Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Position Statement

Chimeric Antigen Receptor T Cell Therapy During the COVID-19 Pandemic

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A B S T R A C T

The SARS-CoV-2 coronavirus (COVID-19) pandemic has significantly impacted the delivery of cellular therapeutics, including chimeric antigen receptor (CAR) T cells. This impact has extended beyond patient care to include logistics, administration, and distribution of increasingly limited health care resources. Based on the collective experience of the CAR T-cell Consortium investigators, we review and address several questions and concerns regarding cellular therapy administration in the setting of COVID-19 and make general recommendations to address these issues. Specifically, we address (1) necessary resources for safe administration of cell therapies; (2) determinants of cell therapy utilization; (3) selection among patients with B cell non-Hodgkin lymphomas and B cell acute lymphoblastic leukemia; (4) supportive measures during cell therapy administration; (5) use and prioritization of tocilizumab; and (6) collaborative care with referring physicians. These recommendations were carefully formulated with the understanding that resource allocation is of the utmost importance, and that the decision to proceed with CAR T cell therapy will require extensive discussion of potential risks and benefits. Although these recommendations are fluid, at this time it is our opinion that the COVID-19 pandemic should not serve as reason to defer CAR T cell therapy for patients truly in need of a potentially curative therapy.

INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapy represents a paradigm shift in the management of pediatric B-cell acute lymphoblastic leukemia (ALL) and adult B-cell non-Hodgkin lymphomas (NHL) [1]. Two anti-CD19 CAR T-cell products are currently approved by the United States Food and Drug Administration (FDA) and other international regulatory agencies: axicabtagene ciloleucel (axi-cel; Yescarta®; Kite/Gilead) for the treatment of adult relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) [2], and tisagenlecleucel (tisa-cel; Kymriah®; Novartis Pharmaceuticals), both for adult R/R DLBCL [3] and pediatric R/R ALL [4]. Additional FDA approvals for DLBCL, mantle cell lymphoma, and myeloma are expected in the coming months. To better evaluate cellular therapy treatment strategies, investigators from 8 US academic institutions formed the CAR T-cell Consortium to pool resources to aid the evaluation and optimization of cellular therapy treatment. This group has previously presented data on the safety, efficacy, and resource utilization of cellular therapy in the commercial setting [5]. Through this collaboration, we strive

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to advance cellular therapy strategies to enhance patients' survival and quality of life.

The SARS-CoV-2 coronavirus (COVID-19) pandemic presents unprecedented challenges to the delivery of cellular therapy to patients with hematologic malignancies. These challenges extend to the delivery of potentially life-saving complex treatments, such as CAR T cell therapy. To harmonize opinions on the use and management of CAR T cell therapy during the COVID-19 pandemic, experts from the CAR T-cell Consortium convened to formulate consensus recommendations. In this report, we review the numerous facets of CAR T-cell treatment, including patient selection, delivery, and prioritization of resources during the current COVID-19 pandemic. Although each recommendation might not be uniformly applicable, it is paramount that each treatment facility carefully review internal policies and procedures, and modify and potentially adopt these recommendations as needed to best fit a center's needs.

Question 1: What are the resources required for the safe administration of cellular therapy during the COVID-19 pandemic?

In the setting of a pandemic or other major incident, one of the first steps most healthcare systems will take is to activate the hospital incident command system. Similarly, cellular therapy services should be able to quickly respond to a pandemic, or other major incident, through a centralized and coordinated response that takes into account the unique needs and priorities of the health system. Along with the clinical and logistical complexities inherent to cellular therapy, in the era of COVID-19, or a similar pandemic, additional anticipated challenges include staff shortages due to potential exposure, limitation of resources in personal protective equipment, hospital beds, intensive care unit (ICU) beds, and mechanical ventilation, as well as potential delays in shipment of cellular therapy products. Therefore, careful assessment, planning, allocation of resources, and utilization of existing infrastructure is essential. This mandates a coordinated effort between the cellular therapy program and their hospital's emergency planning group.

