



# Biology of Blood and Marrow Transplantation

journal homepage: [www.bbmt.org](http://www.bbmt.org)



## Cellular Therapy

# American Society for Blood and Marrow Transplantation Pharmacy Special Interest Group Survey on Chimeric Antigen Receptor T Cell Therapy Administrative, Logistic, and Toxicity Management Practices in the United States



Zahra Mahmoudjafari<sup>1</sup>, Kelly G. Hawks<sup>2</sup>, Angela A. Hsieh<sup>3</sup>, Dragos Plesca<sup>4</sup>, Katie S. Gatwood<sup>5</sup>, Kathryn A. Culos<sup>5,\*</sup>

<sup>1</sup> Department of Pharmacy, University of Kansas Hospital, Kansas City, Kansas

<sup>2</sup> Department of Pharmacy, Virginia Commonwealth University Health System, Richmond, Virginia

<sup>3</sup> Clinical Strategic Intelligence & Pharmacy, McKesson Specialty Health, The Woodlands, Texas

<sup>4</sup> Department of Pharmacy, Levine Cancer Institute, Atrium Health, Charlotte, North Carolina

<sup>5</sup> Department of Pharmaceutical Services, Vanderbilt University Medical Center, Nashville, Tennessee

### Article history:

Received 8 August 2018

Accepted 16 September 2018

### Key Words:

Cellular therapy

Chimeric antigen receptor (CAR)

T cell

Cytokine release syndrome (CRS)

CAR T cell–related encephalopathy syndrome (CRES)

Tisagenlecleucel

Axicabtagene ciloleucel

### A B S T R A C T

Administration of immune effector cell (IEC) therapy is a complex endeavor requiring extensive coordination and communication of various healthcare and administrative teams. Chimeric antigen receptor (CAR) T cells are the most established IEC therapy available. As of July 2018 two commercial gene therapy products, tisagenlecleucel and axicabtagene ciloleucel, have been approved by the US Food and Drug Administration. To gain insight into the infrastructure and practices across the country, the American Society for Blood and Marrow Transplantation Pharmacy Special Interest Group conducted an electronic survey on the current administrative, logistic, and toxicity management practices of CAR T cell therapy across the United States. This survey consists of 52 responses from institutions of varying sizes, most of which (~80%) had previous investigational experience with CAR T cell therapy. Absorbing the energy of this exciting new treatment has challenged hematopoietic cell transplant programs across the country to strengthen department infrastructure, develop new committees and policies, and implement significant education to ensure safe administration. With the variety of experience with CAR T cell therapy, we hope this survey can contribute to the existing published literature and provide support and consensus to established and developing IEC programs and practice guidelines.

© 2018 American Society for Blood and Marrow Transplantation.

## INTRODUCTION

Immune effector cell (IEC) therapy includes a variety of cell types used to modulate an immune response for therapeutic effect [1]. Chimeric antigen receptor (CAR) T cells are the most established IEC therapy available. As of July 2018 two commercial gene therapy products, tisagenlecleucel and axicabtagene ciloleucel, have been approved by the US Food and Drug Administration (FDA) [2]. Providing this innovative therapy is a complex endeavor requiring extensive coordination and communication of various healthcare and administrative teams. With guidance from the FDA, the foundation for the accreditation of cellular therapy and pharmaceutical manufacturers, institutions across the country are working rapidly to

establish IEC programs and develop new service lines in uncharted territory. Recently, authors from Memorial Sloan Kettering published their 8 essential tasks to define CAR T cell workflow, further shedding light on the complexity and challenges of safe CAR T cell administration [3]. To gain insight into infrastructure and practices across the country, the American Society for Blood and Marrow Transplantation (ASBMT) Pharmacy Special Interest Group conducted an electronic survey of its membership. Herein we present the results of the survey focusing on the current administrative, logistic, and toxicity management practices in the United States.

## METHODS

The ASBMT Pharmacy Special Interest Group Research Working Committee drafted an online survey that was reviewed by committee members before circulation. This survey was distributed electronically to all members of the Pharmacy Special Interest Group listserv, with 52 total responses. The Pharmacy Special Interest Group membership is not limited but is largely composed of pharmacists practicing hematology oncology at community and

*Financial disclosure:* See Acknowledgments on page 32.

\* Correspondence and reprint requests: Mrs. Kathryn A. Culos, PharmD, BCOP, Vanderbilt University Medical Center, 1301 Medical Center Drive, The Vanderbilt Clinic, 2639, Nashville, TN 37232.

E-mail address: [katie.culos@vumc.org](mailto:katie.culos@vumc.org) (K.A. Culos).

<https://doi.org/10.1016/j.bbmt.2018.09.024>

1083-8791/© 2018 American Society for Blood and Marrow Transplantation.

academic medical centers. Most responders (~80%) had previous investigational experience with CAR T cell therapy.

## ADMINISTRATIVE CONSIDERATIONS

### Product Approval

The survey addressed the processes of CAR T cell product approval for formulary addition and clinical data review for treatment plan and patient selection (Table 1). Forty-five of 52 surveyed institutions (87%) responded that each commercial CAR T cell product requires review and approval for formulary addition. Additionally, 31 of 52 surveyed institutions (60%) indicated that each patient being considered for CAR T cell therapy requires clinical data review and approval by an institutional committee before treatment. Regarding which institutional committees are responsible for approval of CAR T cell therapy for potential patients, 17 of 31 respondents (55%) reported use of a hematopoietic cell transplant (HCT) committee, 5 (16%) used an immunotherapy or cell therapy committee, 4 (13%) had an administration or high-cost drug committee, 3 (10%) reported a pharmacy and therapeutics committee, and 2 (6%) a breakthrough therapy committee.

