

Anti-CD19 CAR T-Cell Therapy for Adult Patients With Refractory Large B-Cell Lymphoma

KATHLEEN McDERMOTT, RN, BSN, OCN®, BMTCN®, and
LAUREN SPENDLEY, AGNP, MSN, AOCN®

From Dana-Farber Cancer Institute/Brigham and Women's Cancer Center, Boston, Massachusetts

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Kathleen McDermott, RN, BSN, OCN®, BMTCN®, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. E-mail: Kathleen_McDermott@dfci.harvard.edu

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Abstract

Chimeric antigen receptor (CAR) T-cell therapies represent a new paradigm in targeted cancer therapy. T cells play a key role in immune surveillance, but tumors have developed multiple mechanisms for evading that surveillance. CAR T-cell technology aims to enhance the innate ability of the body to fight foreign invaders, and in this way, effectively fight cancer and potentially reduce the number of treatments required. In fact, many patients have had long-lasting clinical responses to therapy with a single treatment. The journey to receiving CAR T-cell therapy involves a number of steps prior to infusion, including an initial consultation and workup, apheresis, bridging therapy, and lymphodepletion. Patients are then closely monitored after infusion. Successful treatment requires collaboration between the patient, caregivers, and the multidisciplinary team. Here we discuss the biology of CAR T-cell technology, clinical trial data, and the path to accessing this revolutionary and potentially curative treatment.

In late 2017 and mid-2018, the U.S. Food and Drug Administration (FDA) approved the first two cancer therapies that genetically engineer a patient's own immune cells for the treatment of refractory large B-cell lymphoma. Axicabtagene ciloleucel (Yescarta) is indicated for adults with relapsed or refractory large B-cell lymphoma after more than two lines of systemic therapy. This includes diffuse large B-cell lymphoma (DLBCL), primary

mediastinal large B-cell lymphoma (PMBCL), DLBCL arising from follicular lymphoma (FL), and high-grade B-cell lymphoma. It is not indicated for patients with primary central nervous system lymphoma (PCNSL; Kite Pharma Inc., 2017). Recently, tisagenlecleucel (Kymriah) was also approved for the treatment of DLBCL, DLBCL arising from FL, and high-grade B-cell lymphoma. Tisagenlecleucel is also indicated for the treatment of B-cell precursor

acute lymphoblastic leukemia that is refractory or in second or later relapse in patients up to 25 years of age (Novartis Pharmaceuticals Corporation, 2018a). These chimeric antigen receptor (CAR) T-cell therapies represent a new paradigm in targeted cancer therapy that works differently than conventional chemotherapy or chronic treatment with targeted inhibitors. Instead, the approach of CAR T-cell therapy is to enhance the innate ability of the immune system, effectively fighting cancer and potentially providing sustained remissions (Abbas, Lichtman, & Pillai, 2018; Abramson et al., 2018; Locke et al., 2019; Schuster et al., 2019).

MECHANISM OF ACTION OF CAR T-CELL THERAPY

In contrast to the innate (nonspecific) immunity mediated by macrophages, granulocytes, and natural killer cells, T cells are a critical component of the body's learned adaptive immune response (B cells also contribute to the adaptive response but will not be discussed here). For a T cell to become activated, two things must happen concurrently: (1) a receptor on the T cell must recognize and bind to an antigen presented from the tumor cell, and (2) a costimulatory molecule must bind to its ligand on the cell presenting the tumor antigen. Once both of these signals occur, T cells proliferate and induce the programmed cell death (apoptosis) of foreign cells (Abbas, Andrew, & Pillai, 2014; Schwartz, 2003).

Ideally, a patient could independently generate a T-cell-mediated response against cancer cells. However, cancer has developed multiple ways of evading immune surveillance. Tumors lack the costimulatory molecules required to initiate T-cell activation (Abbas et al., 2018). In fact, they often express negative costimulatory molecules that inhibit T-cell activation (Maus & Levine, 2016). Tumors may also carry genetic mutations that prevent appropriate antigen presentation, making it difficult for T cells to recognize them as foreign (Maus & Levine, 2016).

