NCCN: Continuing Education

Target Audience: This activity is designed to meet the needs of oncologists, hematologists, nurses, pharmacists, physician assistants, and other health care professionals treating patients on CAR T-cell therapy.

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Fees: There are no fees associated with participation in this activity.

Release date: September 10, 2018

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Learning Objectives:

Following this activity, participants should be able to:

- Outline fundamental elements of chimeric antigen receptor (CAR) design and CAR T-cell therapy development
- Summarize key studies using CD19-targeted CAR T-cell therapy in relapsed/refractory B-cell malignancies and their outcomes
- Identify current and emerging management strategies for CAR T-cell therapy-associated toxicities
- Discuss preclinical and clinical strategies being developed for CAR T-cell therapy use in solid tumors
- Summarize recommended considerations for CAR T-cell persistence and disease surveillance
- Outline seminal components required to establish institutional CAR T-cell therapy programs
- Discuss current coverage/reimbursement structures and proposed reimbursement strategies for CAR T-cell therapy

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Chimeric Antigen Receptor T-Cell Therapy

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Abstract

Patients with relapsed or refractory (R/R) cancers have a poor prognosis and limited treatment options. The recent approval of 2 chimeric antigen receptor (CAR) autologous T-cell products for R/R B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma treatment is setting the stage for what is possible in other diseases. However, there are important factors that must be considered, including patient selection, toxicity management, and costs associated with CAR T-cell therapy. To begin to address these issues, NCCN organized a task force consisting of a multidisciplinary panel of experts in oncology, cancer center administration, and health policy, which met for the first time in March 2018. This report describes the current state of CAR T-cell therapy and future strategies that should be considered as the application of this novel immunotherapy expands and evolves.

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Background

Chimeric antigen receptor (CAR) T cells are genetically engineered cells that represent a novel class of cancer immunotherapy.¹ The development of adoptive cellular therapy using CAR T cells spans almost 30 years, with the seminal study by Gross et al² laying the groundwork for the development of first-generation CAR T cells. CARs are rationally designed synthetic receptors that target surface antigens in their native conformation.^{1,3} They are composed of a tumor targeting moiety, most often an antibody single-chain variable fragment, linked to a hinge region, a transmembrane domain, and an intracellular activation motif made up of the CD3 zeta (CD3ζ) chain of the T-cell receptor (TCR) complex.⁴ Due to these molecular features, T cells expressing CARs are not major histocompatibility com-

plex-restricted. In more recent clinical trials, second-generation CARs have been used, and these include one costimulatory signaling domain—typically either CD28 or 4-1BB—which have been shown to enhance T-cell proliferation and cytokine production.⁴ Some studies suggest that 4-1BB-containing CARs have longer T-cell persistence.^{5–7} Third-generation CARs, which have at least 2 costimulatory domains, have shown activity but need further evaluation in clinical studies to determine whether such constructs are superior to those containing a single costimulatory domain.^{8,9}

In general, the process of autologous CAR T-cell therapy begins with collecting WBCs from the patient via leukapheresis, followed by TCR activation (eg, anti-CD3/anti-CD28 beads), and genetic engineering via retroviral or lentiviral transduction. After the CAR T

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cells are generated, they are expanded to clinically relevant numbers, undergo quality control testing, and are cryopreserved. Manufacturing of commercial CAR T-cell products occurs at a centralized facility, necessitating transfer of the apheresis product to the manufacturing site, and the final cryopreserved CAR T-cell product back to the treatment facility. Typically, the patient undergoes lymphodepleting chemotherapy to create a favorable immune environment for CAR T-cell activity prior to receiving a single intravenous infusion of the product.¹⁰ Once the CAR T cells are infused, several factors may impact their efficacy and toxicity profile, including extent of previous treatments, intensity of the lymphodepleting chemotherapy regimen, and disease burden at the time of infusion. Other factors that may impact CAR T-cell activity and safety include immunogenicity, immunosuppressive components in the microenvironment, and on-target/off-tumor effects.⁴ Several strategies are being explored to enhance CAR designs that will maximize functionality and minimize toxicity, and will be discussed later.^{4,11,12}

CD19 CAR T-Cell Therapy and Disease Management

Leukemias

Prognosis and overall survival (OS) rates in adult and pediatric patients with relapsed and refractory (R/R) acute lymphoblastic leukemia (ALL) is poor.^{13–15} However, recent advances in immunotherapy are expanding treatment options for these patients, including CD19/CD3 bispecific antibody blinatumomab, CD22 antibody-drug conjugate inotuzumab ozogamicin, and CD19 CAR T cells.¹⁶ The initial phase I clinical evaluation by several institutions of anti-CD19 CARs, with either a CD28 or 4-1BB costimulatory domain in adult and pediatric R/R CD19-positive ALL, have demonstrated unprecedented clinical efficacy, with >70% to 90% of patients achieving a complete response (CR) within 28 days.^{17–22} These clinical findings set the foundation for the development of tisagenlecleucel, a CAR platform initially established by a research group at the University of Pennsylvania (CTL019) and now commercialized. The phase I Pedi CART19 single-institution trial in pediatric patients with R/R ALL demonstrated minimal residual disease (MRD)–negative CR in 88% of patients 1 month after infusion.²³