This survey also investigated the involvement of pharmacy staff in establishing practice standards for the cellular therapy service. Twenty-nine of 52 surveyed institutions (56%) indicated that a cellular therapy committee had been established. Moreover, 34 of 47 respondents (72%) reported that a pharmacist representative is involved in the cellular therapy service or committee.

### Discussion

Considering the high cost of CAR T cell products and the risk associated with these therapies, the efficacy and safety data of CAR T cell products should be evaluated by an institutional committee before formulary addition. Furthermore, to afford careful consideration in selecting the appropriate CAR T cell therapy product based on established clinical criteria, clinical data of each patient being considered for CAR T cell therapy should be presented to a multidisciplinary team, such as an HCT or an immunotherapy committee, for review and discussion of treatment plan before initiating CAR T cell therapy. When appropriate, each patient case may also be reviewed by a high-cost drug or medical executive committee for care value assessment and coverage investigation.

From cell collection, processing, and infusion to postinfusion care, CAR T cell therapy requires the close collaboration of many departments within an institution. Building a dedicated multidisciplinary cellular therapy team and creating practice guidelines, efficient workflows, and clear communication are vital to ensure safe administration of CAR T cell therapy.

**Table 1**

Survey Responses for Institutional-Approval Process (N = 52).

Questions	Responses
Does each commercial CAR T cell product need formulary addition approval?	Yes: 45 (87%) No: 7 (13%)
Does each patient need approval by a committee? If so, what committee?	Yes: 31 (60%)- HCT Committee: 17- Immunotherapy or Cell Therapy Committee: 5- Administration or High-cost Drug Committee: 4- P&T Committee: 3- Breakthrough Therapy Committee: 2 No: 21 (40%)

P&T indicates Pharmacy & Therapeutics.

### Reimbursement

The survey inquired about the general practice of product reimbursement and process of financial investigation. The results were highly variable. A charge markup is applied to the cost of the CAR T cell product by 15 of 36 respondents (42%), whereas 10 (28%) did not report such an approach. However, 11 respondents (31%) stated that product billing is unclear or undetermined. When asked which department is responsible for CAR T cell therapy contract negotiation, 4 of 35 respondents (11%) stated pharmacy, 20 (57%) HCT department, 1 (3%) hematology department, 6 (17%) financial services, and 4 (11%) indicated unclear or undetermined. Similarly, regarding which department is responsible to ensure financial coverage for CAR T cell therapy and related care, 3 of 37 respondents (8%) stated pharmacy, 23 (62%) HCT department, 1 (3%) hematology department, 2 (5%) immunotherapy department, 7 (19%) financial services, and 1 (3%) reported unclear or undetermined.

### Discussion

Further complexities related to billing and reimbursement of CAR T cell therapy include cell collection, processing, infusion, and supportive care needed for this treatment modality. Additionally, these services may be provided in both the inpatient and outpatient setting. The high cost associated with CAR T cell therapy places hospital and pharmacy administration in a uniquely challenging situation because a conventional drug markup may not be applicable. Currently, there is inadequate reimbursement of CAR T cell therapy because of variable Medicare Severity Diagnosis-Related Groups assignment for CAR T cell cases, the lack of CAR T cell specific Medicare Severity Diagnosis-Related Groups or a New Technology Add-on Payment, and, most importantly, charge compression of the product acquisition cost. The Centers for Medicare & Medicaid Services (CMS) have been evaluating the possibility of allowing hospitals to use a cost-to-charge ratio of 1.0 when determining if a case qualifies for outlier payments [4]. This approach could lead to greater outlier payments and higher new technology add-on payments. Furthermore, the current absence of a National Coverage Determination (NCD) can potentially place institutions in a financially challenging situation with uncertain reimbursement. Commercial payers and Medicare Advantage Plan payers generally consider NCD necessary to ensure the existence of coverage for patients and to ensure the coverage eligibility criteria is evidence-based and consistent nationally. In May 2018 a National Coverage Analysis was initiated by the CMS and is expected to conclude in May 2019. An NCD has a strong potential to hinder access to CAR T cell therapy and may delay new uses of products; therefore, there are concerns related to using an NCD to resolve a financial contracting issue specific to payers. Professional organizations, including the ASBMT, have urged the CMS to provide clarification on the requirements for coverage of medically accepted uses of CAR T cell therapy and the intended scope of the NCD process. In August 2018 the CMS released its final rules on Medicare hospital inpatient prospective payment systems for fiscal year 2019 and declined to make immediate changes to the current payment structure until more clinical and cost experiences can be collected [5]. These changes included but are not limited to the creation of a pass-through payment; structural changes in new technology add-on payments for the drug therapy; changes in the usual cost-to-charge ratios used in rate-setting and payment, including those used in determining new technology add-on payments, outlier payments, and payments to inpatient prospective payment systems excluding cancer hospitals; and the creation of a new Medicare Severity Diagnosis-

Related Group specifically for CAR T cell therapy. The uncertainty of CAR T cell therapy reimbursement is likely to continue in the immediate future. Successfully navigating the complex and continuously changing coding and reimbursement process for CAR T cell therapy requires each institution to remain constantly engaged and informed about both national and regional policy decisions.

