The Role of Advanced Practitioners in Optimizing Clinical Management and Support of Patients With Cytokine Release Syndrome From CAR T-Cell Therapy

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Abstract

CAR T-cell therapy is rapidly emerging as a promising treatment for many hematologic malignancies. However, CAR T cells can be associated with unique toxicities, including cytokine release syndrome (CRS), which can be severe or fatal if not recognized promptly and treated appropriately. Therefore, it is essential that advanced practitioners caring for patients who have received CAR T-cell therapy to be knowledgeable regarding the signs and symptoms of CRS and understand how to grade and manage toxicities. Understanding the risk factors that may be associated with the development of toxicities as well as the incidence, severity, and timing of CRS with different CAR T-cell products will allow for earlier recognition and treatment, and therefore improvement of outcomes in patients receiving this novel therapy.

CASE STUDY

Mr. M, a 45-year-old male with a history of relapsed/refractory diffuse large B-cell lymphoma (DLBCL), is 5 days post CAR T-cell therapy and develops a fever of 40°C and sinus tachycardia. His blood pressure is at baseline at 118/70 mm Hg. His respiratory rate is normal and oxygen saturation is 95% on room air. He is pancytopenic with a hemoglobin of 9.6 gm/dL, platelet count of 90 K/µL, and absolute neutrophil count of 0.5 K/µL.

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Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment, management, and outlook for patients with incurable B-cell malignancies. This approach involves harvesting and genetically modifying the patient's T cells to express a CAR that redirects the cells to target specific tumor cell antigens, resulting in tumor cell death.

Currently, two anti-CD19 CAR T-cell products (axicabtagene ciloleucel and tisagenlecleucel) have received U.S. Food & Drug Administration (FDA) approval, and a third product, isocabtagene maraleucel, has received a Breakthrough Therapy designation (Chavez, Bachmeier, & Kharfan-Dabaja, 2019). Given the durable remissions associated with approved and emerging CAR T-cell therapies, it is likely that these approaches will gain further ground and their use will be expanded to additional centers and other cancers. Despite remarkable promise, CAR T-cell therapies are also associated with varied adverse effects, including cytokine release syndrome (CRS), neurotoxicity, cytopenias, hypogammaglobulinemia, and hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS; Neelapu et al., 2018). Notably, CRS is a potentially fatal toxicity reported among many patients receiving CAR T-cell therapy (Riegler, Jones, & Lee, 2019). Therefore, it is imperative that advanced practitioners have the necessary know-how to effectively prevent, treat, and manage CRS related to CAR T-cell therapy.

PATHOPHYSIOLOGY AND SYMPTOMS OF CRS

Among patients with relapsed or refractory B-cell malignancies for whom CAR T-cell therapy is indicated, T cells are separated from peripheral blood cells obtained from the patient, which are next expanded, activated, and transduced with the CAR gene via a replication-defective lentivirus or retrovirus vector. The patient-derived anti-CD19 CAR-expressing T cells are expanded in vitro and then infused back in to the patient. Since CD19 is expressed on B-lineage leukemias and lymphomas, the CD19-directed CAR enables the engineered T cells to bind specifically to tumor cells, ultimately leading to their destruction (Wang & Riviere, 2016). Concomitantly, this interaction of immune cells (both autologous CAR T cells and other host immune effectors cells) results in the production of various inflammatory cytokines such as interleukin-6 (IL-6), interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), IL-2, and IL-10. These cytokines are known to further increase immune cell signaling, activation, and recruitment of other inflammatory cells and nonimmune cells such as endothelial cells. This unleashes a cytokine storm that overwhelms regulatory homeostatic mechanisms and precipitates CRS, which can have deleterious effects on the patient (Shimabukuro-Vornhagen et al., 2018). The National Cancer Institute defines CRS as a systemic inflammatory state caused by a robust and widespread immune activation induced by a cell-mediated immune response that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T cells (Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018).