Treatment centers may potentially be affected at different times during a pandemic based on their geographic location, as well as concomitant impacts on supply chains. As a result, this outline might not apply to all treatment centers at the same time; however, it does provide general guidance. Given the complex nature of cellular therapy, it is critical to anticipate changes in healthcare resources as the COVID-19 pandemic rapidly evolves. Once the chemotherapy and/or CAR T cell infusion has been initiated, the process cannot be aborted.

Table 1 provides an overview of the resources required to perform CAR T cell therapy and potential disruptions as a consequence of the COVID-19 pandemic.

Practical considerations for safe administration of CAR T cell therapy in light of these disruptions include:

- Establish a triage algorithm to delay and/or cancel as many CAR T-cell activities as possible. Preferentially select patients who are most likely to benefit, who have no effective alternative treatment options, and in whom the risk of CAR T-cell toxicities is lower.
- Apheresis and cell lab staff: Ensure dedicated and adequate cell lab staff for product receipt, processing, and infusion.
- Outpatient treatment: Prioritize products that can be given on an outpatient basis. For patients treated in the outpatient setting, ensure appropriate follow-up and availability for rapid evaluation in those who experience toxicity.
- Initiate lymphodepleting chemotherapy only following CAR T cell product receipt onsite, given the potential impact on supply chain operations.
- Inpatient resources: encourage virtual team rounding and perform one examination per patient per day, if appropriate. In selected patients in whom an exam is unlikely to inform assessment and management, consider forgoing the physical exam.
- Housing: Ensure a clear plan as to where patients will be housed during the immediate 4 weeks surrounding their CAR T cell therapy, if not returning home.
- Outpatient follow-up care: Perform outpatient visits via telemedicine, when feasible.
- Radiology and laboratory services: Minimize all nonessential lab work and radiology appointments.
- Pharmacy: Preferentially use oral over parenteral administration when appropriate.
- Pandemic-specific considerations: Ensure the continuous availability of a cellular therapy team member with the capacity to respond to COVID-19 issues. Establish a center-specific workflow for COVID-19-positive patients. Consider creating COVID-19-specific inpatient units with dedicated rounding teams.

Table 1
CAR T Cell Resources and Potential Disruptions During a Pandemic

Resources	Potential Disruptions
Apheresis and cell processing lab	Staff shortages
Shipping/logistics	Air travel restrictions
Manufacturing	Staff shortages, site closures, limited capacity
Hospital capacity	Lack of availability
ICU capacity	Lack of availability
Blood bank	Blood and platelet shortages
Laboratory testing	Staff and reagent shortages
Radiology	Staff shortages, lack of availability, need for additional visits
Pathology	Staff shortages, sample processing
Caregiver	Caregivers may not be able to travel or are unavailable; restrictive hospital visitor policy
Housing	Local housing closures

A multidisciplinary team approach is essential to orchestrate appropriate adjustments to ensure the best outcome for patients while protecting the safety of health care professionals.

Question 2: Should the current COVID-19 pandemic determine cellular therapy utilization?

CAR T cell therapy has brought about unprecedented responses in patients with R/R DLBCL and ALL. The rate of complete response is approximately 40% to 54% in DLBCL and 81% in ALL. Most remissions are minimal residual disease-negative and sustained without further interventions with a median follow-up now exceeding 2 years and a follow-up of >6 years in many cases. Given this long follow-up, and because most relapses occur by 6 to 12 months [2–4], we believe many of the patients previously destined to die of these highly refractory diseases have indeed been cured.

However, CAR T cell therapy is associated with significant toxicities, including prolonged cytopenias, cytokine release syndrome (CRS), and neurotoxicity [2–6]. Anti-CD19 CAR T cells may result in prolonged B cell aplasia with the associated inability to mount antibody responses necessary for numerous illnesses, but especially relevant with COVID-19 [7–9]. Furthermore, many CAR T cell recipients are treated as inpatients to facilitate intensive monitoring due to the severity and rapidity of onset of CRS and neurotoxicity and frequent need for ICU care [5].