Understanding care coordination and billing challenges is 1 of the key components in a successful CAR T cell therapy program [6]. At this time the 2 manufacturers of the FDA-approved CAR T cell products suggest the following best practices in obtaining coverage for therapy: (1) ensure the internal financial team understands what is involved in the clinical treatment and monitoring of CAR T cell patients within their health system, (2) start clinical discussion early with top payers, (3) begin single-case agreement template discussion with preferred case rate negotiation before identifying patients, (4) ensure that contracting and patient financial service teams understand the urgency of patient treatment, and (5) have continuous follow-up with payers [7]. Finally, the financial implications resulting from including this therapy in the annual budget have to be given careful consideration, and institutions may have a different department responsible for budgeting this therapy (eg, pharmacy, cell processing laboratory, transplant program etc.).

### CAR T Ordering and Infusion

Forty-three survey participants responded to questions related to the administration of CAR T cell products. Nearly all respondents reported patients were cared for by the HCT or a combined hematology and HCT service (Figure 1). Administration of lymphodepleting chemotherapy varied among respondents, with 41.9% infusing outpatient and approximately one-third infusing inpatient. The remaining respondents noted the location for chemotherapy administration depended on the patient population, with many centers reporting that pediatric patients receive inpatient chemotherapy and adults receive therapy as outpatients. Some programs

have also established parameters to determine infusion location based on patient risk factors, such as comorbid conditions and risk for tumor lysis syndrome. Regardless of the site for chemotherapy administration, 76.7% of respondents noted that CAR T cell product infusion is performed in the inpatient setting. Approximately half of respondents described generating a pharmacy label for dispensing and administration documentation. Some of these respondents also noted labeling being used for the purpose of charge capture in medical billing.

The Risk Evaluation and Mitigation Strategy (REMS) requirement associated with CAR T cell products was another aspect of administration that was highly variable among survey respondents. Distribution of the required medication guide and wallet card is handled by a variety of members on the HCT team, such as a pharmacist, nurse, patient coordinator, nurse practitioner, or attending physician. Standard operating procedures for the REMS program encompassing the management of all CAR T cell products have been developed at most institutions (58.5%), whereas the remaining respondents are creating a standard operating procedure for each individual product (36.6%) or have not yet determined if they will create single or multiple standard operating procedures (4.9%).

### Discussion

The lymphodepleting chemotherapy administered before CAR T cell infusion is composed of fludarabine and cyclophosphamide and is generally considered a low toxicity regimen. Therefore, it is feasible to administer the chemotherapy in the outpatient setting for most patients. However, the infusion of the CAR T cell product itself may or may not be reasonable to administer in the outpatient setting depending on the product used as well as patient comorbidities and risk factors for cytokine release syndrome (CRS) and CAR T cell–related encephalopathy syndrome (CRES). Given that tisagenlecleucel has a lower rate of CRS and CRES compared with axicabtagene ciloleucel, there is consensus that it is appropriate to consider outpatient infusion for this product [8]. However, it is critical for CAR T cell programs who chose to perform outpatient infusion

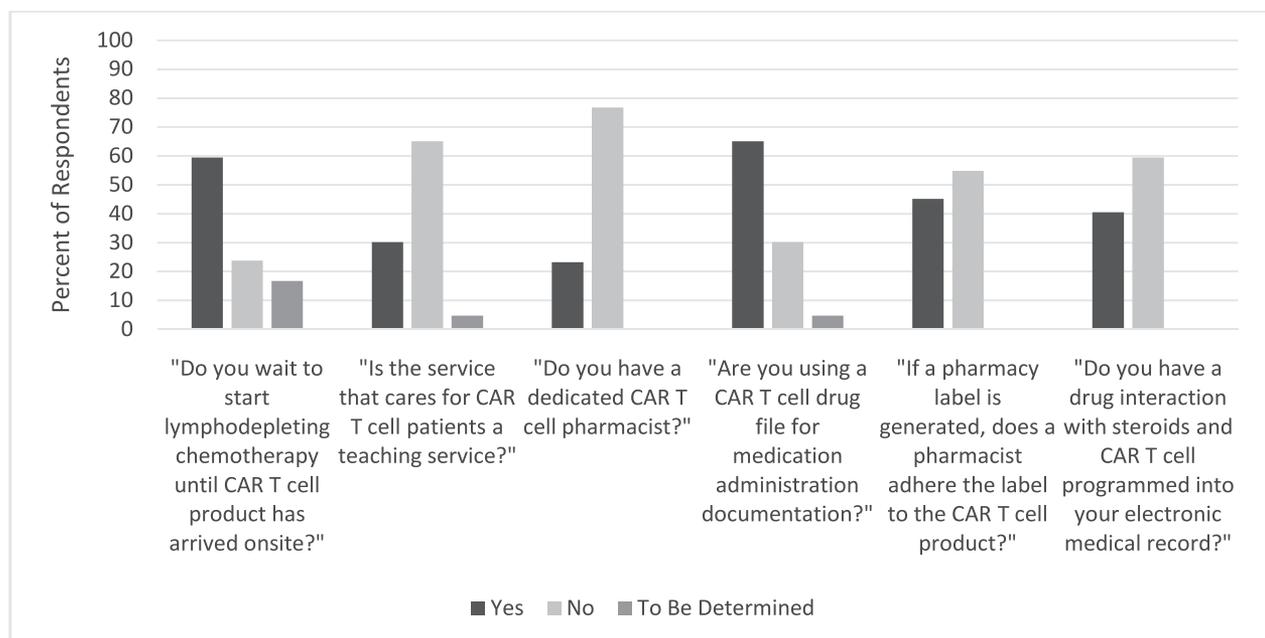


Figure 1. Survey responses of key CAR T administration practices.

to have a system in place to efficiently admit patients emergently if toxicities develop. It is also advisable for programs to create standard criteria for which patients will be considered eligible for outpatient infusion based on their risk factors for toxicity, such as baseline C-reactive protein level, age, burden of disease, and so on [9].