While CRS is associated with a constellation of clinical symptoms including fever, hypotension, and widespread organ dysfunction, the first presenting symptom is usually fever that occurs within hours to several days following infusion of CAR T cells (Lee et al., 2014). Clinical trials of commercially available CAR T-cell products showed a median time of CRS onset of 2 to 3 days, with a median duration of 7 to 8 days; however, it is important to note that CRS symptoms have also occurred up to 3 weeks post CAR T-cell therapy (Chavez et al., 2019; Neelapu, 2019).

The initial fever could be followed by sinus tachycardia, hypotension, depressed cardiac function, and hypoxia. Clinically, CRS can present with mild flu-like symptoms (headache, fever, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia), skin rash, respiratory signs and symptoms (tachypnea, hypoxia, pulmonary edema), coagulopathy (increased D-dimer, prothrombin time, partial thromboplastin time, hypofibrinogenemia), renal dysfunction, hepatic dysfunction, and cardiovascular dysfunction, which could potentially lead to multiorgan system failure, and even death (Lee et al., 2014).

Elevated IFNγ and TNFα are generally responsible for fever, chills, headache, dizziness, and fatigue (Shimabukuro-Vornhagen et al., 2018).

TNFα is also known to cause watery diarrhea, vascular leakage, cardiomyopathy, and lung injury. Highly elevated IL-6 levels are considered a major contributor for the pathophysiology of CRS and result in characteristic symptoms of severe CRS such as cardiomyopathy, vascular leakage, and activation of the complement and coagulation cascade inducing disseminated intravascular coagulation (DIC; Matthys et al., 1993).

Some patients receiving CAR T-cell therapy and experiencing CRS can develop a HLH/MAS-like syndrome and are associated with additional elevated cytokines, including IL-18, IL-8, IP10, MCP1, MIG, and MIP1β (Belot, 2014). A study of a cohort of 35 pediatric and adult acute lymphoblastic leukemia (ALL) patients receiving anti-CD19 CAR T-cell therapy reported that peak levels of IL-6, soluble IL-6 receptor, IFNγ, and soluble gp130 correlated with the risk of severe CRS, thereby indicating their utility as biomarkers of CRS (Teachey et al., 2016).

RISK OF CRS

The risk and severity of CRS can vary based on the underlying disease burden, individual patient characteristics, and the type of therapy (Shimabukuro-Vornhagen et al., 2018). For example, a higher disease burden has been reported to increase the severity of CRS among patients with ALL receiving CAR T-cell therapy (Davila et al., 2014). The administered dose or number of CAR T cells infused per kilogram, the strength of T-cell activation, and the degree of T-cell expansion have also been shown to influence CRS severity (Lee et al., 2015). Additionally, pediatric patients are at a higher risk for developing CRS with CAR T-cell therapy as compared to adults, thereby suggesting a role for an immature immune system (Lee et al., 2015; Maude et al., 2014).

Furthermore, the type of the CAR construct strongly correlated with the severity and time to clinical manifestation of CRS. For instance, second-generation CAR T-cell constructs that include costimulatory domains are more frequently associated with CRS as compared with first-generation constructs that only contained T-cell receptor domains (Savoldo et al., 2011; van der Stegen, Hamieh, & Sadelain, 2015). Approved and emerging second-generation CAR constructs contain an extracellular antigen-recognition domain, a transmembrane domain, and an intracellular signaling domain that includes costimulatory domains from either CD28 or 4-1BB.

Recent evidence from two randomized trials seems to suggest that CD28 costimulatory domains in CAR constructs may be associated with a higher risk of CRS. In these trials, among patients with non-Hodgkin lymphoma (NHL) receiving CAR T-cell therapy, the incidence of CRS was 93% with a CD28-containing CAR and 57% with a 4-1BB-containing CAR (Neelapu et al., 2017; Schuster, Hong, Arnold, & White, 2014). Definitive conclusions regarding the correlation between costimulatory domains in CAR constructs and CRS risk, however, are elusive since there were differences in the patient populations and definition of CRS in the aforementioned studies.