Subsequent data from the ELIANA study, a global multicenter phase II trial evaluating the efficacy of tisagenlecleucel in pediatric and young adults with R/R ALL, confirmed these initial results, demonstrating an overall remission/response rate (ORR) of 81% within 3 months of infusion, and OS rates of 90% and 76% at 6 and 12 months, respectively.²⁴ Together, these data facilitated the accelerated FDA approval of tisagenlecleucel as a therapeutic option in patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or greater relapse.

Additional studies evaluating the efficacy of CD19 CAR T cells in the adult population are underway, with promising responses.^{21,25,26} For instance, after infusion of anti-CD19 CAR with a CD28 domain (19-28z CAR T) in 53 adults with R/R ALL, complete remission was observed in 83% of patients, with a sustained impact on OS.²¹ Similar data are emerging from an ongoing phase I trial of KTE-C19 (a different CD28-based anti-CD19 CAR T-cell product), where in an 88% MRD-negative CR rate was observed.¹⁷

Although observed remissions in clinical trials are encouraging, several factors impact the durability of responses to CAR T-cell therapy. Disease relapses can occur and may involve multiple mechanisms, including suboptimal CAR T-cell expansion or persistence, disrupted antigen trafficking, and antigen escape through acquired mutations, splice variants, or leukemic lineage switching.^{27–34} Some studies suggest that fludarabine and cyclophosphamide lymphodepletion may enhance CAR T-cell persistence,^{18,22,35,36} whereas other studies suggest that T-cell subset selection may positively impact CAR T-cell efficacy^{22,29,37}; however, further studies are warranted. To reduce the potential of antigen escape, alternative or multiple antigens could be targeted.^{16,38,39} One alternative to CD19 is CD22, which is expressed in most cases of pre-B-cell ALL.⁴⁰ A novel anti-CD22-CAR demonstrated antileukemic activity in a phase I study involving pediatric and adult patients with ALL previously treated with CD19-directed immunotherapy.²⁹

Other considerations for CAR T-cell use in R/R ALL therapy include whether it should be evaluated as a bridge to hematopoietic stem cell transplant (HSCT), or potentially as a replacement for HSCT, if long-term durable remissions can be achieved.¹ More clinical studies are needed to determine whether CAR T-cell therapy in ALL can be expanded for use in additional settings, such as after first re-

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lapse, in first remission with persistent MRD, or even as initial induction or consolidation therapy. Future studies to determine the criteria that contribute to maximal therapeutic benefit will shed light on these considerations and optimize CAR T-cell therapy use.

Lymphomas

Patients with multiply relapsed diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma (NHL), have poor outcomes.^{41–43} Multiple clinical studies evaluating anti-CD19 CAR T-cell therapy in refractory CD19-positive B-cell lymphomas have demonstrated promising antilymphoma activity.^{44–48} These encouraging clinical outcomes have provided the rationale for efforts to seek FDA approval for CD19 CARs for the treatment of NHL, and the clinical results of the lead commercial CAR T-cell products are summarized in this section.

KTE-C19/axicabtagene ciloleucel (axi-cel) was the first CAR T-cell therapy to be FDA-approved for the treatment of NHL in October 2017. Axi-cel is an anti-CD19 CD3 ζ /CD28-based CAR T-cell therapy, which was originally developed and clinically tested at the NCI and subsequently commercially developed. The multicenter phase I study, ZUMA-1, evaluated KTE-C19/axi-cel in 7 patients with refractory DLBCL⁴⁹; the ORR was 71% (5/7) at 4 weeks postinfusion, with 3 of 7 patients still in remission at 24 months. In the phase II expansion of ZUMA-1, 101 of 111 enrolled patients with refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma were treated with axi-cel.⁴⁶ The CR rate and ORR were 54% and 82%, respectively. After a median follow-up of 15.1 months, 40% of patients remained in CR. Of 34 patients with partial response at 1 month, 11 (32%) subsequently achieved CR without additional therapy.⁵⁰ In addition, landmark analysis of progression-free survival (PFS) determined that among the 60 patients with disease control (ie, stable disease or better) at 3 months, the 12-month PFS rate was 73%.⁵⁰ Subset analyses suggest that low-burden disease may be associated with a higher rate of durable responses. These data facilitated accelerated FDA approval of axi-cel in R/R DLBCL.

The second commercial product to be FDA-approved in May 2018 for the treatment of DLBCL was tisagenlecleucel. In the multicenter pivotal phase II

JULIET study examining the efficacy of tisagenlecleucel in adults with R/R DLBCL, the best ORR was 53.1% among 81 infused patients.⁴⁷ In addition, 74% of patients who experienced a CR at 3 months continued to show ongoing remission at 6 months, suggesting that, as with axi-cel, long-term durable remissions may be observed in a substantial minority of patients.