It is acknowledged that CAR T cell therapy requires intensive and precious resources, necessitating significant logistical planning [10]. The sudden emergence of the COVID-19 pandemic is a threat to disrupt the delivery of cellular therapy. In preparation for this surge of virally infected patients, hospitals worldwide have instituted measures to defer multiple patient care interventions, including such treatments as autologous stem cell transplantation for multiple myeloma. With the COVID-19 pandemic, travel is risk-laden and constrained. Local housing, such as the American Cancer Society Hope Lodges, and many hotels are now closed. Visitor policies, including caregivers, are highly restrictive, and hospital resources, particularly those involving intensive care support, are experiencing critical shortages. These circumstances dictate that healthcare providers must be good stewards of limited resources and make very challenging and difficult choices in the utilization of our resources.

Given that CAR T cells are potentially curative for patients with an otherwise dismal prognosis [11–14], we believe that centers should continue to offer CAR T cells for patients with R/R DLBCL and ALL using appropriate selection criteria and strict infection control precautions. In light of the rapidly evolving COVID-19 pandemic, institutions are urged to develop strategic triage algorithms to facilitate continued delivery of potentially life-saving treatments while balancing unique risks.

The cellular therapy community can help in this regard by continuing to identify prognostic factors that may help guide decisions regarding offering CAR T cell therapy, such as determination of pretreatment disease bulk, assessment of performance status, review and identification of preexisting organ comorbidities, and use of serum biomarkers for guidance, such as serum lactate dehydrogenase (LDH). Medical teams can also develop algorithms focused on inpatient or outpatient delivery according to institutional resources and needs. Therapeutic decision making regarding cellular therapy product selection also may be driven by resource utilization demands; efforts to manage patients as much as possible in the outpatient setting to preserve inpatient resources should be considered. Other considerations include early intervention to attenuate CRS and neurotoxicity and prophylactic/preemptive strategies to prevent infection. A proposed algorithm for optimal patient selection is discussed in questions 3 and 4 below.

Delaying cellular therapy as a consequence of the COVID-19 pandemic is not a realistic option for the overwhelming majority of patients with R/R DLBCL and ALL, given concerns regarding disease progression and patient demise. Furthermore, noncellular therapy strategies in these patients are unlikely to be durable and are typically associated with significant immunosuppression, risk for infectious complications, potential hospitalizations, and the need for advanced supportive care.

Another relevant consideration in this population is the wide variety of cellular therapy clinical protocols. During the COVID-19 pandemic, it seems prudent to place on hold phase I trials designed primarily to demonstrate safety. Conversely, phase II trials, which may offer substantial long-term benefit and the possibility of cure, should be considered essential and continue during this challenging time, if feasible. Studies of early intervention with CAR T cells as part of first-line therapies, or phase III studies comparing CAR T cells with standard of care options, such as autologous stem cell transplantation, remain of unproven benefit and are best placed on hold for now. It is advisable to continue enrollment in trials aimed at mitigating toxicity through the use of novel CRS and neurotoxicity prevention strategies, which may offer life-saving therapy while potentially minimizing resources.

The decision to pursue therapy for an underlying medical condition is always dictated first by an analysis of the safety and efficacy of a particular therapy, balanced against the natural history of the treatable illness. Treatment should be undertaken with clear upfront identification of goals of care. In light of the COVID-19 pandemic, the decision to proceed with treatment will require dedicated discussions of the risks and benefits in an effort to characterize and outline the uncertainties of the near future. Therefore, very cautious continued application of this treatment option should proceed at approved treatment centers.

Question 3: How do you approach patient selection for cellular therapy in R/R aggressive B-NHL in the era of COVID-19?

In line with the FDA label, we recommend offering anti-CD19 CAR T cell therapy for patients with R/R aggressive B cell lymphoma after failure of two or more prior lines of therapy [15,16]. During the COVID-19 pandemic, it is imperative to delineate criteria to identify optimal therapeutic candidates who may achieve meaningful remission, as well as those at potentially lower risk of toxicity, to minimize resource utilization. The pivotal phase II studies revealed that many of the traditional patient- and disease-specific characteristics associated with poor outcomes with chemotherapy-based treatment were not poor prognostic features in the setting of CAR T cell therapy. These include double- or triple-hit features, lymphoma subtype (germinal center or activated B cell-like), international prognostic index, and age >65 years [2,3]. Although tumor bulk was not significantly different between responders and nonresponders, there was a trend toward a benefit among those with lower tumor bulk in both studies. These prospective trials restricted eligibility to those with good performance status and limited comorbidities.