Finally, a higher risk of CRS appeared to be influenced by the type of lymphodepletion that was used prior to CAR T-cell infusion, with a higher incidence of CRS being observed after lymphodepletion with cyclophosphamide and fludarabine (Hay et al., 2017).

ASSESSING FOR CRS

Cytokine release syndrome can present with a variety of symptoms ranging from mild flu-like malaise to severe life-threatening symptoms among patients who have received CAR T-cell therapy. Patients with CRS may also have cytopenias, elevated creatinine and liver enzymes, deranged coagulation parameters, and high C-reactive protein levels. From a clinical perspective, these symptoms and laboratory abnormalities are not characteristic of any specific syndrome, thereby adding to the complexity in making a definitive diagnosis of CRS (Shimabukuro-Vornhagen et al., 2018).

For instance, patients with tumor lysis syndrome may also present with acute renal failure, cardiac arrhythmia, and seizures, but can be differentially diagnosed based on laboratory findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia (Howard, Jones, & Pui, 2011). It is often difficult to determine if a patient with fever and neutropenia is experiencing infection as opposed to CRS, as lymphodepleting chemotherapy regimens often result in neutrope-

nia during the same time frame as CRS. Cytokine release syndrome can also be confused with sepsis since patients with severe CRS would present with organ dysfunction defined as an increase of 2 points or more in the Sequential Organ Failure Assessment score. In addition, characteristics of severe CRS such as elevated lactate necessitating vasopressors fulfill the criteria for septic shock (Singer et al., 2016). Other key differential diagnoses for CRS include heart failure, renal failure, respiratory failure, hepatitis, pulmonary embolism, allergic reactions, and HLH/MAS (Lee et al., 2014).

Recognizing CRS early and optimally grading its severity are critical for further management of patients receiving CAR T-cell therapy. Over the years, several attempts have been made to develop a consistent and consensus-based grading system for CRS associated with CAR T-cell therapy since CRS grading has varied widely among institutions and between products (Riegler et al., 2019).

Previously, the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) was used to grade CAR T-cell–induced CRS, but it was more applicable to antibody infusion–related toxicities rather than cell infusions and did not include fever as a requirement. Other published grading systems for CRS include the CTCAE v5.0, Lee criteria, Penn criteria, MSKCC criteria, and CARTOX criteria (Riegler et al., 2019). These are summarized in Table 1.

Recently, experts from the American Society for Transplantation and Cellular Therapy (ASTCT) have tried to harmonize the definitions and grading systems for CRS (Lee et al., 2019). Per this consensus document, CRS is defined as "a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction." The ASTCT consensus grading approach for CRS considers the temperature of the patient, does not include strict laboratory parameters, and is based upon the degree and type of interventions required for management of hypotension and hypoxia.

For instance, the criteria for grading do not define a specific level of oxygen saturation and use the type of oxygen delivery device to determine the level of oxygenation deficit. Likewise, the grading criteria do not specify values for hypotension and rely on the number of vasopressors required to maintain adequate blood pressure. Table 2 has summarized the ASTCT CRS Consensus Grading criteria to assess the severity of CAR T-cell–associated CRS. The authors of the consensus document affirm the need to ensure that fever is not attributable to any other cause such as tumor lysis syndrome, infection, sepsis, septic shock, etc. They note that once patients with CRS are administered an antipyretic or anticytokine therapy, instead of fever, hypotension and/or hypoxia should be used to grade subsequent CRS toxicity. Additionally, grade 4 CRS does not include patients who are intubated for airway protection or to enable a procedure. Finally, the authors suggest the use of CTCAE v5.0 for grading other organ toxicities (Lee et al., 2019). Taken together, these consensus criteria are expected to decrease variability in the assessment of CRS and ensure improved CRS assessment to inform adequate treatment decisions (Riegler et al., 2019).