Other CAR T-cell products being commercially developed for treatment of NHL include JCAR017/lisocabtagene maraleucel, a CD3 ζ /4-1BB-based CD19 CAR evaluating a defined ratio of CD4 and CD8 T-cell subsets, which was originally developed and clinically tested at Fred Hutchinson Cancer Research Center. In the TRANSCEND study, the efficacy of lisocabtagene maraleucel was evaluated in R/R B-cell NHL.⁴⁴ The best overall response and CR rates were 75% and 56%, respectively, and 80% of patients experiencing CR at 3 months remained so at 6 months.⁴⁴ Similar to the ZUMA-1 study, patients with low-burden disease or relapse after transplant had improved ORR relative to patients with high tumor burden or primary refractory disease.⁴⁴

On the Horizon

Given the results observed with CAR T-cell therapy in ALL and DLBCL, several studies are in progress to determine whether other tumors will respond and whether toxicities will differ.^{51–58} Using CAR T cells to target the anti-B-cell maturation antigen (BCMA) in heavily treated R/R multiple myeloma (MM) has demonstrated encouraging preliminary responses.^{51,52,59,60} In a multicenter phase I study examining the efficacy of bb2121, a second-generation anti-BCMA CAR, in 21 patients with R/R MM, the ORR for 18 evaluable patients in the group treated with at least 150×10^6 CAR T cells was 94%.⁶¹ Emerging clinical studies have also demonstrated sustained remissions using anti-CD19 CARs in heavily pretreated patients with chronic lymphocytic leukemia.^{54,55,57}

Overall, the data in hematologic malignancies suggest that some patients with R/R disease will experience sustained remissions with CAR T-cell therapy, and the duration of response may correlate with the persistence of CAR T cells. An important consideration for future clinical studies will be standardizing protocols so that any factors that contribute to improvements or differences in outcomes can be clarified.

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Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- CAR T cells are a novel class of cancer immunotherapy with promising efficacy in R/R hematologic cancers.
- CD19 CAR T-cell therapy is now approved in pediatric and young adult R/R ALL, as well as adult R/R DLBCL, with further studies underway using alternative antigen targets across these and other hematologic malignancies.
- CAR persistence, efficacy, and safety are influenced by many features, including disease burden, conditioning chemotherapy, and perhaps CAR design.
- Where feasible, the task force recommends standardization of eligibility criteria across clinical trials to better inform clinical and disease features that may influence efficacy and toxicity.

Management of CAR T-Cell Associated Toxicities

Current Structures

Several toxicities are associated with CAR T-cell therapy, but 2 of the most common and well-described toxicities in patients with hematologic malignancies are cytokine release syndrome (CRS) and neurologic toxicity, also called CAR-related encephalopathy syndrome (CRES).^{62,63} Ensuring that multidisciplinary clinical staff, including physicians and nurses who monitor patients for toxicity and oncology pharmacists, are trained and familiar with toxicity presentations and management strategies is key to providing timely care.⁶⁴ CRS onset typically begins within 24 to 48 hours after infusion, but may occur up to 1 week after infusion, with an average duration of 1 week. The first sign of CRS is usually fever, which can progress to hypotension and/or hypoxia; other signs and symptoms may include arrhythmias, coagulopathies, tachycardia, and other organ toxicities.^{62,63} Management strategies have been refined by integrating multi-institutional experiences with CD19 CAR T cells. Low-grade CRS management involves supportive care, including antipyretics for fevers, and evaluation for alternative sources of fever, intravenous fluids for hydration, and antiemetics for nausea. Higher-grade toxicities may require intravenous fluid boluses and pressor support for hypotension, and high-flow oxygen for

hypoxia, in addition to interleukin (IL)-6 antagonists (ie, tocilizumab or siltuximab) and/or corticosteroids.

Neurotoxicity/CRES, an extension of vascular dysfunction, typically begins within 4 to 6 days postinfusion and can last from 1 to several weeks. Symptoms include changes in speech and fluency, mild disorientation, confusion, and changes in wakefulness or somnolence.^{62,63} Conducting a good baseline neurologic assessment is imperative for subtle changes to be detected on subsequent examinations. Crucial information may also be observed by the patient's caregiver. Management strategies for low-grade CRES include primarily corticosteroids, supportive care, and appropriate precautions. Higher-grade neurotoxicity may require antiepileptic therapy and corticosteroids.^{62,63} If CRES treatment is indicated while the patient still has active CRS, tocilizumab is recommended; if this is not effective, siltuximab can be used. In patients with CRES alone, IL-6 antagonists are not effective. Pharmacists are also involved in supportive care and play a role in the administration of antimicrobial, antiviral, and antifungal prophylaxis and seizure prophylaxis medications.