Real-world data suggest that approximately one-half of patients treated in the United States with axi-cel or tisa-cel would have characteristics excluding them from the pivotal phase II studies [5,17,18], yet early efficacy and toxicity appear comparable to the pivotal trials. Multivariate analyses of patients treated with commercial axi-cel identified poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status >2) and elevated LDH before lymphodepleting chemotherapy as being strongly associated with inferior progression-free survival and overall survival [17]. Although tumor bulk has not been consistently associated with poor efficacy outcomes among commercial CAR T cell recipients, it has been associated with higher rates of acute toxicity [17,19,20]. Performance status (ECOG >2) and elevated LDH may be surrogates of rapid tumor growth and identify patients at high risk of CAR T cell failure. In light of these characteristics and given the constrained resources and uncertain therapeutic environment during the COVID-19 pandemic, we suggest deferring these patients from CAR T cell therapy.

Advanced age (>65 years) has not been associated with outcomes following CAR T cell therapy. The pivotal phase II studies included patients age >65 (accounting for approximately 25% of

the study population). These trials have not reported comorbidities or functional status among this population, and more data are needed to address patient selection among the elderly. Real-world outcomes suggest elderly patients do as well as younger patients when identified by age alone [17,21]. Careful consideration of functional status and comorbidities is critical when contemplating cellular therapy in patients of advanced age during the COVID-19 pandemic.

In summary, patients with R/R aggressive B-NHL with preserved performance status (ECOG $\leq$2), limited comorbidities (cardiac, renal, hepatic, and bone marrow reserve), and tumor kinetics that afford the necessary time to undergo leukapheresis and CAR T cell manufacturing should be considered for cellular therapy at this time. As capacity and resources to provide cellular therapy fluctuate based on the evolving pandemic, we recommend considering more restrictive eligibility criteria when considering cellular therapy.

Question 4: How do you approach patient selection for cellular therapy in R/R ALL in the era of COVID-19?

Tisa-cel is FDA-approved for patients with R/R ALL up through age 25 years [16]. For centers able to access this commercial therapy, the general approach at this point in the pandemic is to regard this as life-saving therapy and to proceed with treatment. Considerations for access include ICU bed availability and availability of tocilizumab, as required by Risk Evaluation and Mitigation Strategies (REMS), for CRS. In pediatric centers, there is currently less of a bed shortage as centers have focused on decreasing the inpatient census in anticipation of the pandemic peak. Given that few children are currently being admitted with COVID-19, the focus has shifted to staff availability in pediatric hospitals. Several adult centers are providing this therapy in the 18- to 25-year age group, although ICU bed availability may remain a relevant concern. In such cases, it may be practical to transfer those patients to a pediatric center with more healthcare resources.

Although CRS rates are higher in ALL compared with DLBCL [3,4], recent analysis of current trial data as well as real-world data is reassuring. Myers et al [22] looked at ICU admission rates over time, seeing rates drop from 40% to 13% over a four-year period. Similarly, high grade (grade 3-4) CRS rates seen in the ELIANA registration trial for tisa-cel were 48%, compared to 14% during recent commercial use [23]. Reasons for lower rates of severe CRS may include earlier referral patterns, where the proportion of refractory patients with high disease burden may be lower. Additionally, earlier CRS intervention with tocilizumab may play a role. A recently published prospective trial of preemptive tocilizumab administration met its predefined study endpoint of 1/3 reduction in grade 4 CRS in patients with a high disease burden, suggesting that earlier CRS management might reduce the risk of severe CRS [24]. These lower ICU admission rates make it more practical to consider tisa-cel in R/R ALL, especially given potential concerns about ICU bed availability.

In the era of COVID-19, it would be reasonable to select patients with lower disease burden with concomitantly lower CRS risk. However, in ALL, the disease burden that is most predictive of CRS is that which is measured at the end of lymphodepleting chemotherapy [4], at which point the patient will go immediately to CAR T cell infusion. Since this is somewhat unpredictable, it is difficult to select patients on this basis. On the other hand, a strong case could be made for critically assessing the risk for toxicity in patients with refractory and accelerating disease, where the risk/benefit ratio might not be favorable.