Case Study Continued

Mr. M is determined to have a grade 1 CRS per the ASTCT grading scale, which is treated with acetaminophen and cooling measures. Due to the neutropenia, infection also remains high on the differential. He is pan-cultured and started on empiric antibiotic therapy. A chest x-ray is negative. Mr. M continues to have intermittent fevers and the following day develops hypotension with a blood pressure of 88/50 mm Hg. His C-reactive protein and ferritin levels are trending up. The advanced practitioner recognizes that Mr. M may have developed grade 2 CRS and/or possible sepsis. The cultures are negative to date. A lactic acid level is drawn and is within normal limits. Mr. M is given a dose of tocilizumab 8 mg/kg and a 500 cc normal saline fluid bolus with improvement in his blood pressure to 115/76 mm Hg, and his maintenance intravenous fluid is increased to 83 cc/hour. He continues to be monitored closely with continuous cardiac and pulse oximetry monitoring.

CYTOKINE RELEASE SYNDROME PREVALENCE IN APPROVED AND EMERGING CAR T-CELL PRODUCTS

The incidence of CRS among approved and emerging CAR T-cell therapies is known to vary and has also been graded in differing ways (Chavez et al., 2019). For example, in the ZUMA-1 trial, axicabtagene ciloleucel infusion–related CRS was reported among 93% of patients within a median of 2 days. Grade 3 or 4 CRS was reported for 13% patients and severity was assessed using the Lee criteria (Lee et al., 2014; Neelapu et al., 2017). On the other hand, in the JULIET trial, CRS onset occurred within a median of 3 days of tisagenlecleucel infusion and was reported among 58% of patients (Schuster et al., 2019). While the severity of CRS was graded based on the Penn criteria (Porter, Frey, Wood, Weng, & Grupp, 2018), grade 3 or worse CRS was observed among 22% of patients receiving tisagenlecleucel (Chavez et al., 2019; Neelapu et al., 2017; Schuster et al., 2019). Recently, data from the TRANSCEND trial investigating the efficacy of isocabtagene maraleucel reported CRS onset within 5 days of infusion and among 35% of infused patients, with only 1% experiencing grade 3 or 4 CRS, based on the Lee criteria (Abramson et al., 2018). Indeed, axicabtagene ciloleucel, tisagenlecleucel, and isocabtagene maraleucel are distinct CAR T-cell products with both similarities and differences, which are described in Table 3 (Chavez et al., 2019).

For example, axicabtagene ciloleucel consists of a CD3 ζ /CD28 CAR construct designed to transduce cells with a replication defective retroviral vector. It was approved by the FDA in 2017 for the treatment of adult patients with refractory/relapsed large B-cell lymphoma after two or more lines of systemic therapy (including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma). The recommended dose for a single intravenous infusion is a target of 2×10^6 CAR-positive viable T cells per kg body weight, preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.

Tisagenlecleucel has a 4-1BB costimulatory domain and is transduced using a lentiviral vector. It has been approved for patients up to 25 years of age with B-cell precursor ALL and for adult patients with refractory/relapsed large B-cell lymphoma after two or more lines of systemic therapy. Two lymphodepletion protocols using fludarabine/cyclophosphamide and bendamustine have been described for tisagenlecleucel.

Similarly, isocabtagene maraleucel contains a 4-1BB costimulatory domain, is delivered through a lentiviral, vector and its lymphodepletion protocol is based on fludarabine/cyclophosphamide. It is manufactured in a controlled process that enables administration of a fixed ratio of CD4 and CD8 CAR T cells (Chavez et al., 2019).