Future Considerations

Several clinical studies have established toxicity grading criteria and management algorithms,^{29,54,62,65,66} and institutions use varying algorithms for toxicity management. However, as the use of CAR T-cell therapy expands to treat multiple malignancies, there is a need for standardization in terms of management strategies, antimicrobial prophylaxis, and patient selection to minimize toxicities and maximize the efficacy of treatment. Given the efficacy of tocilizumab in treating CRS, there may be a potential benefit for earlier administration before the onset of severe CRS symptoms; prophylactic administration is currently being investigated.⁶⁷ Emerging preclinical and clinical studies suggest a role for potential alternatives to tocilizumab and corticosteroids for managing toxicities, including anakinra, ruxolitinib, and siltuximab,^{65,68–72} although the mechanism of action and efficacy of these agents needs to be established. In addition, emerging studies are seeking to determine the prognostic utility of cytokine profiles or serum biochemical markers in predicting toxicity or response.^{49,73–77}

Some studies suggest that certain factors may predict the severity of CRS and CRES symptoms. For instance, low disease burden at the time of infu-

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sion may correlate with decreased incidence of CRS/CRES symptoms and improved survival.^{21,44,78} Conversely, higher numbers of infused CAR T cells may increase a patient's likelihood of experiencing intermediate or severe levels of neurotoxicity.^{18,79} Other toxicities associated with CAR T-cell therapy include prolonged cytopenias, hemaphagocytic lymphohistiocytosis, disseminated intravascular coagulation, and macrophage activation syndrome,^{48,63,72} all of which merit further study so that effective management strategies can be developed. Future studies will also need to determine whether existing comorbidities, including prior thrombosis, cardiac and respiratory dysfunction, venoocclusive disease, central nervous system disease, and autoimmune disease, affect the efficacy of CAR T cells and negatively impact patient outcomes. Considering that there are a myriad factors that impact response to CAR T-cell therapy, a clearer understanding of major factors will inform future management strategies and may help stratify toxicity management.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Multidisciplinary team education and communication is essential for CAR T-cell–associated toxicity management.
- Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicities.
- CAR T-cell–associated toxicities and effective management strategies need to be further investigated and defined.
- The task force recommends the development of standardized toxicity grading and management algorithms to optimize outcomes after CAR T-cell therapy.

Moving Beyond Hematologic Malignancies and Considerations for Follow-Up

Solid Tumors

With improvements in CAR designs and the development of more streamlined T-cell manufacturing processes, preclinical and clinical studies aim to expand the use of CAR T cells in solid tumors.^{80–82} Indeed, treatment of solid tumors has proved highly challenging due to heterogeneous antigen expres-

sion, immunosuppressive networks in the tumor microenvironment limiting CAR T-cell function and persistence, and suboptimal trafficking to solid tumors.^{83,84} The field is still in the early stages of defining the most promising tumor-associated antigens for eliminating malignant disease while maintaining patient safety. Although clinical trials to date have not observed high clinical response rates, they have demonstrated feasibility and safety and modest anti-tumor activity in a subset of patients. These initial data have provided insights for both the challenges that must be addressed and the therapeutic potential of CAR T cells in the setting of solid tumors.

Clinical experiences with CD19 T-cell trials demonstrating that CAR T cells accumulate in the cerebrospinal fluid (CSF) and reduce the incidence of metastatic leukemic disease in the brain^{19,85} have raised enthusiasm for evaluating this therapy for malignant brain tumors. To date, most trials have focused on treatment of glioblastoma (GBM), but significant efforts are also being applied to pediatric brain tumors and tumors that metastasize to the brain. One of the first examples of CAR T-cell use in brain tumors targeted the glioma-associated protein IL-13 receptor alpha 2 (IL13R α 2).^{86–88} Initial clinical findings demonstrate that local delivery of IL13R α 2-targeted CAR T cells into the tumor and/or CSF is safe⁸⁹ and, remarkably, has elicited a CR in a patient with recurrent multifocal GBM, including metastatic lesions in the spine.⁸⁰ Clinical trials have also demonstrated safety for targeting other GBM-associated antigens, including HER2 and EGFRvIII,^{90,91} supporting the notion that even immune-specialized sites such as the brain will be amenable to CAR therapy.