Development of standard procedures for REMS program management is crucial as more CAR T products enter the market. Subtle differences exist between the 2 currently available products' REMS program requirements. However, both available products require live training and completion of knowledge assessments for all practitioners who are involved prescribing, dispensing, or administering [10,11]. Institutional audits have also been conducted by manufacturers to ensure REMS compliance. CAR T cell programs should strive to create a standard operating procedure that will ensure the requirements of all commercial CAR T cell REMS programs are met to avoid confusion for frontline staff and maintain compliance.

### TOXICITY PROPHYLAXIS

IEC therapy presents a new toxicity profile to be closely monitored during and after cell infusion. The following section outlines the current practices for preventative strategies to minimize common and serious adverse events.

#### Seizure Prophylaxis

In our survey 31 respondents commented on the use of seizure prophylaxis. Most respondents (65%) offer prophylaxis, whereas 20% of respondents do not or initiate it only with signs of neurotoxicity. The final 15% of respondents administer seizure prophylaxis depending on the product and associated risk for CRES. Levetiracetam was the agent of choice in all survey respondents who indicated use of seizure prophylaxis; however, duration seemed to vary from institution to institution. Fifty-seven percent of respondents administer prophylaxis for less than 30 days and 43% administer prophylaxis for 30 to 60 days.

#### Discussion

There is currently no method to consistently identify patients at high risk of developing convulsive or nonconvulsive seizures after CAR T cell infusion. Expert opinion suggests considering seizure prophylaxis for patients receiving CAR T cell therapies known to cause CRES [8,12]. The prescribing information for tisagenlecleucel does not provide guidance on the use of seizure prophylaxis, and expert opinion suggests routine prophylaxis is not necessary [10,13]. For axicabtagene ciloleucel the prescribing information recommends considering seizure prophylaxis for patients who develop any grade 2 or higher neurologic toxicity after CAR T cell infusion [11].

If antiseizure prophylaxis is administered, it is important to select an agent with minimal potential to cause somnolence or confusion so patients can be optimally monitored for neurotoxicity. Levetiracetam (750 mg orally every 12 hours) has been identified as an ideal agent because of its favorable side effect profile and minimal drug interactions [12]. Additionally, cytokine levels, including IL-6 and tumor necrosis factor- $\alpha$ , are not impacted by levetiracetam [14]. These considerations have been universally adopted based on the results of our survey. Regarding optimal seizure prophylaxis duration, about half of survey respondents indicated use for less than 30 days, whereas the other half of respondents indicated use for 30 to 60 days. Thirty days would encompass the median time to onset and median duration of CRES with tisagenlecleucel (6 days and 6 to 14 days, respectively) and axicabtagene

ciloleucel (4 days and 17 days, respectively) [10,11]. Given that among patients who had neurologic toxicity, 88% and 98% occurred within 8 weeks after tisagenlecleucel and axicabtagene ciloleucel infusions, respectively, a longer prophylaxis period of 60 days could also be reasonable. Our survey did not query the management of patient's experiencing seizures after CAR T cell therapy. Expert opinion suggests a combination of benzodiazepines plus levetiracetam 500 mg i.v. bolus followed by maintenance dosing of 1000 mg i.v. every 12 hours for patients with nonconvulsive and convulsive status epilepticus [12].

#### Infection Prophylaxis

In this survey 30 respondents described their use of bacterial, viral, and fungal prophylaxis. Ninety percent of respondents reported using bacterial prophylaxis (96% with a fluoroquinolone and 4% with cefepime). Of respondents using bacterial prophylaxis, 96% discontinued at neutrophil recovery.

All survey respondents reported using viral prophylaxis (70% with acyclovir, 27% with valacyclovir, and 3% with either acyclovir or valacyclovir). The duration of antiviral prophylaxis varied among respondents, with 71% indicating a duration greater than 60 days, 18% indicating a duration less than 60 days, 7% indicating until CD4 count greater than 200 cells/mm<sup>3</sup>, and 4% indicating variability depending on the patient's indication.

Regarding fungal prophylaxis, 87% of survey respondents reported using antifungal prophylaxis and 13% did not. The most commonly used agent was fluconazole (92%), with 1 respondent each indicating micafungin and a mold-active azole antifungal. Most respondents (67%) discontinue antifungal prophylaxis at neutrophil recovery, with 29% continuing for greater than 60 days and 4% indicating a duration based on patient-specific characteristics.

