8	≥9	Impossible
	AVPU scale	Alert	Response to verbal	Response to pain	Un-response
	Seizure (any age)	X	X	O (any clinical seizure)	O (life threatening prolonged seizure >5 mins, repetitive clinical or electrical seizures)
	Motor weakness (any age)	X	X	X	O (deep focal motor weakness: hemiparesis, paraparesis)
	Elevated ICP/cerebral edema (any age)	X	X	O (focal/local edema on neuroimaging)	O (decerebrate/decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, diffuse cerebral edema on neuroimaging)
Management	Supportive care & anticonvulsants	- Close full vital sign monitoring, suspend oral nutrition, change oral drugs to i.v. - EEG, MRI, and lumbar puncture as clinically indicated (differential diagnosis) - If seizure, levetiracetam and status with benzodiazepines - If cerebral edema, consider osmotherapy - For grade 4 ICANS, consider mechanical ventilation for airway protection			
	Transfer to ICU	No (alert your ICU)		Transfer to ICU	
	Corticosteroids	X	① Dexamethasone i.v. 10 mg/6 h (in children <30 kg →0.5 mg/kg/6 h, max 10 mg) **or** mPD i.v. 1–2 mg/kg/day divided every 6–12 h ② Increase dexamethasone dose to 20 mg/6 h, if absence of improvement		mPD i.v. 1,000 mg/day for 3days followed by rapid taper
	Alternative treatment	X	X	Consider IL-1 receptor antagonist (anakinra), systemic or intrathecal chemotherapy (e.g., etoposide i.v.) for refractory grade 3–4 ICANS	

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; AVPU, alert, verbal, pain, unresponsive; CAPD, Cornell Assessment of Pediatric Delirium; CARTOX, MD Anderson Cancer Center CAR T-cell Therapy-Associated Toxicity; EBMT, European Society for Blood and Marrow Transplantation; EEG, electroencephalography; EHA, European Haematology Association; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune effector Cell Encephalopathy; ICP, intracranial pressure; ICU, intensive care unit; IL-1, interleukin-1; i.v., intravenous; JACIE, Joint Accreditation Committee of ISCT and EBMT; mPD, methylprednisolone; MRI, magnetic resonance imaging; PALISI, Pediatric Acute Lung Injury and Sepsis Investigators.

steroids is preferred as the initial treatment. Patients with grade 1 (mild) ICANS were offered supportive care with intravenous hydration and aspiration precautions. Corticosteroids (dexamethasone or methylprednisolone) should be initiated for ≥grade 2 ICANS and continued until symptoms improve to grade 1 and then be rapidly tapered. There is no clear therapeutic role for tocilizumab in ICANS because of its poor BBB penetration [58]; therefore, tocilizumab is only considered in patients with concurrent CRS [13]. Results of two clinical trials, NCT04148430 and NCT04359784, have suggested that when patients' symptoms deteriorate after the addition of high-dose methylprednisolone, anakinra alleviates clinical symptoms (NCT04148430, NCT04359784). The management recommendations for the ICANS are listed in Table 4.

B-CELL APLASIA (BCA)

BCA, which results in the "on-target, off-tumor" activity of CAR T-cells targeting B-cell markers (CD19), provides a surrogate for the persistence of potentially functional CAR T-cells. Patients with ongoing remission show prolonged BCA for months or years; thus, BCA is regarded as an indicator of CAR T-cell treatment effectiveness. However, persistent BCA can lead to hypogammaglobulinemia, an immunological immaturity-related risk factor for sinopulmonary and other infections [59]. According to the ELIANA study, 71% and 59% of pediatric B-ALL patients developed BCA at 12 and 24 months, respectively. In this review, the most frequent grade 3/4 adverse event occurring >1 year after the infusion was infection, with a prevalence of 20.4% [7]. In adults, pathogen-specific antibodies can be detected in the blood due to CD19-negative plasma cells [60]. However, after tissue treatment, plasma cell and serum antibody counts decline progressively [61]. Periodic intravenous immunoglobulin (IVIG) supplementation is recommended for children and young adults during BCA [13-15]. Hill *et al.* [62] proposed a practical algorithm for hypogammaglobulinemia management: first, screening for serum IgG within the first three months after CAR T-cell therapy; second, if patients have IgG ≤400 mg/dL, prophylactic IVIG should be considered; and third, in adults with infection and IgG ≤400 mg/dL, IVIG replacement is the only recommendation three months after infusion, while IVIG replacement is routine in children [13].