One of the significant challenges for solid tumor CAR T-cell therapy is that many antigens are not restricted to tumor cells, and targeting such antigens risks on-target/off-tumor toxicities. In addition, tumor heterogeneity and the existence of several mechanisms that contribute to tumor escape, including tumor cell plasticity,⁹² raises the concern that many antigens might need to be targeted to induce a durable response and overcome selecting clonal variants that are resistant to therapy. Use of mixed, dual, tandem, or transient CARs aims to address this concern and is currently being investigated.^{93–95} Other studies have demonstrated the potential of affinity tuning CARs to induce antitumor effects only in the presence of amplified tumor-associated antigen ex-

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pression.^{96,97} Solid tumors are also heterogeneous in terms of composition, and immunosuppressive components of the microenvironment can impact CAR T-cell activity.^{98,99} Approaches to mitigate immunosuppression include combining CAR T cells with inhibitors of immune checkpoints (eg, PD-1), use of cytokines to remodel the microenvironment, and preconditioning of patients.^{100–108}

Another complex issue is effective delivery and trafficking of CAR T cells to the solid tumors. Although different routes of delivery present with advantages and disadvantages, preclinical studies using several tumor models suggest that locoregional delivery may be more effective than systemic delivery for solid tumors.^{86,109–111} However, these findings will need to be refined in clinical trials.^{80,89,112,113} In addition, some studies suggest that matching the tumor-derived chemokine profile with the chemokine receptors expressed on CAR T cells may improve trafficking to the tumor.^{114–116} Once the CAR T cells reach the tumor site, their efficacy may be limited if sufficient numbers do not widely infiltrate the tumor. To address this barrier, some research groups are designing CAR T cells that target tumor stroma.^{117–119}

Overall, there is active investigation into the potential of expanding CAR T-cell therapy to the treatment of solid tumors. As more light is shed on solid tumor features that impact T-cell biology, optimized CAR designs can be developed that effectively treat solid tumors.¹²⁰

Virus-Specific Cellular Therapy

Infections and posttransplant lymphoproliferative disorder are complications that can occur after HSCT, and subsequently contribute to procedure-related mortality and morbidity.¹²¹ Some studies have shown that matched donor-derived virus-specific T cells specific for Epstein-Barr virus (EBV), cytomegalovirus (CMV), or adenovirus are effective at managing viral infections in patients who have undergone transplantation.^{122–126} However, some factors, including appropriate HLA-restricted donor availability, immune status of the patient, and time needed to generate the cell products (40–60 days), may limit use of this technology.^{121,127} Strategies are being explored to address this issue, including developing banks of virus-specific T cells, which would significantly improve treatment feasibility.^{121,127}

Surveillance

Data regarding long-term clinical effects of CAR T cells are currently sparse, and there is a need for follow-up and survivorship monitoring. Some known effects of CAR T-cell therapy in B-cell lineage–targeting are B-cell aplasia and hypogammaglobulinemia.^{20,49,128} However, with frequent monitoring of immunoglobulin G (IgG) levels, hypogammaglobulinemia can be corrected with intravenous or subcutaneous IgG replacement therapy.⁶³ Patients should also be screened for hepatitis B and C and HIV prior to CAR T-cell infusion to prevent viral reactivation. Although no consensus exists on the impact of vaccination in patients with persistent CAR T cells against B-cell lineage, data show that CD19-negative plasma cells can retain B cell–independent humoral immunity despite persistent CD19 targeting and B-cell aplasia.¹²⁹

Another issue that must be considered is the development of infections, both in the acute period following CAR T-cell infusions¹³⁰ and in long-term follow-up, where it has yet to be determined whether prolonged B-cell aplasia increases risk of infection. Routine surveillance for disease recurrence is also important, given uncertainty regarding the durability of remission, with some targets likely having curative potential in a subset of patients, and other targets only providing a limited period of remission.^{28–30}

With initial gene therapy studies, there were reports of the development of lymphoproliferative disorders secondary to transgene insertional mutagenesis.¹³¹ With more modern technologies, the risk of insertional mutagenesis is lower,¹³² but monitoring in the follow-up period remains important. In clinical trials, patients undergo routine sampling during long-term follow-up to test for ongoing persistence of CAR T cells, and testing of clonality is included if clinically indicated. Although no reports of a lymphoproliferative disorder have been reported in CAR T-cell studies, a single case report described a patient in whom antigen-negative tumor cells expressed the CAR.¹³³ It was determined that during the culture for CAR T-cell manufacturing, an antigen-negative tumor cell was transduced by the vector and subsequently infused into the patient.¹³³ Such scenarios and their impact require further clinical investigation. To minimize the potential for inclusion of non-targeted leukemic cells taking up CAR vectors, it may be advantageous to deplete malignant cells from the starting apheresis product or to select for CD4/

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CD8 T cells to enhance T-cell activity while minimizing risk of reinfusion of a malignant cell.²²

An additional area of interest is monitoring for replication-competent lentivirus (RCL) or replication-competent retrovirus. Vectors used for transduction during CAR T-cell manufacturing are replication-incompetent, but there is a theoretical risk of vector rearrangement to create a replication-competent virus or potentially activate proto-oncogenes. In clinical trials, there have been no reports of RCL in patients who received CAR T-cell infusions using the vesicular stomatitis virus G protein as a marker.¹³⁴ For long-term analysis, the FDA requires that clinical study sponsors using investigational new drugs involving gene therapy test patient samples for replication-competent virus at 3, 6, and 12 months postinfusion in the first year and, if samples are negative, bank samples yearly through year 15 postinfusion. In clinical trials that used lentiviral vectors for transduction, there have been a few reports of false-positive HIV test results.^{135–137} This test result is based on the amplification of HIV long terminal repeat sequence, and the result appeared to be assay-dependent in one report.¹³⁵ Based on these findings, it is important to educate treated patients that false-positive results for HIV may occur. The lack of standardized and commercially available tests to measure CAR T-cell persistence is a challenge.