Question 5: How do certified treatment centers support cellular therapy patients during the COVID-19 pandemic?

The COVID-19 pandemic has caused significant constraints globally in the delivery of cellular therapy. This includes partial closures of outpatient clinics, decreased infusion suite capacity, and a resultant decrease in clinical staff. Closure or reduction in outpatient housing resources has led to additional challenges in how cellular therapy is currently provided. Strict hospital and clinic visitation policies and updates to institutional caregiver agreements to remain compliant with current social distancing mandates have further compounded the burden on caregivers.

Outpatient CAR T cell administration should be considered whenever feasible to reduce inpatient healthcare utilization [25]. Admittedly, this might not be practical to uniformly institute in all centers in light of current resources and viral burden in the surrounding community. Consequently, inpatient admission may be more appropriate at certain centers.

As the pandemic rapidly evolves, clinicians must monitor the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines for COVID-19 management in cellular therapy patients [26]. The treatment of COVID-19 in a CAR T cell recipient should be done in coordination with infectious disease experts and based on recent Center for Disease Control and Prevention (CDC) and ASTCT guidelines. There are currently no proven therapies available for the treatment of immunocompromised patients with COVID-19. Adjunctive therapy may be considered, although it is important to recognize that the clinical benefit remains unknown. Each center will likely be, and should be, encouraged to consider these patients for available clinical trials. We encourage programs to work with their infectious disease and pulmonary colleagues to ensure that this patient population is not excluded from trials enrolling COVID-19-positive patients.

Given the potentially detrimental effects of long-term steroid use on COVID-19 outcomes [27–29], steroids should be used judiciously in the management of CRS/neurotoxicity in COVID-19-positive patients. CAR T cell recipients are considered severely immunocompromised as a result of heavy pretreatment, lymphodepleting chemotherapy, neutropenia, hypogammaglobulinemia, and the use of steroids to treat CAR T-cell toxicities. Vulnerability spans both opportunistic and community-acquired infections, including COVID-19. Animal studies suggest that neutropenia and defects in innate immunity markedly increase the lethality of severe viral lung infections [30]. We recommend continuing institutional supportive care measures, such as the use of G-CSF for prolonged neutropenia along with standard antiviral, antifungal, and antimicrobial prophylaxis.

In line with REMS program requirements for each cell therapy product, patients should continue following with certified treatment centers for their immediate post-CAR T cell therapy. These visits must be adapted to harmonize with current ASTCT and CDC guidelines along with governmental mandates. Centers should consider adopting HIPPA-compliant telemedicine platforms to facilitate continuity of care while mitigating exposure risk. Additional principles aimed to guide care both pre- and post-CAR T cell therapy during the COVID-19 pandemic are outlined in Table 2.

Interim guidelines for COVID-19 management have been developed by the ASTCT to help guide management in cellular therapy and stem cell transplantation recipients [26]. These recommendations must be adapted to best fit each center's needs, taking into consideration current resources and workflow. It is a testament to the astounding pace of change

Table 2
Recommended Guidance to Manage CAR T Cell Recipients at Risk for COVID-19

