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Reviews

Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy

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Chimeric antigen receptor (CAR)-modified T cells (CAR-Ts) targeting CD19 have resulted in unprecedented durable remissions for patients with relapsed and refractory B cell malignancies. Cytokine release syndrome (CRS), resulting from rapid immune activation induced by CAR-Ts, is the most significant treatment-related toxicity. CRS initially manifests with fever and can progress to life-threatening capillary leak with hypoxia and hypotension. The clinical signs of CRS correlate with T cell activation and high levels of cytokines including IL-6. Tocilizumab, an anti-IL-6 receptor antagonist, is the standard for CRS management, but optimal timing of administration is unclear. The development of a supportive infrastructure by treatment centers is important to maintain safe administration as access expands. Collaborative efforts are underway to harmonize the definition and grading of CRS to allow for better interpretation of toxicities across CAR-T products and clinical trials and allow for informed management algorithms.

INTRODUCTION

Chimeric antigen receptor (CAR)-modified T cells (CAR-Ts) targeted to CD19 result in unprecedented durable remissions for many patients with chemotherapy-refractory B cell malignancies [1–12]. With the US Food and Drug Administration (FDA) approvals of tisagenlecleucel and axicabtagene ciloleucel, these agents are now commercially available, broadening use beyond a few specialized centers. The role of CAR-T therapy beyond CD19 is also ensured by the ongoing development and early promise of CARs targeting other antigens and malignancies [13–16]. With increasing use of CAR-Ts, it is important to understand their unique side effects. The potent systemic immune activation responsible for the success of CAR-Ts also drives the life-threatening toxicity of cytokine release syndrome (CRS). Fortunately, risk factors and management strategies for CRS have become better defined over the course of several clinical trials with clinical advances often informed with investigational correlates [1,3,4,7,10,17-19].

WHAT IS CRS?

CRS is a clinical syndrome resulting from generalized immune activation correlating with CAR-T expansion and marked elevations of serum inflammatory markers and cytokines. The first clinical signs of CRS are fevers, myalgias, and fatigue. Often, fevers are low grade and escalate over several days with temperatures above 105°F/40.5°C commonly observed. CRS can progress to life-threatening vasodilatory shock, capillary leak, hypoxia, and end-organ dysfunction. CRS can either be self-limited (requiring only supportive care with antipyretics and intravenous fluids) or it may require intervention with anticytokine-directed therapy such as corticosteroids or tocilizumab. CRS occurs within 1 to 14 days after infusion depending on the product, clinical trial design, and population being treated. The duration of CRS is variable and dependent on intervention, with full resolution typically by 2 to 3 weeks after CAR-T infusion. Table 1 summarizes the incidence of CRS for selected trials.

Clinically available laboratory markers of inflammation including C-reactive protein and ferritin are elevated in patients with CRS from CAR-Ts [4,20]. Cytokine profiles also correlate with the clinical syndrome of CRS [2–4,17,19,20]. Effector cytokines such as INF-γ and soluble IL-2 receptor α are elevated, but so are cytokines traditionally associated with macrophage activation such as IL-6 and IL-10. Indeed, most patients with severe CRS have clinical and laboratory features overlapping with those of macrophage activation syndrome/hemophagocytic lymphohistiocytosis [21]. These features resolve with treatment of CRS.

GRADING OF CRS

A CRS grading system allows for an objective assessment of severity based on clinical signs and symptoms. It can also be

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Table 1
Outcomes after Anti-CD19 CAR-Ts

First Author and Reference	Program CAR	Population	Response	CRS	Neurologic Toxicity
		ALL			
Maude [4]	PENN 4-1BB	n = 30 (r/rALL) Pediatrics and adults	CR = 90%	100% CRS 27% severe	43% total
Maude [5]	Novartis Multicenter 4-1BB	n = 75 Pediatrics and AYA	CR = 81% MRDNeg = 81%	77% total	13% grade 3
Park [7]	MSKCC CD28	n = 53 Adults	CR = 83% MRDNeg = 67%	85% total 26% severe (1 grade 5)	42% grades 3-4
Lee [3]	NCI CD28	n = 21 Pediatrics and AYA	CR = 67%	76% CRS 28% severe	29% total
Turtle [10]	Seattle 4-1BB	n = 30 Adults	CR = 93%	83% CRS	50% severe
Gardner [1]	Seattle 4-1BB	Pediatrics and AYA n = 45	CR = 93% MRDNeg = 93%	93% CRS 23% severe	49% total 21% grades 3-4
NHL and CLL					
Schuster [9]	PENN 4-1BB	n = 28 (DLBCL/FL)	CR = 57%	57% CRS 18% severe	11% severe
Schuster [12]	Novartis Multicenter 4-1BB	n = 93 (DLBCL)	CR = 40%	58% CRS 9% severe	12% ≥ grade 3
Neelapu [6]	KITE Multicenter CD-28	n = 111 (DLBCL /TFL/PMBCL)	CR = 54%	93% CRS 13% severe	28% ≥ grade 3
Abramson [11]	Juno Multicenter 4-1BB	n = 91 (DLBCL/FL/PMBCL/MCL)	CR = 46%	35% CRS 1% severe	Total 35% 12% ≥ grade 3
Kochenderfer [2]	NCI CD28	n = 15 (NHL/CLL)	CR = 53% PR = 27%	27% severe	40% total
Porter [8]	PENN 4-1BB	n = 14 (CLL)	CR = 29% PR = 29%	64% total 28% severe	43% total 1/14 grade 4