Thirty-one respondents (60%) reported on their use of pneumocystis prophylaxis, with all but 1 respondent indicating a preferred agent. Of the 30 respondents providing agents of choice, 28 (93%) reported using sulfamethoxazole-trimethoprim and 2 (7%) reported using pentamidine. Duration of pneumocystis prophylaxis varied, with 56% of respondents continuing based on CD4 count, 26% continuing for 30 to 90 days, and 18% continuing for 91 to 180 days.

#### Discussion

Patients receiving CD19 CAR T cell therapies are at an increased risk of infection due to multiple factors. Presently, these therapies are approved for patients with relapsed or refractory hematologic malignancies and therefore present with poor immune function at baseline [15]. The lymphodepleting chemotherapy administered before CAR T cell infusion suppresses T cell function and immune response and can cause cytopenias and compromise mucosal barriers. Additionally, treatment of CRS and CRES with corticosteroids and/or IL-6 receptor monoclonal antibodies can further increase the risk of infection. Finally, B cell aplasia and hypogammaglobinemia may result from depletion of normal B cells expressing CD19.

Patient-specific characteristics should also be considered when assessing risk of infection. A report of 133 adult patients evaluated risk factors for infection within the first 90 days after lymphodepleting chemotherapy and infusion of CD19 targeted CAR T cells [13]. These risk factors include diagnosis of acute lymphoblastic leukemia, receipt of  $\geq 4$  prior treatment regimens, absolute neutrophil count  $< 500$  cells/mm<sup>3</sup> before CAR T cell infusion, receipt of higher CAR T cell dose ( $2 \times 10^7$  cells/kg), and severity of CRS.

**Table 2**  
Neutropenia and Infectious Complications for Approved CAR T Cell Therapies [9,10]

	Infection, All Grade	Infection, Grades 3-4	Neutropenia, Grades 3-4	Neutropenia not Resolved by Day +28	Febrile Neutropenia, Grades 3-4
Tisagenlecleucel (ALL)	55	33	Not reported	40	37
Tisagenlecleucel (BCL)			81	25	17
Axicabtagene ciloleucel (BCL)	38	23	93	15	36

Values are percents. ALL indicates acute lymphoblastic leukemia, BCL, B cell lymphoma.

These numerous risk factors for increased risk of infection translated into high incidences of infectious complications reported in clinical trials (Table 2).

Based on the high rate of neutropenia and infectious complications observed in clinical trials, infection prophylaxis should be offered to patients undergoing CD19 targeted CAR T cell therapies consistent with current guideline recommendations for cancer-related infection [16,17]. For example, both the Infectious Disease Society of America and the National Comprehensive Cancer Network recommend fluoroquinolone and antifungal prophylaxis for patients with an expected duration of neutropenia greater than 7 days. For CAR T cell patients receiving lymphodepleting chemotherapy with fludarabine, further consideration for antifungal and pneumocystis prophylaxis should be given because of the lymphocytotoxic effects of purine analogs [17]. The risk for these opportunistic infections may be further compounded if patients receiving fludarabine require corticosteroids after CAR T cell infusion. These recommendations were widely adopted among survey respondents, with ~90% administering bacterial and antifungal prophylaxis and 100% of respondents administering pneumocystis prophylaxis. Our survey did not query on time of initiation of pneumocystis prophylaxis. Because sulfamethoxazole-trimethoprim may cause significant myelosuppression, starting this agent after count recovery would minimize concern that it could increase the risk of neutropenia and neutropenia-related infection.

Use of antiviral prophylaxis was also universally reported in our survey. However, the duration of antiviral prophylaxis varied among respondents. This variability likely reflects the broad range of patients' baseline immune function when presenting for treatment and our understanding of immune-reconstitution after CAR T cell therapy. For example, in a patient presenting for CAR T cell therapy after allogeneic HCT, it would be important to comply with HCT guidelines recommending antiviral prophylaxis for 1 year after HCT [18].

Finally, although not addressed in our survey, because of concern for B cell aplasia and hypogammaglobulinemia, the prescribing information of both approved CAR T cell products recommends serum immunoglobulin monitoring and consideration for intravenous immunoglobulin replacement [10,11]. The duration of monitoring and the frequency for IgG replacement have not yet been determined. Some practices administer intravenous immunoglobulin when the serum IgG level is below 400 mg/dL; however, this practice has not been supported by clinical evidence [9]. Further, research is also needed to address the utility of repeating vaccine series upon B cell recovery. Obtaining titers for vaccine-preventable diseases may also aid in identifying patients who would benefit from repeating a vaccine series.

### Growth Factor

In our survey 28 respondents reported on use of growth factor support with varying practices. Forty-six percent of respondents use growth factor if allowed by product labeling, 29% never administer growth factor, 14% determine the use of

growth factor on a patient-specific basis, and 11% administer growth factor to all patients.

### Discussion

Recommendations on the use of growth factor after CAR T cell infusion vary, with some experts administering filgrastim as standard of care during periods of neutropenia and others recommending filgrastim only for patients with neutropenic fever [9,12]. Of particular importance, the prescribing information for tisagenlecleucel recommends avoiding use of myeloid growth factors, especially granulocyte-macrophage colony-stimulating factor, during the first 3 weeks after cell infusion or until CRS has resolved [10]. Although data are not provided to address this recommendation, it is likely based on the potential for myeloid growth factors to promote antigen-presenting cell function that could theoretically exacerbate the severity or incidence of CRS [19]. Prescribing information for axicabtagene ciloleucel does not comment on the use of myeloid growth factors [11]. Given the high rates of neutropenia and associated infectious complications in patients undergoing CAR T cell therapies and the theoretical concern for promotion of CRS with the use of growth factors, more studies are required to determine the safety of growth factors in this setting.