	Measures to Mitigate the risk of COVID-19 or Its Complications [26]
Pre-CAR T cell	
Screening measures	Assess for signs/symptoms of COVID-19 at relevant time points, including before apheresis, before lymphodepleting chemotherapy, and before CAR T cell infusion
	Consider laboratory PCR testing for COVID-19 for all patients (including asymptomatic) within 48-72 hours before apheresis
	Perform laboratory PCR testing for COVID-19 on all patients (including asymptomatic) within 48-72 hours of lymphodepleting chemotherapy and within 7 days of CAR T cell infusion
	Consider repeating laboratory PCR testing for COVID-19 within 72 hours of CAR T cell infusion to enhance sensitivity and ensure no interim infection
	Once routinely available, consider serologic testing for COVID-19 seroconversion
	Use multiplex PCR to rule out other viruses for symptomatic patients
Preventive measures	Limit in-person visits and substitute with telemedicine visits, as appropriate
	Ensure patient access to a thermometer and other vital sign monitoring equipment
	Patients to use facemasks in public, including at healthcare facilities
Post-CAR T cell	
Care delivery	Limit in-person visits after day +7, but continue close monitoring via telemedicine, as feasible
	Encourage caregiver participation
Education	Provide education to caregivers about vital sign monitoring and ICANS questionnaires to log daily following hospital discharge/transition to outpatient care
	Establish a contingency plan for CAR T cell recipients who present with fever and/or COVID-19
Supportive care	Consider G-CSF for periods of prolonged neutropenia after CAR T cell therapy
	Consider thrombopoietin mimetics for severe prolonged thrombocytopenia after CAR T cell therapy to limit transfusion needs and clinic visits
Infection prophylaxis	Antimicrobial prophylaxis during periods of neutropenia
	Antiviral prophylaxis for HSV and VZV
	Antifungal prophylaxis with a mold-active agent for patients with >7 days of high-dose steroids or neutropenia >14 days
	PJP prophylaxis with bactrim, dapsone, or atovaquone. Consider avoiding pentamidine during the COVID-19 pandemic
IVIG	Prophylactic IVIG is not currently recommended to prevent COVID-19
	Consider IVIG to prevent other infections if IgG <400 mg/dL
PUI/COVID-19-positive and CAR T cell therapy	Delay T cell apheresis, lymphodepleting chemotherapy, and/or CAR T cell infusion at least 14 days from symptom resolution, depending on clinical course
	Consider repeat laboratory PCR testing for COVID-19-positive patients after 14-day delay

ICANS, immune effector cell-associated neurotoxicity syndrome; HSV, herpes simplex virus; VZV, varicella zoster virus; PJP, *Pneumocystis jiroveci* pneumonia; IVIG, intravenous immunoglobulin; PUI, person under investigation.

associated with the pandemic and our understanding of the COVID-19 infection that guidelines may continue to rapidly evolve.

At present, we recommend COVID-19 testing at various time points during the CAR T-cell treatment process. Testing within 48 to 72 hours of leukapheresis may be considered, based on institutional guidelines, although this practice is not currently adopted at all centers. In addition, COVID-19 testing should be performed within 48 to 72 hours of lymphodepleting chemotherapy and 7 days of CAR T cell infusion. A second test may be considered within 72 hours of CAR T cell infusion to enhance sensitivity and ensure that no interim infection has occurred, given that viral infections (COVID-19 or otherwise) may potentiate CRS [31]. The frequency and timing of testing will be dependent on the availability and turnaround time of the COVID-19 assay, which is a rapidly changing and improving resource.

When making therapeutic decisions for COVID-19-positive patients, clinicians must balance the risk of delaying CAR T-cell treatment against the risk of progression of the underlying disease. We suggest delaying patients who test positive for a minimum of 14 days from symptom resolution, if feasible, with consideration of interim testing. Whether repeat testing at the 14-day milestone will predict future illness is unclear. After a 14 day delay, options include proceeding with cellular therapy, retesting, and, if positive, considering chest imaging before proceeding or further treatment delays. Proceeding with CAR T cell therapy in an asymptomatic COVID-19-positive patient or in a patient recovering from COVID-19 should be done in collaboration with local infectious disease colleagues and in accordance with current CDC and ASTCT guidelines.

Question 6: How do you use and prioritize tocilizumab in the era of COVID-19?

Tocilizumab (Actemra®; Genentech), a recombinant monoclonal antibody to the IL-6 receptor, has become the mainstay in management of patients experiencing advanced (grade >2) CRS after CAR T cell therapy [32–35]. FDA approval of tocilizumab was granted based on retrospective data demonstrating that the majority of patients with severe or life-threatening CRS responded to treatment with 1 or 2 doses [36]. Since regulatory approval, there has been a shift toward earlier intervention with tocilizumab in light of data showing a decrease in the severity and duration of CRS without a signal of reduced CAR T cell efficacy [33–35,37]. There are a growing number of anecdotal reports of a possible benefit of tocilizumab in patients with severe respiratory symptoms from COVID-19 [38–40]. Indeed, there are accounts of tocilizumab reducing the duration and severity of COVID-19 symptoms and even permitting weaning from ventilatory support [39]. This has led to the initiation of several clinical trials and the off-label use of tocilizumab in symptomatic COVID-19 patients. This raises a concern that the supply of tocilizumab may become limited, prompting rationing among patients with COVID-19 and patients with other FDA-approved indications.