CR indicates complete remission; PR, partial remission; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic leukemia; TFL, transformed follicular lymphoma; PMBCL, primary mediastinal B cell lymphoma; MCL, mantel cell lymphoma; AYA, adolescent young adult; MRDNeg, minimal residual disease negative.

used to help guide and assess response to anticytokine treatment algorithms. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 description for CRS has been used in describing outcomes in recipients of blinatumomab and other therapeutic antibodies. This grading system, however, is most appropriate for traditional drugs, with grading linked not only to severity of clinical signs and symptoms but whether the infusion of drug needs to be held and/or intervention occurs. Given the unique nature of cellular therapy, several alternative CRS grading systems have been developed in attempts to better capture CAR-T–induced CRS. A consensus grading scale with input from several programs was presented in 2014 and has been used by the NCI to grade CRS in their anti-CD19 CAR-T clinical trial programs [18]. The University of Pennsylvania and Children's Hospital of Philadelphia clinical trial programs use a different modified grading scale [22]. It is important to note that a patient with CRS would receive a different grade depending on which scale is used. As an example, a patient with hypotension requiring low dose vasopressors after anti-CD19 CAR-Ts would have a grade 2 CRS on the NCI scale, a grade 3 CRS on the University of Pennsylvania and Children's Hospital of Philadelphia scale, and a grade 4 CRS on the Common Terminology Criteria for Adverse Events version 4.0 scale [23]. These differences are important to note when evaluating outcomes across different CAR-T trials.

Fortunately, the importance for the field to have a unified definition and grading scale for CRS has been recognized. The American Society for Blood and Marrow Transplantation sponsored a consensus meeting on June 20, 2018 with goal of developing a consensus grading scale. A report from this meeting is in development.

CRS: RISK FACTORS AND PREVENTION

CRS-related deaths have rarely been reported [7,24]. Given that CRS is potentially life threatening, a major focus of clinical trials has been to identify potentially modifiable risk factors (Table 2). Many centers have shown that for acute lymphoblastic leukemia (ALL), disease burden before CAR-T infusion is a strong predictor for CRS severity supporting cytoreductive strategies [3,4,7,10,17].

There are clear data that the infusion dose of CAR-Ts impacts both safety and efficacy, with higher doses associated with more severe CRS [3,10,24,25]. Interpretation of infusion dose and outcome is complicated by the fact that it markedly underestimates the final expanded active dose and is only 1 of

Table 2
Risk Factors and Prevention Strategies for CRS

Risk factors and predictors for severe CRS
• High disease burden (in ALL)
• High infusional dose
• Fludarabine containing lymphodepletion
• Concurrent infectious illness
• Early cytokine elevations
Prevention strategies under investigation
• Pretreatment cytoreduction
• Inverse dose adjustment by disease burden
• Fractionated dosing schemes
• Prophylactic anticytokine therapy

many factors that may correlate with peak in vivo expansion. Different dosing strategies have been used in attempts to limit toxicity. Some centers deliver an initial lower dose of cells to ALL patients with higher disease burden in an "adaptive dosing" strategy [7,10]. For example, after a CRS-related death, the group at Memorial Sloane Kettering Cancer Center treated patients with high disease burdens (over 5% bone marrow blasts) with a lower dose of cells (1×10^6 versus 3×10^6 CAR-Ts/kg). No further CRS-related deaths were observed [7]. Using CAR-Ts for adult ALL, we have studied both dose and schedule of infusions in response to CRS-related death. A fractionated dosing scheme was optimal to maintain efficacy while minimizing CRS-related toxicity. The total planned CAR-T dose is infused over 3 days with day 2 and/or day 3 doses held for early signs of CRS, allowing for real-time dose modification in response to early toxicity [24].