EARLY AND LATE HEMATOLOGIC TOXICITY

Cytopenia is usually observed within 28 days (early cytopenia) after CAR T-cell infusion; however, it may occasionally persist for >90 days (late cytopenia) [63]. CAR T-cell-associated cytopenia is exceedingly common in both CD28-based and 41BB-based costimulatory CAR products, with an incidence range of 50–80% [64]. CAR T-cell-associated cytopenia is biphasic (even triphasic) in nature [65]. With tisa-cel for R/R/B-cell ALL in children and young adults, 43% and 53% of patients had grade 3–4 thrombocytopenia and neutropenia, respectively, which persisted beyond day 30 after infusion [6]. Early cytopenia is attributed to the intensity of bridging chemotherapy, lymphodepletion chemotherapy pre-infusion, severe CRS, and carHLH [63-65]. While standard lymphodepletion chemotherapy generally does not cause prolonged cytopenia, it might exert additional myelosuppression in patients with pre-existing bone marrow infiltrating disorders [66, 67]. High levels of IFN-γ, which are increased in patients with severe CRS or carHLH, may suppress hematopoietic stem cell homeostasis, resulting in stem cell exhaustion [68].

The prolonged duration (>3 mo after infusion) of cytopenia is a unique aspect of the hematologic toxicity of CAR T-cell therapy. Delayed grade 3–4 cytopenia is often observed at a rate of 17–32% after tisa-cel therapy [6, 10]. Although the mechanism of prolonged cytopenia remains unclear, data suggest that baseline cytopenia, severe CRS, and allogeneic hematopoietic stem cell transfusion within 1 year are risk factors associated with late cytopenia [64, 66]. In a retrospective analysis, the levels of stromal cell-derived factor 1 correlated with neutropenia in patients with prolonged cytopenia [64]. More research on bone marrow should be considered in patients with late cytopenia to differentiate it from marrow dysplasia [69]. Since persistent cytopenia may be linked to susceptibility to opportunistic infections and significant morbidity, the use of granulocyte colony-stimulating factor (G-CSF) for hematologic recovery from day 14 after infusion (following the resolution of CRS and ICANS) is recommended according to the institutional protocol [14]. Recent data showed that the early use of prophylactic G-CSF did not negatively impact CAR T-cell expansion or prognosis [70]. While prophylactic treatment against infection, including viruses and *Pneumocystis carinii* pneumonia, is recommended, there is no consensus on a specific antibacterial or antifungal prophylaxis for patients with late cytopenia [13, 14].