In the face of such a challenge, we recommend that centers continue to follow REMS guidelines as outlined on the package inserts and have at least 2 doses of tocilizumab available for each patient before CAR T cell infusion. In addition, we recommend strongly considering the practice of early tocilizumab use at the onset of grade 2 CRS. Patients undergoing CAR T cell therapy are receiving potentially life-saving treatment; therefore, it is paramount to ensure the availability of tocilizumab to mitigate serious toxicity and the need for advanced supportive care measures. Thought has been given to reducing the

dose of tocilizumab in the absence of adequate studies to determine optimal dose and frequency in CRS. Early phase I and II trials of tocilizumab demonstrated efficacy and significant declines in surrogate inflammatory markers with doses as low as 4 mg/kg [41,42]; however, subsequent pharmacokinetic studies revealed the observed mean maximum concentration of tocilizumab after the first dose was 41% lower in patients with CRS than in patients with systemic juvenile idiopathic arthritis, suggesting faster clearance of tocilizumab in patients experiencing CRS [36]. Therefore, we would not recommend altering the FDA-approved dose at this time. We do, however, recommend that no more than 2 doses of tocilizumab be administered per patient, because the overwhelming majority of patients with grade >3 CRS in the FDA cohorts responded by the second dose. It is surmised that responses may be even higher with early administration. When managing CRS, it is imperative that treating centers be mindful of the potential for limitations in tocilizumab supply. Although many clinical trials of unproven benefit are on hold during the COVID-19 pandemic, we believe that rational studies of CRS prevention and treatment should continue because they may provide significant advantages to patients by improving safety, limiting the need for scarce intensive care support, and preserving a possibly limited supply of tocilizumab. We acknowledge that these assessments and recommendations are fluid and may require modification as tocilizumab availability changes.

Question 7: How can certified treatment centers collaborate with referring oncologists to facilitate care in the era of COVID-19?

Despite the COVID-19 pandemic, patients will continue to present with R/R DLBCL and ALL. Deferral of procedures and surveillance imaging due to social distancing mandates may cause patients to present with more advanced or symptomatic disease requiring immediate therapy. The risks related to contracting COVID-19 are not trivial in elderly individuals, in whom mortality upward of 15% to 20% has been reported [43]. Nevertheless, CAR T cell therapy provides a potential for cure when limited or no other options are available. In light of these facts, continued CAR T cell referrals are appropriate for patients with R/R disease.

Open lines of communication are key to maintaining collaboration between community oncologists, who provide the bulk of our referral base, and certified treatment centers. Unfortunately, social distancing induced by the COVID-19 pandemic has led to a decrease in outpatient visits and complicated referral of patients to treatment centers. We recommend the adoption of telemedicine to facilitate timely consultative care, mitigate travel constraints, and bridge the social distancing gap. Indeed, it is possible that telemedicine will actually speed consultations and limit unnecessary travel for patients obviously ineligible or inappropriate for CAR T cell therapy.

Although COVID-19 has impacted the collaboration between community oncologists and cellular therapy treatment centers, problems can be minimized by following specific guidelines and addressing relevant barriers. Important considerations to mitigate exposure include, when possible, early transition of care to their referring oncologist in communities not as heavily affected by the pandemic. Such measures can alleviate pressure on constrained healthcare resources and optimize care delivery to other high-acuity patients. Other strategies to mitigate exposure include providing referring providers with a detailed overview of the cellular therapy treatment course, highlighting the expected duration of care at the certified treatment center, and expected date of transition back to their community. Similarly, treating institutions should formulate a long-term care plan to help guide continued management by community oncologists. To comply with pandemic-necessitated travel restrictions, efforts should be made to limit in-person visits to care centers. During the pandemic, physicians need to consider forgoing routine surveillance procedures, as appropriate, in patients in complete remission and without clinical concern for relapse.