CAR T-cell therapy attempts to address evasion. During the CAR T-cell therapy treatment process, genetic material is inserted that assists T cells with their targeting and costimulation steps (Camicia, Winkler, & Hassa, 2015). Specifically, a targeting domain that recognizes a specific anti-

gen present on tumor cells (known as the single-chain variable fragment) is engineered to appear on the surface of the T cell (Maus & Levine, 2016). B cells express CD19 on their cell surface, which is maintained in most B-cell malignancies, including 88% of B-cell lymphomas (Wang, Wei, & Liu, 2012). Therefore, axicabtagene ciloleucel and tisa-genlecleucel are engineered with CD19-targeted single-chain variable fragments. Additionally, internal costimulatory and signaling domains are present that boost the signals from the recognition interaction and provide the costimulatory signal required for full T-cell activation (Figure 1; Lee, Barrett, Mackall, Orentas, & Grupp, 2012). This engineering is designed to help a patient's T cells recognize tumor cells as foreign (Lee et al., 2012; National Cancer Institute, 2017). Inside the body, the CAR T-cell population may also expand and differentiate into memory cells, potentially maintaining an antitumor response many months after infusion (Abbas et al., 2018).

CAR T-Cell Mechanism of Action: Key Takeaways

- CAR T-cell engineering is designed to overcome multiple mechanisms that tumors have developed to evade the immune system and recognize tumor cells as foreign (Camicia et al., 2015).
- CAR T cells may also contribute to immune memory by expanding and differentiating into memory cells (Abbas et al., 2018).

CAR T-CELL THERAPY FOR PATIENTS WITH REFRACTORY LARGE B-CELL LYMPHOMA

There is a large unmet need for alternative therapy options for patients with relapsed or refractory large B-cell lymphoma because outcomes with current therapies are exceptionally poor. In the SCHOLAR-1 study, the largest-ever ($n = 636$) retrospective analysis of patients with refractory DLBCL (defined as progressive disease or stable disease as best response at any point during chemotherapy [> 4 cycles of first-line or 2 cycles of later-line therapy] or relapsed at ≤ 12 months from autologous stem cell transplantation [ASCT]) across

multiple institutions in multiple countries, only 26% had any response to conventional therapy (7% had complete responses [CR]), and median overall survival (OS) was 6.3 months (Crump et al., 2017).

Results from pivotal CAR T-cell therapy clinical trials have consistently demonstrated high rates of durable responses. In ZUMA-1, a pivotal, multicenter, phase I/II study of 108 patients with refractory large B-cell lymphoma, 82% responded to axicabtagene ciloleucel therapy and 42% continued to have a response with 1 year of follow-up (Locke et al., 2017; Neelapu et al., 2017). Long-term activity and safety outcomes have also been reported (Locke et al., 2019). In 101 patients with a median follow-up of 27.1 months, 83% had an objective response and 58% had a CR. Median duration of response was 11.1 months. Median OS was not reached and median progression-free survival was 5.9 months (Locke et al., 2019). Patients in ZUMA-1 had advanced, highly refractory disease, including 85% with disease stage III or IV, 76% with disease resistant to second-line or later therapies, and 21% with disease relapsed less than 1 year after ASCT (Locke et al., 2019).

JULIET, the pivotal phase II study of tisagenlecleucel in 93 patients, has demonstrated an overall response rate of 52% of patients, including 40% CRs. At 12 months after infusion, the rate of relapse-free survival was 65% (79% among patients with a CR). The study included patients who had received two or more lines of prior therapy and approximately half were refractory to or had relapsed after their last therapy (Schuster et al., 2019)

Additionally, lisocabtagene maraleucel (JCAR017), which is not an approved therapy but is also an anti-CD19 CAR T-cell therapy under investigation in patients with refractory large B-cell lymphoma, has shown responses in 80% of patients, with 59% CRs in 73 patients treated in the phase II TRANSCEND NHL 001 study (Abramson et al., 2018).

Notably, these studies were not without significant risks. CAR T-cell therapy is associated with class-specific toxicities, such as cytokine release syndrome (CRS) and neurologic events, which can be potentially life-threatening. In ZUMA-1, severe CRS and neurologic events of grade 3 or higher were observed in 11% and 32% of patients, respectively (Locke et al., 2019). In JULIET, severe CRS

and neurologic events of grade 3/4 occurred in 22% and 12% of patients, respectively (Schuster et al., 2019). In TRANSCEND NHL 001, severe CRS and neurologic events of grade 3 or higher occurred in 1% and 15% of patients, respectively (Abramson et al., 2018). In most cases, the toxicities were reversible.