CONCLUSION

This review summarizes the current knowledge on common complications after anti-CD19 CAR T-cell therapy in children and adults with B-cell malignancies. The management of CAR T-cell toxicities has evolved rapidly, and well-established guidelines based on expert recommendations exist. Future clinical trials should concentrate on the prevention and mitigation of these toxicities by refining CAR products, optimizing CAR T-cell counts, and developing novel therapies. Additionally, prospective and comprehensive studies investigating the late effects and establishing long-term follow-up guidelines for survival are imperative in this field.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med 2015;373:1541-52.
2. Inaba H, Pui CH. Advances in the diagnosis and treatment of pediatric acute lymphoblastic leukemia. J Clin Med 2021;10:1926.
3. Jeon W, Koh YK, Kang S, Kim H, Koh KN, Im HJ. Clinical characteristics and treatment outcomes of children and adolescents with aggressive mature B-cell lymphoma: a single-center analysis. Blood Res 2022;57:41-50.
4. Hunger SP, Raetz EA. How I treat relapsed acute lymphoblastic leukemia in the pediatric population. Blood 2020;136:1803-12.
5. KYMRIAH prescribing information. East Hanover, NJ: Norvatis Pharmaceuticals Corporation, 2022. (Accessed December 7, 2022, at https://www.us.kymriah.com/).
6. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-48.
7. Laetsch TW, Maude SL, Rives S, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. J Clin Oncol 2022:JCO2200642.
8. Locke FL, Neelapu SS, Bartlett NL, 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 2017;25: 285-95.
9. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-44.
10. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021;22: 1403-15.
11. Lee DW, Kochenderfer JN, Stetler-Stevenson M, 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 2015;385:517-28.
12. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
13. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol 2022;33:259-75.
14. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. J Clin Oncol 2021;39:3978-92.
15. Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol 2019;16:45-63.
16. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.
17. Dreyzin A, Jacobsohn D, Angiolillo A, et al. Intravenous anakinra for tisagenlecleucel-related toxicities in children and young adults. Pediatr Hematol Oncol 2022;39:370-8.
18. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv 2020;4:3123-7.
19. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47-62.
20. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 2017;130:2295-306.
21. Curran KJ, Margossian SP, Kernan NA, et al. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. Blood 2019;134:2361-8.
22. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322-31.
23. Maude SL. Tisagenlecleucel in pediatric patients with acute lymphoblastic leukemia. Clin Adv Hematol Oncol 2018;16:664-6.
24. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014; 371:1507-17.
25. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol 2022;22:85-96.
26. Sheth VS, Gauthier J. Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant 2021;56:552-66.
27. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 2018;24:731-8.
28. Norelli M, Camisa B, Barbiera G, 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 2018;24:739-48.
29. Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov 2016;6:664-79.
30. Yan Z, Zhang H, Cao J, et al. Characteristics and risk factors of cytokine release syndrome in chimeric antigen receptor T cell treatment. Front Immunol 2021;12:611366.
31. Penack O, Koenecke C. Complications after CD19+ CAR T-cell therapy. Cancers (Basel) 2020;12:3445.
32. Siddiqi T, Abramson JS, Li D, et al. Patient characteristics and pre-infusion biomarkers of inflammation correlate with clinical outcomes after treatment with the defined composition, CD19-targeted CAR T cell product, JCAR017. Blood (ASH Annual Meeting Abstracts) 2017;130(Suppl):193.