### TOXICITY TREATMENT

CRS and CRES are the 2 most commonly reported toxicities associated with axicabtagene ciloleucel and tisagenlecleucel. Symptoms can be mild and self-limited or can be life-threatening. Symptoms often can be nonspecific, such as fever, tachycardia, and malaise, but can also impact any organ system in the body [20]. Risk and severity of CRS are typically increased in patients with a high disease burden (>50% blasts in bone marrow), uncontrolled or accelerating tumor burden, active infections and/or inflammatory processes, increased age, and early onset of CRS [10,13]. Symptoms of CRES include headache, delirium, tremor, and seizures. Reported onset of CRS and CRES varies between the 2 products (Table 3), but the typical onset is within 2 weeks after cell infusion [9].

### Tocilizumab

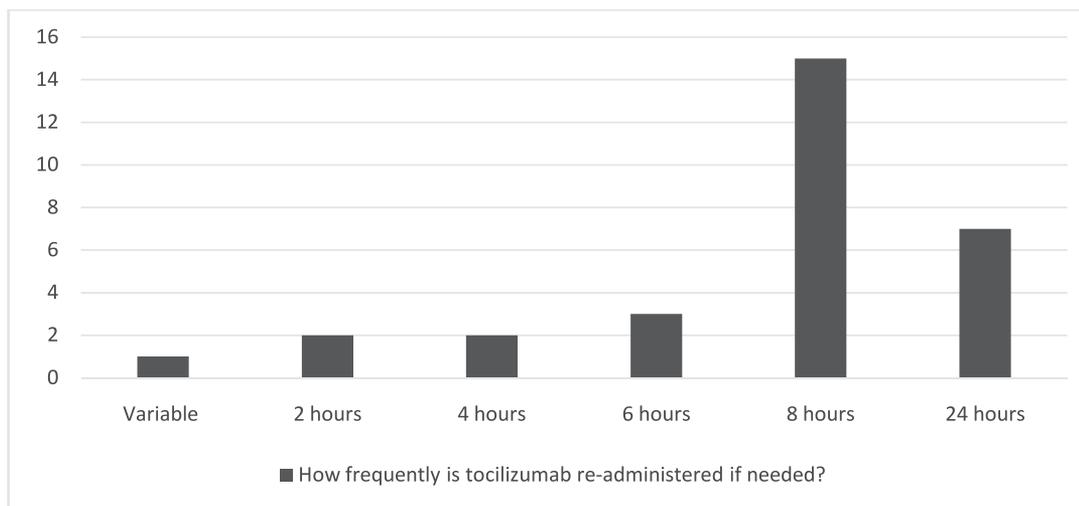
In our survey 30 respondents noted 8-mg/kg dosing of tocilizumab for adult patients and pediatric dosing for patients weighing less than 30 kg. One respondent noted dosing of 6 mg/kg.

Our survey also addressed frequency of tocilizumab dosing. Thirty respondents replied, with 15 noting a dosing frequency of every 8 hours (50%). Seven replied dosing every 24 hours (23%), 2 respondents every 4 hours (7%), 3 every 6 hours (10%), and 3 responded as little as every 2 hours and dosing was primarily dependent on the provider at the time of service (10%) (Figure 2). The maximum number of tocilizumab doses also varied between respondents. Of the 29 respondents to this question, 16 noted a maximum of 4 doses and 10 noted a

**Table 3**  
Median Onset of CRS and Neurotoxicity for Approved CAR T Cell Therapies [9,10]

	CRS		Neurotoxicity	
	Median Time to Onset (days)	Median Duration(days)	Median Time to Onset(days)	Median Duration(days)
Tisagenlecleucel (ALL)	3 (1-51)	8 (1-36)	6 (1-359)	6
Tisagenlecleucel (BCL)				14
Axicabtagene ciloleucel (BCL)	2 (1-12)	7 (2-58)	4 (1-43)	17

Values in parentheses are ranges.

**Figure 2.** Survey responses on frequency of tocilizumab readministration.

maximum of 3 doses, 1 noted a maximum of 1 dose, and 2 respondents had no defined limit.

One requirement of the REMS program for tisagenlecleucel and axicabtagene ciloleucel includes a stock of a minimum of 2 doses of tocilizumab in the inpatient pharmacy for each patient before CAR T cell administration. Therefore, a survey question was posed regarding the amount of tocilizumab stock on hand by milligrams. Responses varied, but most noted the minimum of 2 doses (1600 mg) per patient, and many highlighted that this stock was labeled as patient-specific stock. Other responses ranged from as low as 2400 mg to 9600 mg.

### Discussion

With the approval of tisagenlecleucel, tocilizumab was concurrently FDA approved for the management of CRS [21]. Tocilizumab is a humanized monoclonal antibody that is an IL-6 receptor antagonist. Traditionally, it has been used in the management of rheumatologic disorders but has also demonstrated efficacy in

decreasing CRS-related symptoms after administration of CAR T cells [22]. Tocilizumab dosing in the setting of adverse event management for these therapies varies based on the patients weight. The FDA-recommended dose is 8 mg/kg for adults (maximum, 800 mg) and 12 mg/kg for patients weighing less than 30 kg. Dosing is generally calculated using actual body weight and infused over 1 hour. Tocilizumab can be given for up to 4 doses with at least an 8-hour interval between consecutive doses [21]. In the clinical trials tocilizumab usage varied (Table 4). One study of patients with acute lymphoblastic leukemia and CRS found a median time to defervescence with tocilizumab of 4 hours and suggested administering tocilizumab every 4 to 8 hours depending on resolution of symptoms [23]. Most respondents in our survey dosed tocilizumab 8 mg/kg for adult patients every 8 hours as directed on the FDA-approved labeling and used maximum dosing of 4 doses.