MANAGEMENT OF CRS

In light of the fact that severe CRS can be fatal, it is critical that advanced practitioners minimize the risk of CRS among patients receiving CAR T-cell therapy. However, there are no studies to inform on prophylactic therapy for CAR T-cell–induced CRS. As a result, CAR T-cell infusion should be delayed among patients who present with signs of infection. Other considerations for determining the eligibility of patients for CAR T-cell therapy include age and tumor burden (Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018). Although elevated levels of C-reactive protein, ferritin, and cytokines such as IFNγ, IL-6, soluble IL-2Rα, and IL-10 have been associated with CRS, accurate predictors of severe CRS remain to be identified due to confounding variables of age, gender, ethnicity, and disease-related factors. Since fever is known to precede the onset of CRS by at least 1 to 3 days, patients receiving CAR T-cell therapy who develop fever should be frequently monitored for signs of CRS.

While low-grade CRS can be treated with antihistamines, antipyretics, and fluids, patients need to be regularly evaluated for ruling out confounding diagnoses and an increase in severity of CRS. Given that IL-6 is a key mediator in the signaling cascade of CRS and a central driver of the symptoms of CRS, it represents an attractive therapeutic target.

Studies have reported rapid resolution of CRS symptoms with administration of monoclonal antibodies against IL-6 (siltuximab) and its receptor (tocilizumab; Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018). The FDA has approved the

Table 1. Previously Used Grading Systems for Cytokine Release Syndrome

	CTCAE v4.03	CTCAE v5.0	Lee Criteria	Penn Criteria	MSKCC Criteria	CARTOX Criteria
Grade 1	Mild reaction; infusion interruption not indicated; intervention not indicated	Fever, with or without constitutional symptoms	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Mild symptoms requiring observation or supportive care only (e.g., anti-pyretics, antiemetics, pain medication)	Temperature ≥ 38°C Grade 1 organ toxicity[b]
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Hypotension responding to fluids. Hypoxia responding to < 40% FiO_2	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to IV fluids or low dose of one vasopressor OR • Grade 2 organ toxicity[a]	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for IV therapies (not including fluid resuscitation for hypotension)	Hypotension requiring any vasopressors < 24 h Hypoxia or dyspnea requiring supplemental oxygen < 40%	Hypotension responds to IV fluids or low-dose vasopressor Hypoxia requiring FiO_2 < 40% Grade 2 organ toxicity
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrate)	Hypotension managed with one pressor. Hypoxia requiring ≥ 40% FiO_2	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥ 40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity[a] or grade 4 transaminitis	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Hypotension requiring any vasopressors ≥ 24 h Hypoxia or dyspnea requiring supplemental oxygen ≥ 40%	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥ 40% Grade 3 organ toxicity[b] or grade 4 transaminitis

Table 1. Previously Used Grading Systems for Cytokine Release Syndrome (cont.)

Grading system	CTCAE v4.03	CTCAE v5.0	Lee Criteria	Penn Criteria	MSKCC Criteria	CARTOX Criteria
Grade 4	Life-threatening consequences; pressor or ventilatory support indicated	Life-threatening consequences; urgent intervention needed	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity[a] (excluding transaminitis)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity[b] except grade 4 transaminitis

Note. NSAIDs = nonsteroidal anti-inflammatory drugs; LFTs = liver function tests; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure. Adapted from Lee et al. (2019).
[a]As per CTCAE version 4.03. [b]Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum alanine aminotransferase, aspartate aminotransferase, bilirubin level), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatologic (rash), or coagulopathy (disseminated intravascular coagulation; Lee et al., 2019).

use of tocilizumab for the treatment of severe or life-threatening CAR T-cell–induced CRS in adults and pediatric patients ≥ 2 years old based on a 69% response rate in patients with severe or life-threatening CRS (Le et al., 2018). Like CRS grading criteria, there is significant variability among centers for the use of tocilizumab for CRS, and there is no consensus on the optimal time for tocilizumab administration. Tocilizumab should be immediately available for grade 3 CRS or higher but can be considered for grade 2 CRS. The recommended dose for intravenous application is 8 mg/kg body weight for adults and 12 mg/kg body weight for patients < 30 kg body weight up to a maximum of 800 mg per dose with an interval between consecutive doses of at least 8 hours (Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018). Tocilizumab can also be provided to certain patients with grade 2 CRS who appear to be at risk for grade 3 CRS (Neelapu, 2019).