Late complications remain a relevant concern in this population, with as many as 61% of CAR T cell recipients suffering from late infectious sequelae [44]. Treating clinicians should provide supporting documentation to permit these vulnerable patients to avoid work, school, and similar obligations while there is a continued risk of community transmission of the infection. CAR T cell recipients with new respiratory symptoms should be screened for COVID-19 along with evaluation for common bacterial and fungal etiologies [44–46]. CAR T cell recipients with confirmed infection should be managed locally, if safe and feasible, to prevent overburdening treatment centers and to limit viral transmission.

CONCLUSION

As of April 5, 2020, there were >300,000 confirmed cases of COVID-19 in the United States with >8000 deaths, recognizing that the number of cases still represents an underestimate owing to the limited availability of testing. While the incidence of COVID-19 in the community continues to rise, patients with R/R DLBCL and ALL remain a significant unmet medical need. CAR T cell therapy has emerged as a standard and potentially curative approach for these R/R patients, yet the COVID-19 pandemic presents unique challenges to its implementation and management. Proceeding with CAR T cell therapy during the pandemic will require dedicated discussions of the risks/benefits while balancing the uncertainty of the near future. If a patient is in need of CAR T cell therapy, and can likely benefit, we affirm that treatment should be provided. There is an assumption that we can wait out this infection crisis, but there are no reliable data demonstrating that this reduction will happen or when it will occur. In a competition for resources, those with R/R DLBCL and ALL will fail when compared with the sheer number of COVID-19-infected patients; therefore, clinicians must continue to strongly advocate for this treatment and their patients. Today, a deferral of CAR T cell therapy, although with temporary intent, could prove to be permanent and thus eliminate an otherwise potentially curative therapy.

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CRISPR Therapeutics, Kite Pharma/Gilead, Incyte, Intellia Therapeutics, Kadmon, Omeros, and PACT Pharma; serves on a scientific board for Artiva Biotherapeutics; has served on data and safety monitoring boards for Novartis and Athersys; served as chair of the scientific steering committee for the phase II tisagenlecleucel study sponsored by Novartis; and has received research support from Novartis. He also holds patents from Athersys. J.P.M. has received research/grant support from Novartis, Fresenius Biotech, Astellas, Bellicum Pharmaceuticals, Gamida Cell, and Pluristem; has served on advisory boards/speakers bureaus for and received travel accommodations and expenses and research funding from Kite Pharma/Gilead and BMS/JUNO; and has received honoraria, travel expenses along with grant/research funding from AlloVir. L.J.N. has received honoraria from Bayer, Celgene, Gamida Cell, Genentech, Kite Pharma/Gilead, Novartis, MEI, and TG Therapeutics along with research support from Celgene, Genentech, Karus Therapeutics, Merck, Novartis, and TG Therapeutics. O.O.O. has served on scientific advisory boards for Pfizer, Spectrum, Bayer, and Kite Pharma/Gilead; has received honoraria from Pfizer; and has received research support from Novartis. M.-A.P. has received honoraria from AbbVie, Bellicum, BMS, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda; serves on data safety and monitoring boards for Servier and Medigene and on scientific advisory boards of MolMed and NexImmune; and has received research support for clinical trials from Incyte, Kite Pharma/Gilead, Miltenyi Biotec, and Novartis. D.L.P. reports spousal employment along with stock and other ownership interests in Genentech and Roche; has served in a consulting/advisory capacity for Novartis, Kite Pharma/Gilead, Incyte, Gerson Lehrman Group, Glenmark, and Janssen; has received travel expenses from Kite Pharma and Novartis; has received research funding from Novartis; is a listed as an inventor on a patent for CTL019; and serves on the Board of Directors of the National Marrow Donor Program and on the Board Examination Writing Committee of the American Board of Internal Medicine. P.A.R. has served on speakers bureaus for Kite Pharma/Gilead and Bayer and on advisory boards for Verastem Oncology, Novartis, Celgene/BMS, and Bayer; has received honoraria from Novartis; and has received research support from Celgene/BMS, Kite Pharma, and Novartis.

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