Tocilizumab should be available for immediate administration within at least 2 hours per the REMS requirements

**Table 4**  
Tocilizumab Use for Approved CAR T Cell Therapies [22-24]

No. of patients with CRS	Tocilizumab Use			Additional Treatment (Corticosteroids)
	Total	1 Dose	2 Doses	
Tisagenlecleucel (ALL) (54/68 patients)	37 (69)	27 (50)	7 (13)	3 Doses 3 (6)
Tisagenlecleucel (BCL) (78/106 patients)	16 (21)	6 (8)	10 (13)	–
Axicabtagene ciloleucel (BCL) (102/108 patients)	49 (45)	Not reported	Not reported	Not reported

Values in parentheses are percents.

[10,11]. Institutions can have guidelines that are stricter, but this should be clearly defined in policies and procedures. Most respondents housed the REMS-required 2 doses per patient in the pharmacy. Some respondents noted these doses were labeled to be patient specific, whereas others maintained general stock.

### **Siltuximab**

In our survey 30 respondents completed the question regarding siltuximab as an option at their institution, with 18 replying yes (60%). Of these that responded yes, 6 (33%) replied use for second-line treatment and 9 (50%) responding for third-line treatment, and 3 (17%) replied that it could be used on a case by case basis if needed.

### **Discussion**

For CRS that is unresponsive to tocilizumab, siltuximab may be considered as an alternative, although currently no data are available on its efficacy. As of July 2018 siltuximab is not FDA approved for the treatment of CRS. Siltuximab is a human-murine chimeric monoclonal antibody that binds IL-6 directly versus tocilizumab binding to the IL-6 receptor [24–26]. There is some concern that IL-6 levels increase after administration of tocilizumab, contributing to an increased incidence of neurotoxicity [27]. This does not seem to be a concern with siltuximab, which is the rationale for its proposed benefit in tocilizumab-refractory cases. In our survey respondents uniformly agreed siltuximab should not be used for first-line treatment and should be reserved as a secondary or even third-line option. Dosing of siltuximab is generally 11 mg/kg over 1-hour intravenous infusion [28]. Currently, there are no published reports on the efficacy and safety of the use of siltuximab in this patient population and therefore caution is necessary for use. Finally, our survey did not specifically address the use of other T cell-ablating agents for refractory neurotoxicity associated with CAR T cell administration, and this remains an area of continued research.

### **Corticosteroids**

Twenty-nine respondents completed our survey with information regarding the use of steroids in this patient population. Fourteen (48%) use dexamethasone, 7 (24%) use methylprednisolone, 2 (7%) use hydrocortisone, and 6 (21%) responded “other” and further described that it was dependent on the severity of patient symptoms and whether the patient is experiencing CRS or CRES or both. No respondents use prednisone for this patient population.

### **Discussion**

Systemic corticosteroids have been used effectively to manage toxicities of CAR T cell therapies. They are generally reserved as second-line therapy after tocilizumab for symptoms of CRS because of the risk that they may inhibit CAR T cell persistence and antimalignancy efficacy [29,30].

In general, corticosteroids should be considered first-line treatment of neurotoxicity over tocilizumab because tocilizumab may not cross the blood–brain barrier and result in higher IL-6 levels in cerebrospinal fluid and be ineffective [31]. Dexamethasone may be preferred over methylprednisolone because of strong central nervous system penetration [32,33]. Dosing can be as frequent as every 6 hours and continued until toxicities have improved to grade 1 or baseline [9]. A taper regimen for corticosteroids is both institution and patient specific. Superiority of 1 agent over the other is not known at this time. This variance was consistent among our survey respondents.

The primary agent used was dexamethasone followed by methylprednisolone for more severe cases. Some respondents replied that the choice between the 2 agents depended on the severity of CRS or neurotoxicity. There is limited use of hydrocortisone or prednisone in this setting. Concurrent corticosteroids and tocilizumab can be considered for patients experiencing both CRS and neurotoxicity.

### **Toxicity Documentation**

Of the 28 respondents to this question, our survey found that 25 (89%) responded documentation of adverse events in a daily progress note. One respondent noted using a widget, and 2 responded “other” with a specific flowsheet developed in their electronic medical record system with subsequent grading in the provider's daily progress note.

### **Discussion**

At this time documentation of adverse events is mainly institution specific, but this remains an area of great opportunity. Centers studying CAR T cell therapy developed different grading scales, including the MD Anderson (Lee grading criteria) and the University of Pennsylvania (Penn grading criteria) [34]. Differences in these scales can lead to variation in how patients would be graded and potentially impact outcomes. Our survey did not specifically address what grading scale institutions use specifically; however, most of those surveyed document symptoms and grading of CRS and neurotoxicity in a daily progress note. Order sets and standardized documentation processes are still being developed at most centers both in the United States and Europe, although our survey specifically targeted practices in the United States [3,35]. As additional experience is gained and a standardized grading system for CRS and CRES is developed, more advanced technologic tools can be created and consistently used.