Corticosteroids are not suggested for the frontline treatment of CRS but can be administered in combination with tocilizumab among patients who have simultaneous CRS and neurotoxicity, or with CRS alone that does not respond to tocilizumab.

Alternative experimental options for patients who do not respond to tocilizumab or corticosteroids include blockade of TNFα (etanercept, infliximab), anankira (a recombinant and slightly altered form of the IL-1 receptor antagonist), alemtuzumab (monoclonal antibody towards CD52, T-cell depleting), ATG (anti-thymocyte globulin), ibrutinib (Bruton tyrosine kinase inhibitor), and cyclophosphamide (Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018). Overall, the management of CRS needs to follow a grade- and risk-adapted strategy based on careful monitoring and sound clinical judgment (Table 4; Neelapu, 2019).

Case Study Continued

On day +7, Mr. M continues to have fever. He is hypotensive again with a blood pressure of 78/50 and is treated for grade 2 CRS with a fluid bolus, one dose of tocilizumab 8 mg/kg, and a dose of dexamethasone 10 mg intravenously with normalization of his blood pressure. An echocardiogram shows a normal left ventricular ejection fraction of 60%. Later that evening he develops shortness of breath and oxygen desaturation, requiring ox-

Table 2. ASTCT CRS Consensus Grading

CRS parameter	Fever[a]	with	Hypotension	and/or[b]	Hypoxia
Grade 1	Temperature ≥ 38°C		None		None
Grade 2	Temperature ≥ 38°C		Not requiring vasopressors		Requiring low-flow nasal cannula[b] or blow-by
Grade 3	Temperature ≥ 38°C		Requiring a vasopressor with or without vasopressin		Requiring high-flow nasal cannula[b], facemask, nonrebreather mask, or Venturi mask
Grade 4	Temperature ≥ 38°C		Requiring multiple vasopressors (excluding vasopressin)		Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Note. Grade 5 CRS is characterized by death. Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading. Adapted from Lee et al. (2019).
[a]Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS (Lee et al., 2019).

ygen by face mask. A chest x-ray shows bilateral pleural effusions. He is transferred to the ICU for close monitoring. Due to the increased oxygen requirement, Mr. M is determined to have grade 3 CRS and is treated with another dose of tocilizumab 8 mg/kg and one dose of dexamethasone 20 mg intravenously.

Overnight he becomes hypotensive again, requiring vasopressor initiation with norepinephrine and vasopressin. Dexamethasone 10 mg intravenous every 6 hours is initiated for persistent grade 3 CRS. Mr. M gradually improves and is able to be taken off vasopressors 36 hours later, and his oxygen requirement decreases to 2 liters per nasal cannula. He continues to be monitored for CRS-associated organ dysfunction and supported appropriately.

DISCUSSION

As CAR T-cell therapy approaches become more widely utilized for patients with relapsed/refrac-

Table 3. Comparison of Available and Emerging CAR T-Cell Products

	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Vector delivery	Retrovirus	Lentivirus	Lentivirus
Costimulatory domain	CD28	4-1BB	4-1BB
Defined cells	None	None	Yes, CD4:CD8 fixed ratio
Lymphodepleting chemotherapy (×3 days)	Flu 30 mg/m² × 3 days Cy 500 mg/m² × 3 days	Flu 25/m² × 3 days Cy 250 mg/m² × 3 days or B 90 mg/m² × 2 days	Flu 30 mg/m² × 3 days Cy 300 mg/m² × 3 days
Number of patients enrolled (treated)	111 (101)	165 (111)	134 (114)
Median follow up	27.1 mo	19.3 mo	12 mo
Best ORR (CR)	82% (54%)	52% (40%)	80% (59%)
CRS onset (range)	2 days (1–12)	3 days (1–9)	5 days (2–12)
% CRS all grades	93%	58%	35%
% CRS grade 3 or 4	13%	22%	1%

Note. B = bendamustine; CR = complete response; Cy = cyclophosphamide; Flu = fludarabine; ORR = overall response rate; CR = complete response. Information from Chavez et al. (2019); Neelapu et al. (2017); Schuster et al. (2019).