It is probable that different anti-CD19 CAR-Ts and manufacturing techniques lead to differential safety and efficacy outcomes. In an attempt to improve the therapeutic index of CAR-Ts, the group at the Fred Hutchinson Cancer Research Center implemented a manufacturing approach that results in a defined composition of $CD4^+/CD8^+$ anti-CD19 CAR-Ts (in a 1:1 ratio). In their experience this product results in a consistent product with manageable toxicity [1,10]. To date there are little comparative data and certainly no randomized studies comparing different products. Interpretation of toxicities across studies needs to be done with caution because different diseases, disease stages, trial designs, populations (adult and/or pediatric), and CRS grading scales are represented in each study. Different intensities and choices for pre-CART lymphodepletion are examples of significant variability across studies. The combination of fludarabine and cyclophosphamide has been observed to correlate with higher vivo expansion and perhaps more responses but also with a higher incidence of severe CRS when compared with cyclophosphamide alone [10]. The dose of cyclophosphamide and other lymphodepletion also varies across studies and may further impact CAR-T expansion, persistence, and toxicity.

MANAGEMENT OF CRS

CAR-Ts are "living" drugs with remissions linked to their ability to expand logarithmically in vivo. In addition, the persistence of CAR-Ts after infusion has correlated with durable remissions in ALL [4,10,25]. Management and prevention strategies for toxicities need to be considered with this in mind because agents used to mitigate signs and symptoms of CRS may potentially abrogate the antitumor potential of the T cells.

Since the initial observation that tocilizumab, an antibody against the IL-6 receptor, rapidly reversed severe CRS in a critically ill child with CAR-T–induced CRS, the drug has become a management standard [19]. Tocilizumab has remained at the forefront of CRS treatment and received an FDA approval for this indication with the approval of the first CAR-T product, tisagenlecleucel. Tocilizumab is effective for most patients; those who do not respond to an initial dose often clinically improve with a second administration and/or the addition of corticosteroids. In addition to being an effective tool to manage CRS, tocilizumab is attractive because blocking the IL-6 receptor may provide toxicity management without impacting the antitumor effect of the CAR-Ts. This is in contrast to corticosteroids, which may be necessary in some cases to help control CRS but in high doses may have a detrimental effect on CAR-Ts [17]. For the studies summarized in Table 1, tocilizumab in general was administered at the time of more severe signs of CRS, hoping to minimize any potential effect on efficacy. This has also been the approach in published management algorithms [22,26]. However, the optimal timing of tocilizumab to balance safety and efficacy is unknown and is the subject of ongoing clinical trials. It remains to be determined whether prophylactic or earlier intervention with tocilizumab would improve safety without impacting efficacy. In 1 early report, severity of CRS after early intervention was decreased without an impact on response or functional persistence of CAR-Ts [25]. Of importance, ultimate prevention and management strategies are likely to depend on the CAR-T product, the clinical platform used, and other disease- or patient-related factors.

Although tocilizumab has been an effective management tool, there is interest in other approaches to prevent or manage CRS. There are many candidate anticytokine therapies including siltuximab (binds IL-6), ruxolitinib (a Janus kinase inhibitor), and anakinra (an IL-1 receptor antagonist) that have been used anecdotally, although little data are available regarding these interventions either as first-line therapy or for refractory CRS. As discussed, treatment-related deaths due to CRS have been reported, but there is no standard algorithm to manage patients refractory to tocilizumab and corticosteroids. There are many CAR-Ts in development that incorporate suicide targets as methods to mitigate toxicity. Examples include an inducible caspase 9 system, inclusion of genes for CD20 (to be targeted by rituximab), epidermal growth factor receptor (to be targeted by cetuximab), and herpes simplex virus thymidine kinase (to be targeted by ganciclovir) [27–29]. Another approach is manufacturing CAR-Ts that can be regulated without actually killing them, for example requiring infusion of an additional agent for activation [30]. Further research will determine the impact of these approaches for the management of CRS.

NEUROLOGIC TOXICITY

Neurologic events are not part of most definitions or grading systems of systemic CRS and should be managed with an independent, and as yet to be optimized, treatment algorithm [26]. Similar to CRS, neurologic events occur within the first few weeks of therapy and are considered to be a class effect of CAR-T therapy (Table 1). Observed events include encephalopathy, delirium, aphasia, focal deficits, and seizures, which often develop after CRS or when CRS is resolving. Neurologic signs are usually self-limited, but isolated deaths from cerebral edema have been reported [31,32]. The pathogenesis of neurologic toxicity is unclear, but it may be mediated by diffusion of supraphysiologic cytokines into the central nervous system (CNS) and/or direct T cell infiltration. It is established that anti-CD19 CAR-Ts readily cross the blood–brain barrier and in most treated patients are detectable in the cerebrospinal fluid. Their presence in the cerebrospinal fluid, however, does not always predict for toxicity, although some studies have found a correlation [3,4]. Cytokine profiles are also abnormal in the cerebrospinal fluid of symptomatic and asymptomatic patients. Unlike the fever and hypotension from systemic CRS, neurologic toxicity does not respond readily to tocilizumab; although corticosteroids are the primary therapy, their impact on neurologic toxicity is not well defined [10,23].