33. Schultz LM, Baggott C, Prabhu S, et al. Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a pediatric real-world chimeric antigen receptor consortium report. J Clin Oncol 2022; 40:945-55.
34. Fishman JA, Hogan JI, Maus MV. Inflammatory and infectious syndromes associated with cancer immunotherapies. Clin Infect Dis 2019;69:909-20.
35. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist 2018;23:943-7.
36. Topp MS, van Meerten T, Houot R, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021;195: 388-98.
37. Liu S, Deng B, Yin Z, et al. Corticosteroids do not influence the efficacy and kinetics of CAR-T cells for B-cell acute lymphoblastic leukemia. Blood Cancer J 2020;10:15.
38. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood 2019;134:2149-58.
39. Kadauke S, Myers RM, Li Y, et al. Risk-adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. J Clin Oncol 2021;39:920-30.
40. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood 2020;135:1332-43.
41. Major A, Collins J, Craney C, et al. Management of hemophagocytic lymphohistiocytosis (HLH) associated with chimeric antigen receptor T-cell (CAR-T) therapy using anti-cytokine therapy: an illustrative case and review of the literature. Leuk Lymphoma 2021;62:1765-9.
42. Hines MR, Keenan C, Maron Alfaro G, et al. Hemophagocytic lymphohistiocytosis-like toxicity (carHLH) after CD19-specific CAR T-cell therapy. Br J Haematol 2021;194:701-7.
43. Lee NY, Jo S, Yoo JW, et al. Anakinra to mitigate hemophagocytic lymphohistiocytosis-like toxicity following chimeric antigen receptor T-cell therapy in pediatric B-cell ALL. Clin Pediatr Hematol Oncol 2022;29:92-6.
44. Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and management of secondary HLH/MAS following HSCT and CAR-T cell therapy in adults; a review of the literature and a survey of practice within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol 2020;11:524.
45. Maniscalco V, Abu-Rumeileh S, Mastrolia MV, et al. The off-label use of anakinra in pediatric systemic autoinflammatory diseases. Ther Adv Musculoskelet Dis 2020;12:1759720X20959575.
46. Diorio C, Vatsayan A, Talleur AC, et al. Anakinra utilization in refractory pediatric CAR T-cell associated toxicities. Blood Adv 2022;6:3398-403.
47. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. Arthritis Rheumatol 2020;72:326-34.
48. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. Lancet Rheumatol 2020;2:e358-67.
49. Schubert ML, Schmitt M, Wang L, et al. Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. Ann Oncol 2021;32:34-48.
50. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.
51. Siegler EL, Kenderian SS. Neurotoxicity and cytokine release syndrome after chimeric antigen receptor T cell therapy: insights into mechanisms and novel therapies. Front Immunol 2020;11: 1973.
52. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov 2018;8:958-71.
53. Sievers S, Watson G, Johncy S, Adkins S. Recognizing and grading CAR T-cell toxicities: an advanced practitioner perspective. Front Oncol 2020;10:885.
54. Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. Blood 2019;133:2212-21.
55. Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU*. Crit Care Med 2014;42:656-63.
56. Tan AP. CAR-T cell therapy-related neurotoxicity in pediatric acute lymphoblastic leukemia: spectrum of imaging findings. Pediatr Neurol 2020;111:51-8.
57. Teachey DT, Bishop MR, Maloney DG, Grupp SA. Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. Nat Rev Clin Oncol 2018;15:218.
58. Nellan A, McCully CML, Cruz Garcia R, et al. Improved CNS exposure to tocilizumab after cerebrospinal fluid compared to intravenous administration in rhesus macaques. Blood 2018;132: 662-6.
59. Arnold DE, Maude SL, Callahan CA, DiNofia AM, Grupp SA, Heimall JR. Subcutaneous immunoglobulin replacement following CD19-specific chimeric antigen receptor T-cell therapy for B-cell acute lymphoblastic leukemia in pediatric patients. Pediatr Blood Cancer 2020;67:e28092.
60. Bhoj VG, Arhontoulis D, Wertheim G, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood 2016; 128:360-70.
61. Deyà-Martínez A, Alonso-Saladrigues A, García AP, et al. Kinetics of humoral deficiency in CART19-treated children and young adults with acute lymphoblastic leukaemia. Bone Marrow Transplant 2021;56:376-86.
62. Hill JA, Giralt S, Torgerson TR, Lazarus HM. CAR-T - and a side order of IgG, to go? - Immunoglobulin replacement in patients receiving CAR-T cell therapy. Blood Rev 2019;38:100596.
63. Taneja A, Jain T. CAR-T-OPENIA: chimeric antigen receptor T-cell therapy-associated cytopenias. EJHaem 2021;3(Suppl 1):32-8.
64. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant 2019;54:1643-50.

65. Sharma N, Reagan PM, Liesveld JL. Cytopenia after CAR-T cell therapy-a brief review of a complex problem. Cancers (Basel) 2022;14:1501.
66. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv 2020;4:3776-87.
67. Shalabi H, Gust J, Taraseviciute A, et al. Beyond the storm - subacute toxicities and late effects in children receiving CAR T cells. Nat Rev Clin Oncol 2021;18:363-78.
68. Morales-Mantilla DE, King KY. The role of interferon-gamma in hematopoietic stem cell development, homeostasis, and disease. Curr Stem Cell Rep 2018;4:264-71.
69. Reagan PM, Neelapu SS. How I manage: pathophysiology and management of toxicity of chimeric antigen receptor T-cell therapies. J Clin Oncol 2021;39:456-66.
70. Nahas GR, Komanduri KV, Pereira D, et al. Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT). Leuk Lymphoma 2020;61:940-3.