### **CONCLUSION**

The development and approval of CAR T cell therapy has added a novel treatment approach for cancer patients, rapidly moving into the standard of care setting. Absorbing the energy of this exciting new treatment has challenged HCT programs across the country to strengthen department infrastructure, develop new committees and policies, and implement significant education to ensure safe administration. We hope cancer centers benefit from the results of this survey because it details the current administrative, logistic, and toxicity management practices across the United States. Most importantly, with the variety of experience with CAR T cell therapy, we hope this survey can contribute to the existing published literature and provide support and consensus to established and developing IEC programs and practice guidelines.

### **ACKNOWLEDGMENTS**

The authors would like to thank the ASBMT Pharmacy SIG members for their time and participation in the survey.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

### **SUPPLEMENTARY DATA**

Supplementary data related to this article can be found online at [doi:10.1016/j.bbmt.2018.09.024](https://doi.org/10.1016/j.bbmt.2018.09.024).

## REFERENCES

- Foundation for the Accreditation of Cellular Therapy. Immune effector cell standards. Available at: <http://www.factwebsite.org/iecestandards/>. Accessed June 5, 2018.
- US Food and Drug Administration. Approved cellular and gene therapies. Available at: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm>. Accessed June 14, 2018.
- Perica K, Curran KJ, Brentjens RJ, et al. Building a CAR garage: preparing for the delivery of commercial CAR T cell products at Memorial Sloan Kettering. *Biol Blood Marrow Transplant*. 2018;24(6):1135–1141.
- American Society for Blood and Marrow Transplantation. Letter to CMS re: CMS payment models for chimeric antigen receptor T-cell (CAR-T) therapy [open letter]. Available at: <http://asbmt.org/blogs/user-admin/2017/09/15/letter-to-cms-payment-models-for-car-t-cell-therap>. Accessed September 20, 2018.
- Centers for Medicare & Medicaid Services. Medicare program; hospital inpatient prospective payment systems for acute care hospitals and the long term care hospital prospective payment system and policy changes and fiscal year 2019 rates; quality reporting requirements for specific providers; Medicare and Medicaid electronic health record (EHR) incentive programs (promoting interoperability programs) requirements for eligible hospitals, critical access hospitals, and eligible professionals; Medicare cost reporting requirements; and physician certification and recertification of claims. Available at: <https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-16766.pdf>. Accessed August 20, 2018.
- Centers for Medicare & Medicaid Services. National Coverage Analysis (NCA) tracking sheet for chimeric antigen receptor (CAR) T-cell therapy for cancers (CAG-00451N). Available at: <https://www.cms.gov/medicare-cover-age-database/details/nca-tracking-sheet.aspx?NCAId=291>. Accessed May 26, 2018.
- Farnia S. Money matters: CAR-T. Presented in part at the American Society for Blood and Marrow Transplantation BMT Tandem Meetings. Salt Lake City, UT.
- Neelapu SS, Tummala S, Kebriaei P, et al. Toxicity management after chimeric antigen receptor T cell therapy; one size does not fit 'ALL'. *Nat Rev Clin Oncol*. 2018;15:218.
- Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016;127:3321–3330.
- East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.
- Santa Monica, CA: Kite Pharma Inc.; 2017.
- 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.
- Teachey DT, Bishop MR, Maloney DG, et al. Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat Rev Clin Oncol*. 2018;15:218.
- Guenther S, Bauer S, Hagge M, et al. Chronic valproate or levetiracetam treatment does not influence cytokine levels in humans. *Seizure*. 2014;23:666–669.
- Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood*. 2018;131:121–130.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patient with cancer: 2010 Update by the Infectious Disease Society of America. *Clin Infect Dis*. 2011;52:e56–e93.
- NCCN Clinical practice guidelines in oncology. Prevention and treatment of cancer-related infections, version 1.2018. Available at: NCCN.org. Accessed May 10, 2018.
- Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143–1238.
- Mehta HM, Malandra M, Corey SJ, et al. G-CSF and GM-CSF in Neutropenia. *J Immunol*. 2015;195:13341–13349.
- Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188–195.
- Actemra (tocilizumab) [prescribing information]. San Francisco, CA: Genentech Inc, 2017.
- Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T-cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368:1509–1518.
- Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–448.
- Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Presented in part at the ASH Annual Meeting and Exposition, December 9–12, 2017, Atlanta, GA, Abstract 577.
- 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;377:2531–2544.
- Fitzgerald JC, Weiss SI, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med*. 2017;45:e124–e131.
- Chen F, Teachey DT, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. *J Immunol Methods*. 2016;434:1–8.
- Sylvant (siltuximab) [prescribing information]. Horsham, PA: Janssen Biotech Inc., 2015.
- Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med*. 2013;5:177ra38.
- Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6:224ra25.
- Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood*. 2008;112:3959–3964.
- Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinetics*. 2005;44:61–98.
- Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood*. 2015;125:4017–4023.
- Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with CAR T cell therapy tisagenlecleucel. *J Hematol Oncol*. 2018;11:35.
- Buechner J, Kersten MJ, Fuchs M, Salmon F, Jager U. Chimeric antigen receptor T-cell therapy. Practical consideration for implementation in Europe. *HemaSphere* 2018;(2):1.