The risk factors for developing CNS toxicity and fatal cerebral edema are not clear. Risk may be increased for patients with a high disease burden, more severe systemic CRS, and higher peak cytokine levels and in vivo expansion [10,33,34]. High levels of IL-6 and tumor necrosis factor-α on day 1 after CAR-T infusion independently correlate with the development of grade 4 CNS toxicity [10]. Further studies are needed to

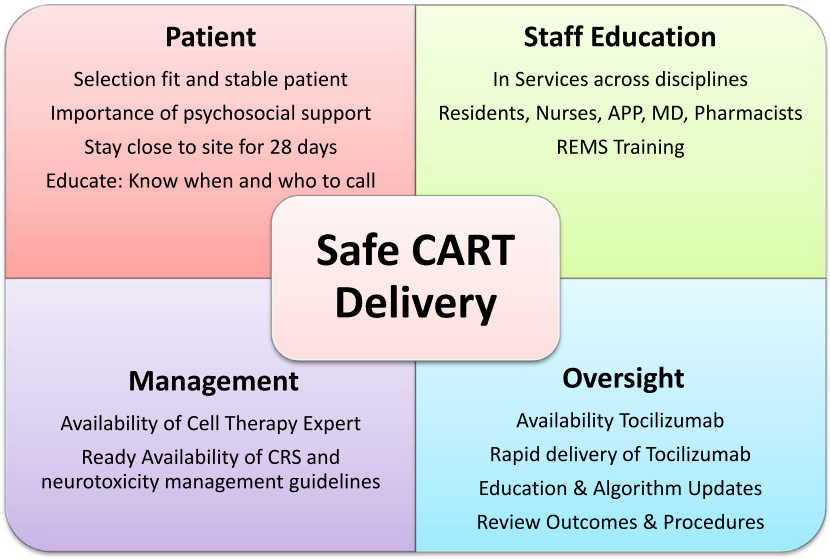

Figure 1. Delivering CAR-Ts safely.

determine the mechanism of action, risk factors, and optimal management of neurologic toxicity after CAR-Ts [26].

DELIVERING CAR-TS SAFELY

The overreaching goal of any CAR-T program needs to be safe access for patients in need. The safe administration of CAR-Ts in the clinical trial or commercial setting is contingent on the treatment center developing a supportive infrastructure (Figure 1). The selection of the appropriate patient is paramount. Disease stability and good performance status predict for successful and safe outcomes. Given the unique toxicities and requirement for experienced management, patients need to commit to stay close to the treatment center during the first few weeks after CAR-T infusion. The development of specific systematic procedures and oversight is needed to ensure tocilizumab is available on site and then rapidly administered when ordered. Infectious illness concurrent with CRS predicts for poor outcomes, supporting the exclusion of patients with active infections and the use of prophylactic antimicrobial strategies [24]. Ongoing education of medical staff (nurses, clinicians, residents, and pharmacists) in disciplines beyond oncology is critical for optimizing patient care. An experienced cell therapist should be available at all times to help direct management. CRS treatment algorithms should be available for all staff who may encounter a patient with CAR-T toxicity. Along these lines, the FDA has required that a Risk Evaluation and Mitigation Strategy be in place for the first 2 approved CAR-T products, tisagenlecleucel and axicabtagene ciloleucel. This may require training hundreds of staff members at a single institution for the use of CAR-Ts. Delivering CAR-Ts safely is indeed a large multidisciplinary endeavor that requires clinical expertise, intensive coordination, and meticulous care and oversight.

CONCLUSION

The outcomes of anti-CD19 CAR-Ts for patients with advanced and refractory B cell neoplasms have been dramatic and are changing the paradigm of cancer therapy in general. However, these therapies are associated with unique and potentially severe toxicities, and in some cases success is limited by severe toxicity from CRS. Although IL-6 blockage is effective for most patients with CRS, the challenge now is to understand the most effective strategies to mitigate toxicity without impacting CAR-T short-term and long-term efficacy. These strategies will be increasingly important as CAR-Ts are being targeted against new antigens both in malignant and nonmalignant diseases and in many different patient populations.

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