Table 4. Recommendations for Management of CRS

ASTCT CRS Grade	Management
Grade 1 Fever with temperature ≥ 38°C but no hypotension or hypoxia	• Antipyretics and intravenous hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula	• Supportive care as in grade 1 • Intravenous fluid boluses and/or supplemental oxygen • Tocilizumab +/− dexamethasone or its equivalent of methylprednisolone (corticosteroids)
Grade 3 Fever with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask	• Supportive care as in grade 1 • Consider monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10–20 mg intravenous every 6 hours or its equivalent of methylprednisolone
Grade 4 Fever with hypotension requiring multiple vasopressors, excluding vasopressin and/or hypoxia requiring positive pressure, e.g., CPAP, BiPAP, intubation and mechanical ventilation	• Supportive care as in grade 1 • Monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1,000 mg/day

Note. BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure. Adapted from Neelapu et al. (2019).

tory B-cell malignancies, advanced practitioners will play a pivotal role in administering CAR T-cell infusions, and evaluating and managing CRS. Regular patient contact will enable advanced practitioners to assess the risk of CRS among patients who are being considered for CAR T-cell therapy. Knowledge about the FDA-approved and emerging CAR T-cell products will improve advanced practitioner ability to gauge CRS risk among individual patients. They can determine the likelihood of CRS toxicity based on patient characteristics (age, tumor burden), clinical trial, and real world data on CAR T-cell products, and the type of lymphodepletion used (Chavez et al., 2019). Advanced practitioners need to be alert about monitoring for the onset of fever among CAR T-cell infused patients and rule out confounding diagnoses of neutropenic fever, infection, and sepsis using optimal laboratory tests and clinical evaluations (Shimabukuro-Vornhagen et al., 2018).

When CRS is diagnosed, its severity can be determined using the ASTCT grading scale (Lee et al., 2019), which is used to guide treatment (Neelapu, 2019). Advanced practitioners should consider dosing of tocilizumab with grade 2 CRS and to ensure immediate tocilizumab administration in grade 3 or 4 CRS toxicity. Tocilizumab may be repeated every 8 hours for up to 2 doses. However, advanced practitioners need to be mindful of cases that are refractory to IL-6 blockade, which will require treatment with corticosteroids (Lee et al., 2014; Neelapu, 2019).

Patients must also be monitored for signs and symptoms of neurotoxicity such as encephalopathy, delirium, aphasia, focal deficits, and seizures. Patients with CRS and concurrent neurotoxicity may be treated with anti–IL-6 agents. Treatment for isolated neurotoxicity alone is corticosteroids. (Neelapu, 2019). Advanced practitioners may consider alternative experimental options such as TNFα inhibitors, anakinra, alemtuzumab, ATG, ibrutinib, or cyclophosphamide for patients who do not respond to both IL-6 blockade and immunosuppressant therapy (Riegler et al., 2019; Shimabukuro-Vornhagen et al., 2018).

CONCLUDING REMARKS

CAR T-cell therapy is a revolutionary and attractive approach for the treatment of otherwise incurable B-cell malignancies. However, the development of life-threatening CRS represents a major deterrent for universal application of CAR T-cell approaches. Management strategies for CRS are continuing to evolve, with best practice approaches relying on early recognition, accurate diagnosis, and optimal grading using the ASTCT criteria. Early and effective intervention with to-

cilizumab and supportive care have the potential to improve the prognosis of severe CRS, thereby leading to improved outcomes for patients receiving CAR T-cell therapy. Indeed, this involves close collaboration between different specialties and personnel, including advanced practitioners.

Disclosure

Ms. Adkins has served as an advisory board member for Celgene and Gilead/Kite.

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