As more patients are treated with CAR T-cell therapies, clinicians will need to counsel patients accordingly. The Foundation for the Accreditation of Cellular Therapy (FACT) has developed new standards specific to the use of immune effector cells (IECs), including gene-modified T cells, which outline guidelines for monitoring and reporting of patient outcomes.¹³⁸ Integration of such programs by study sponsors will provide more insight in this area.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Solid tumors present many complex barriers to CAR T-cell therapy; however, this active area of investigation has the potential to develop novel strategies to overcome specific challenges in solid tumors.
- Emerging data suggest a role for donor-derived and off-the-shelf virus-specific T cells to manage viral infections.

- Standardized procedures for monitoring CAR T-cell persistence and disease surveillance are needed to determine potential long-term effects of CAR T-cell therapy. The task force recommends the following guidelines:
 - ▶ Frequency of follow-up: beginning on day 28 postinfusion of CAR T cells and assuming resolution of acute toxicities, patients should be monitored every 3 months for up to a year (or as clinically indicated). If the patient is fit and in remission, bearing in mind the FDA requirement of at least 15 years of follow-up, subsequent visits may be spaced out as clinically indicated.
 - ▶ CAR T-cell persistence: for CD19 CAR T cells, a reliable surrogate for CAR T-cell persistence is the absence of circulating CD19 cells. As such, flow cytometric measurement of circulating CD19 lymphocytes should be performed at each follow-up visit. More specific testing for circulating CAR T cells is not readily available clinically, but is often incorporated into clinical trial testing.
 - ▶ Disease surveillance: although recommendations in this area are malignancy-dependent, in general for commercially treated R/R Philadelphia chromosome (Ph)-negative ALL and R/R DLBCL, response assessments via imaging and other necessary measures should be performed at day 28 and month 3. Assuming CR, surveillance should be considered every 6 months for 2 years, and subsequently as needed. If a patient is not in CR, clinical judgement is warranted. For Ph-positive ALL, molecular monitoring of peripheral blood may ease follow-up, and can be performed every 3 months if the patient is in complete molecular response 3 months post-CAR T-cell therapy.
 - ▶ Additional follow-up measures should include IgG and B-cell/T-cell recovery monitoring, with considerations for antimicrobial and intravenous immunoglobulin prophylaxis until recovery occurs, and revaccination similar to guidelines for autologous transplantation.¹³⁹

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Operational Considerations

Program Initiation and Institutional Organization

The process of launching FDA-approved CAR T-cell products at cancer centers or institutions involves several important components driven by the institutions and manufacturers, including site audits by the manufacturers, implementing required Risk Evaluation and Mitigation Strategies (REMS) for approved products, developing trade agreements/contracts, pharmacy coordination, setting patient selection criteria, social work screening, prior authorization, payor contracts or single-case agreements, establishing product ordering and institution review processes, developing training and educational processes, and systems for data management and event reporting. The process of securing prior authorization at institutions varies and can take anywhere from a few days to several weeks. Adverse events need to be reported to the FDA or the pharmaceutical sponsor as part of the REMS program, although there is variability regarding what grade event is reported, and some institutions only report events that are grade ≥ 3 .

In addition, although policies and protocols may vary across institutions, dedicated and trained key personnel in each of the clinical and administrative departments that manage work associated with CAR T-cell therapy and agreed-upon workflow processes are essential to help facilitate cross-departmental communication and cross-functional collaboration. Some of these departments include regulatory and quality assurance, finance/legal contracting, apheresis, cell therapy laboratory, outpatient oncology clinic, and inpatient oncology unit. Furthermore, education, training, and collaboration are required across multiple departments, including intensive care unit (ICU)/critical care, emergency medicine, infectious disease, cardiology, and neurology. As clinical operations continue to develop, ideally a balance between standard of care and research programs will continue to evolve and improve these processes. Patient-selection protocols between research and standard of care will also continue to be important.

Program and Infrastructure Development

Each organization that endeavors to deliver CAR T-cell therapy will have a unique challenge, depending on where they are starting. Given the variety of services involved in CAR T-cell therapy, including patient intake/selection, financial clearance, cell

collection and processing, treatment, and monitoring in ambulatory and inpatient settings, organizational assessment and program planning are warranted. In such an assessment, a key decision point will be whether current facilities have the capacity to scale to predicted volume levels or whether additional and/or separate units are needed. Prior to establishing a program, it will be critical to conduct service utilization analysis, metrics, and data development, which will help the institution better understand the service impact and provide a foundation for demand forecasting. Key factors to consider for program development include the desired medical practice and patient care model, clinical and administrative resource needs and reporting structure, teaming concepts, and space planning. Additionally, workflow and process design for work within and across departments and the development of daily management systems can provide a foundation for optimal patient flows and continuous improvement.