Rates of these toxicities vary across studies and are influenced by the specific type of CAR T-cell construct used, as well as by patient and disease factors, such as tumor burden at baseline. It is important to note that these studies were designed very differently, including the allowance of bridging

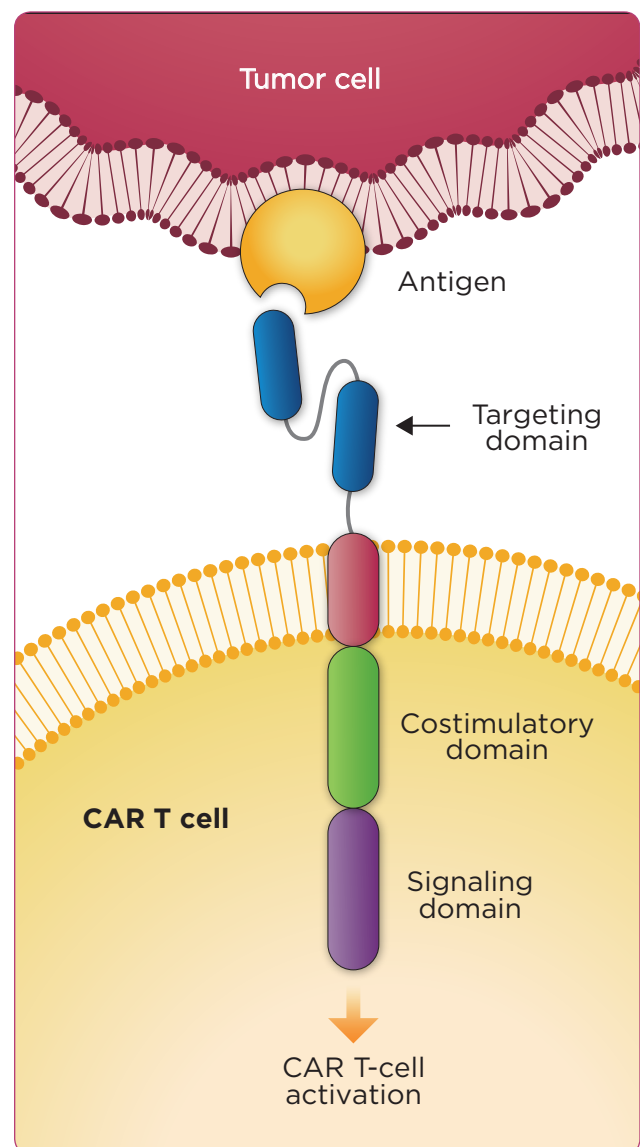


Figure 1. CAR structure and mechanism of action. CAR = chimeric antigen receptor.

therapy before CAR T-cell therapy, which may alter tumor burden and tumor microenvironment. Additionally, different criteria were used for grading and managing toxicities across studies, making it difficult to extrapolate and compare across CAR T-cell constructs. However, results from clinical studies have helped to optimize management guidelines for patients who experience these toxicities, and efforts are ongoing to further improve the safety of CAR T-cell therapy and harmonize toxicity grading and management. In the second article in this supplement, Sherry Adkins, RN, MSN, ANP-C, provides further details on toxicities and their management, including a CRS case study (Adkins, 2019).

Current CAR T-Cell Therapy: Key Takeaways

- Results across initial CAR T-cell therapy trials in relapsed/refractory large B-cell lymphoma have consistently demonstrated appreciable rates of durable responses.
- CAR T-cell therapy is associated with unique toxicities, including CRS and neurologic events, which can be life-threatening but are generally reversible and can be managed with appropriate treatment.