Dedicated cellular immunotherapy programs can be developed, with integration across administrative departments, ambulatory clinics, bone marrow transplantation, and inpatient and outpatient services. When developing a model of care, having well-defined care pathways to provide the patient with uninterrupted access to required services in a continuous flow is crucial to minimize treatment delays. The size and scale of a program may also determine how quickly a service can be created. Patients may also need to transition to an inpatient setting to manage toxicities or other acute care needs. Some of the benefits of dedicated integrated programs include having specialized teams for infusion or triage, enhanced communication through proximity, quick turnaround times for laboratory results or reduced wait times, and overall increased standardization of processes. If departments and services are not integrated, potential challenges can arise before and after CAR T-cell infusion when transitioning patients to other departments (ie, ensuring that there are appropriate staff to manage the patients) and ensuring a continuity of care.

Given the potential toxicities that occur with CAR T-cell therapy, short- and long-term continual cross-care is likely needed between departments to ensure that optimal care is delivered. In addition, given the many variables involved in implementation and conduct of clinical trials, it may be diffi-

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cult to forecast patient volumes, and this will require continual refinement.

Psychosocial Support

As a critical part of the clinical team, oncology social workers provide psychosocial assessments to gather information from patients and their families regarding their strengths and resources, and to identify barriers that may affect treatment. They also offer education and support in terms of advance directives and provide referral to mental health resources when appropriate. Some barriers to treatment include stressors outside of the diagnosis (eg, other life responsibilities, such as career/family) and financial constraints, considering that most patients have likely undergone several rounds of prior therapy, and may find it difficult to also cover costs associated with transportation and local housing, if needed. Some patients may also struggle to access required financial documentation, including insurance documents and most recent tax return. In these cases, oncology social workers can help patients secure appropriate lodging during the treatment. In an effort to mitigate costs to patients, some manufacturers, in concert with institutions, have started support programs to provide travel and copay assistance and facilitate treatment access.

Implementing Institutional Protocols

Multidepartmental infrastructure management is critical for CAR T-cell therapy. In original data from the ELIANA trial, 59% of patients were admitted to the ICU, with a median stay of 8 days.¹⁴⁰ Similarly, grade ≥ 3 adverse events seen in the ZUMA-1 trial¹⁴¹ suggest that intensive management is required to safely administer CAR T-cell therapy. Therefore, comprehensive training of inpatient and outpatient clinic staff (eg, physicians, certified physician assistants, advanced registered nurse practitioners, and pharmacists) who manage patients undergoing CAR T and other gene-modified cellular therapy is required. To develop a consistent approach for managing CAR T-cell–associated toxicities, the CAR-T-cell-therapy-associated TOXicity (CARTOX) Working Group was formed, with representatives from multiple institutions and medical disciplines.⁶³ The CARTOX committee also proposed algorithms for managing CAR T-cell–associated toxicities^{63,65} that can be incorporated into data management sys-

tems. Of note, the American Society for Blood and Marrow Transplantation recently held a meeting to discuss the development of a new singular consensus scale for grading toxicities based on 2 current algorithms—one of which is the CARTOX algorithm—and this scale will be published in the coming months.

Based on experience from the CARTOX program at The University of Texas MD Anderson Cancer Center, all new TCR T cell, natural killer cell, and CAR T-cell clinical programs are presented to the CARTOX group before patients are enrolled. Weekly meetings are held to discuss CAR T-cell or TCR T-cell inpatients, with a focus on ICU patients, and algorithms for diagnosis and management toxicities are developed and revised as needed. Toxicity and efficacy outcomes data for each protocol are presented by the principal investigator of the study annually. Other institutions also have initial reviews conducted by similar working groups, and subsequently, the NCI requires that these protocols are also reviewed by the institutional review board and protocol review and monitoring committees. In addition, as previously mentioned, FACT has published standards for IEC therapy, which were used in the development of the CARTOX program. As more programs emerge, securing FACT accreditation for common standards in IEC therapies in addition to HSCT will be an essential component for institutions delivering CAR T-cell therapies.

Cost and Coverage Considerations

With limited therapeutic options, the FDA approval of CAR T-cell therapies represents a major advancement in the management of R/R ALL and DLBCL. A recent report from the Institute for Clinical and Economic Review concluded that the cost of approved CAR T-cell products aligns with clinical benefit.¹⁴² However, steep costs and limited authorized centers are major barriers to patient access. Presently, authorized centers administer tisagenlecleucel at price points of \$475,000 for R/R ALL and \$373,000 for R/R DLBCL, and axicabtagene ciloleucel at a price point of \$373,000 for R/R DLBCL. Most commercially insured patients have coverage for at least one of the approved products, but some specific plans or employer-sponsored groups may have limitations on patient clinical eligibility.