CAR T-CELL THERAPY PATIENT JOURNEY

The path to accessing CAR T-cell therapy can be complex. The process for patients begins long before they receive their CAR T-cell therapy. Based on our clinical experience at the Dana-Farber/Brigham and Women's Cancer Center, the journey to that point can be broken down into a number of steps: consultation/initial workup, apheresis, bridging therapy, and lymphodepletion. After lymphodepletion, the patient is prepared to receive his/her CAR T-cell infusion. Once infused, patients are closely monitored during the high-risk window for toxicities related to CAR T-cell therapy, followed by close outpatient follow-up and then transition back to their local oncologist for collaborative long-term monitoring (Figure 2). In the third article of this supplement, Alix Beaupierre, RN, BSN, OCN®, Nicole Kahle, MS, RN, OCN®, BMTCN®, Rachel Lundberg, PA-C, MPAS, and Amy Patterson, MSN, APRN,

AOCNS®, BMTCN®, provide best practice recommendations to prepare patients, caregivers, and multidisciplinary care teams for the CAR T-cell therapy journey (Beaupierre, Kahle, Lundberg, & Patterson, 2019).

Consultation/Workup

The initial consultation with the oncology team consists of a thorough review of the patient's diagnosis, treatment history, medical history, detailed medication history, comorbidities, and performance status. Not only does the team need to determine if the patient's disease can be appropriately treated with CAR T-cell therapy, they also need to understand factors that may increase the patient's risk of complications with CRS and/or neurologic events. For example, a patient who has a recent history of thrombosis requiring anticoagulation would be at increased risk for bleeding in the setting of a coagulopathy caused by CRS. A patient with a history of poor cardiac function would be at increased risk of complications from arrhythmias that may occur in the setting of CRS. Organ function assessment should include pulse oximetry, a complete metabolic panel, liver function tests, electrocardiogram, and an echocardiogram.

The physician explains CAR T-cell therapy in detail and discusses the risks associated with this treatment, most notably CRS and neurologic events, and determines that the patient is eligible for the treatment. Eligible patients then review and sign a treatment consent form. Patients and their caregivers also have an educational session with the CAR T-cell therapy nurse navigator, who reviews adverse events (AEs), what to expect at each step in the CAR T-cell therapy process, and financial and social logistics. The nurse navigator makes referrals to other members of the health-care team if indicated (i.e., social work support and/or housing resources specialist) to establish an optimal plan of care through the patient's experience with CAR T-cell therapy. This initial educational session is lengthy and packed full of new information, laying the groundwork for what is to come. The CAR T-cell therapy nurse navigator becomes a resource for patients and their caregivers and the main point of contact from this point forward in their journey.

Apheresis

Once the patient has consented to the therapy, the collection procedure needs to be coordinated. This involves the CAR T-cell therapy nurse navigator communicating with the manufacturer, apheresis center, and cell-processing laboratory to determine a collection date that can be accommodated by all. Ideally, this date is as soon as possible, because the manufacturing process can take up to 4 weeks (Better, Chiruvolu, & Sabatino, 2018; Majors, Spencer, Ericson, & Romanov, 2018). The cell product that is collected is autologous, meaning it is coming from the patient who is going to receive it. Patients are informed about restrictions and told when to stop medications before leukapheresis (i.e., chemotherapy or steroids) to ensure an optimal collection. Unlike stem cell transplant, this collection does not require any cell mobilization. Many patients require placement of a temporary apheresis catheter because of poor venous access. Placement typically is done the day before or morning of apheresis and the catheter is removed after the collection. Before apheresis, the patient's vital signs, blood counts, and electrolytes are assessed by the nurse to ensure it is safe for apheresis to proceed. The apheresis process takes about 4 hours to complete. Patients may feel fatigued after the procedure, but otherwise it is well tolerated.

Once the product is collected, it may be processed fresh or cryopreserved for processing later, depending on each manufacturer's specific requirements. If the product is processed fresh, it is packaged and sent by courier immediately after the collection. If the product is cryopreserved, it will be processed and stored within the cell-processing facility and sent to the manufacturer at a later agreed-upon date. Manufacturing time varies among manufacturers, ranging from 2 to 4 weeks (Better et al., 2018; Majors et al., 2018).

Bridging Therapy

During the manufacturing period, some patients may need treatment to control their disease. This bridging therapy often is used if symptoms from disease are present, such as disease-related pain or shortness of breath. Bridging therapy can include steroids, chemotherapy, or radiation (Jain et al., 2018; Nastoupil et al., 2018). Some CAR T-cell therapies, especially those in clinical trials, may

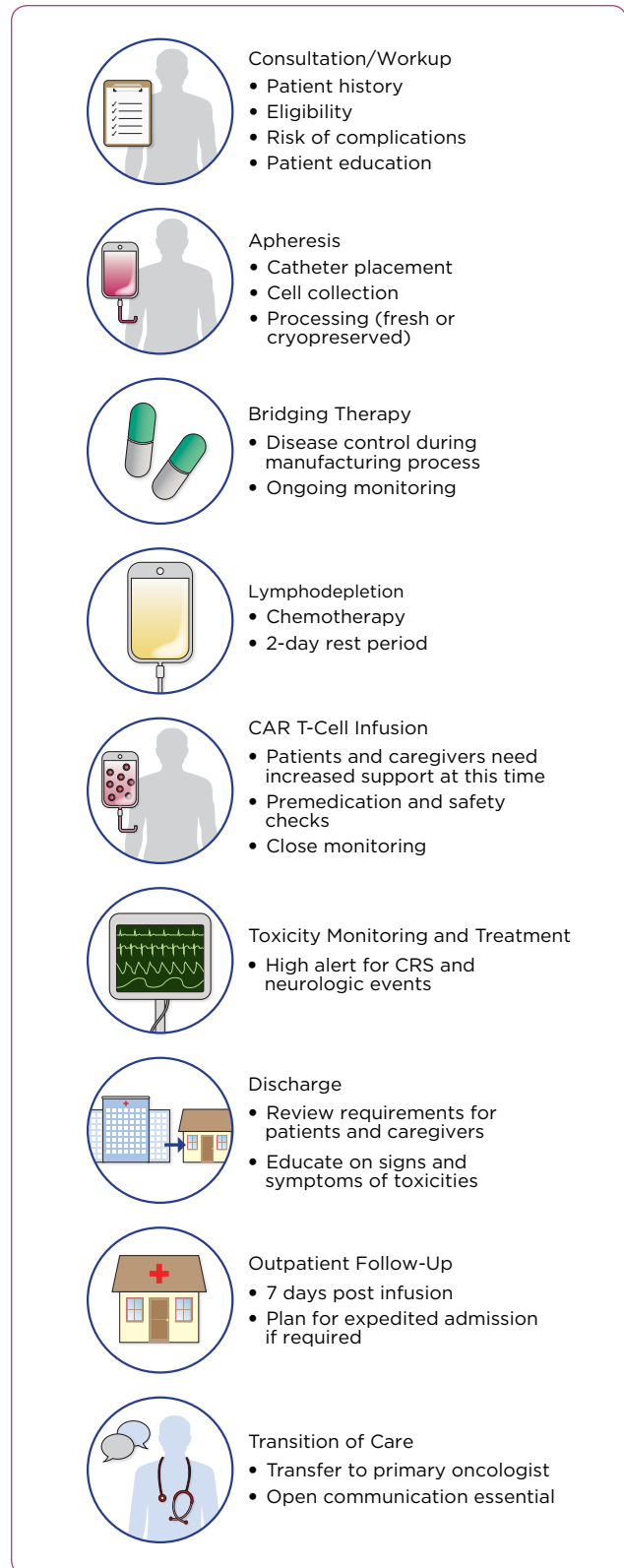


Figure 2. The patient's journey through CAR T-cell therapy. CAR = chimeric antigen receptor; CRS = cytokine release syndrome.

have restrictions on bridging therapy, such as limitations on which therapies can be used and when they must be completed before lymphodepletion (Locke et al., 2019; Schuster et al., 2019). Another reason bridging therapy is used is to reduce tumor burden. A high tumor burden may be correlated with higher-grade toxicities following CAR T-cell infusion (Bonifant, Jackson, Brentjens, & Curran, 2016). Cytoreduction may allow for a less toxic course of CAR T-cell therapy. While the CAR T cells are being manufactured, patients continue to be monitored by their local oncology team, as well as their CAR T-cell therapy team, and are encouraged to alert the team to any clinical changes that could signal symptomatic disease progression.