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To fully estimate the costs associated with CAR T-cell therapy, all aspects of therapy must be considered, including the costs of the product, apheresis, bridging chemotherapy, lymphodepletion, CAR T-cell infusion, inpatient stay (the average length of stay for CAR T-cell treatment is approximately 2–3 weeks), ICU, ambulatory clinical care, laboratory services, and mechanisms for FDA-mandated disease surveillance, including PET scans. It is important to incorporate these estimated costs into agreements with manufacturers to begin to build a framework for standardization in the protocols for insurance coverage. Additionally, controversy exists about whether the product should be “marked up” (ie, billed at a multiple of the purchase price) on par with other drugs due to its very high list price. Without billing through the markup mechanism, institutions have very little opportunity to recoup the significant processing and quality assurance costs associated with shipping, handling, and receiving of the cells when the manufacturer does not reimburse for them. As CAR T-cell treatment becomes more established and expands to other disease sites, the main financial onus is on treatment centers. Many academic medical centers have taken an early-adopter, mission-related risk, understanding that there will be significant financial losses for the first several years as government payers determine their reimbursement strategies.

Based on current institutional experience, manufacturers and payers will likely be looking for centers that have demonstrated clinical trial expertise with CAR T-cell therapy and are compliant with FACT accreditation. Government payers will vary in their coverage and reimbursement policies. Few pediatric Medicaid programs publicly post their coverage policies, but several (Massachusetts, California, and New York) have publicly posted that they will begin coverage of CAR T-cell therapy. The Centers for Medicare & Medicaid Services (CMS) uses codes based on the International Classification of Diseases (ICD) to process reimbursement for inpatient care, and there is an ICD-10 code assigned to the procedure of infusing CAR T-cell products; in fiscal year 2019, this code will be used to assign inpatient CAR T-cell administration to a specific Medicare Severity Diagnosis Related Group (MS-DRG 016 “Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy”).¹⁴³ As the field expands, additional codes will be needed to more specifically

identify individual products and the differing level of severity of cases based on toxicities.

In the Medicare outpatient setting, CMS has issued drug payment codes specific to each product that correspond to payment at the standard drug rate of average sales price (ASP) + 6%. Use of the outpatient payment rate is complicated by the fact that payment defaults to the inpatient rate if a patient is admitted to the hospital within a set period after outpatient infusion; due to this discrepancy, provider societies are seeking a mechanism for site-neutral and equitable reimbursement for provision of CAR T-cell therapy. Separate from the reimbursement mechanism, CMS recently began a national coverage analysis for CAR T-cell therapy that will be in process until May 2019.

Considering the demography of patients with cancer and that patients on Medicare can represent a significant portion of the patient population, a reimbursement solution that covers the issues outlined is paramount. Medicare finalized the Inpatient Prospective Payment System guidelines in early August 2018, but they included limited relief for CAR T-cell therapies. The 2 CAR T-cell products will receive new technology add-on payment (NTAP) status and CAR T-cell therapy was assigned to a specific MS-DRG for payment purposes. However, the NTAP payment is limited to a maximum of half the product cost (\$186,500) and the base MS-DRG rate is approximately \$39,000, which leaves hospitals still substantially short of full reimbursement for incurred costs. If the Medicare reimbursement shortfall continues, increasing pressure will be placed on manufacturers to lower the cost of the product. In the long term, if these issues remain unresolved, this may limit the ability of institutions to keep in step with developments in future CAR T-cell therapy products.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Initiating programs for CAR T-cell products at institutions requires significant specialized expertise, resources, investment, and organization.
- Psychosocial support is an integral part of CAR T-cell–associated patient care.
- Accreditation via FACT is crucial when securing and implementing CAR T-cell therapy–related institutional protocols.

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- CAR T-cell therapy is being performed in an outpatient setting in some centers. The task force recommends close monitoring and rapid transition to an inpatient setting at the first sign or symptom of toxicity to manage acute toxicities and minimize the possibility of a serious adverse event.
- Improved standardized reimbursement structures are needed to enhance the use of CAR T-cell therapy in cancer management.

Conclusions

CAR T-cell therapy represent a significant shift in the landscape of anticancer therapy. This class of therapeutics was recognized as the advancement of the year in the 2018 ASCO annual report.¹⁴⁴ Tremendous

advancements have been made in durable remissions in aggressive B-cell leukemias and lymphomas, and emerging studies suggest potential in other disease sites. The NCCN CAR T-Cell Therapy Task Force discussed these data and identified areas that need to be developed to enhance clinical uptake of this new technology. Based on discussion, considerable interest exists in developing CAR T-cell-specific guidelines. Although ideal, the task force recognizes that it will be challenging to establish uniform approaches for all CAR T-cell therapies at this juncture because of heterogeneous product design, disease application, and clinical study design. However, as the data develop and mature, such guidelines will help stratify commonalities and differences in terms of product-specific management.

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