Lymphodepletion

Once the CAR T cells have been manufactured and are scheduled to return to the hospital, patients begin lymphodepleting chemotherapy (Better et al., 2018). The purpose of this therapy is not to eradicate disease (although it can lessen the disease burden for some) but rather to create an optimal environment for CAR T-cell proliferation by depleting the patient of lymphocytes and their cytokine sink (endogenous cells that reduce the availability of cytokines, resulting in decreased functioning of CAR T cells; Kochenderfer et al., 2017).

Lymphodepleting therapy typically consists of fludarabine and cyclophosphamide for 3 days (days -5, -4, and -3), although the dose and schedule can vary among clinical trials and commercial products (Abramson et al., 2018; Kite Pharma Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). Common side effects of these chemotherapies include cytopenias, fatigue, nausea, and vomiting (Baxter Healthcare Corporation, 2013; Hallek et al., 2001). Alopecia also can occur (Baxter Healthcare Corporation, 2013). Prior to lymphodepletion, clinical providers should consider infection prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP; also known as PCP). After the chemotherapy, which is often completed in the outpatient setting, patients and their caregivers have a couple of days to rest before the CAR T-cell infusion.

CAR T-Cell Infusion

CAR T-cell infusion takes place on day 0 (Locke et al., 2019; Schuster et al., 2019). Patients are often ad-

mitted to the hospital ahead of time, usually day -1, if they are going to be monitored as inpatients. Before infusion of the CAR T cells, the patient's laboratory test results are reviewed and the oncology team conducts a thorough assessment. The day of the infusion is very important for patients and their caregivers, and it often prompts anxiety, excitement, and a lot of questions about what is to come. The nurse who is taking care of the patient should have a thorough understanding of the therapy and associated AEs to best support the patient and caregiver.

To prevent transfusion reactions, patients are premedicated before the infusion, typically with acetaminophen and diphenhydramine (Kite Pharma Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). Prior to infusing the CAR T-cell product, the clinical team should confirm if a leukocyte filter should be used. Current commercially available CAR T-cell therapies should not be administered with a leukocyte-depleting filter (Kite Pharma Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). The CAR T-cell product also needs to be thawed before infusion. Once the patient is premedicated and the product has thawed and been through all the safety checks between the nurses and cell-processing laboratory, the infusion begins. Emergency equipment is at the bedside, and pulse oximetry and telemetry should be continuous during the procedure. Infusion into a central line typically takes about 15 minutes. Patients sometimes react to the dimethyl sulfoxide (DMSO) in the product, which may present as shortness of breath, hypotension, fever, chest tightness, or rash (Syme et al., 2004). Vital signs are measured frequently before, during, and after the infusion.

On the day of CAR T-cell infusion (day 0), patients receive a CAR T-cell therapy identification card with the name of the product they received, the date they received it, important contact information, and reasons to seek urgent care. They are instructed to carry this card with them at all times to present to medical teams in an urgent care or emergency room setting in the event of a medical emergency (Kite Pharma Inc., 2018; Novartis Pharmaceuticals Corporation, 2018b).

Toxicity Monitoring and Treatment

Once the CAR T cells are infused, the nursing and medical team should be on high alert for any evi-

dence of CRS and neurologic events, which are two of the most prevalent and potentially serious toxicities associated with CAR T-cell therapy (Neelapu et al., 2018). If patients receive their CAR T-cell infusion in the outpatient setting, they should be assessed daily for at least 7 days after the infusion. Onset of CRS can be within hours to days from the infusion and typically presents as a fever (Neelapu et al., 2018). This clinical picture would warrant admission for closer inpatient monitoring. Cytokine release syndrome can progress to a sepsis-like picture with hypotension and/or hypoxia. It can also cause organ dysfunction, coagulopathies, profound fatigue and malaise, and gastrointestinal distress (Neelapu et al., 2018). Patients will often have a poor appetite and, therefore, poor oral intake, worsening fatigue, and dehydration. Vital signs are measured at a minimum of every 4 hours to monitor for rising fevers, decreased blood pressure, and decreased oxygen saturation (Neelapu et al., 2018). Daily monitoring of electrolytes, kidney and liver function, blood counts, and coagulopathies is necessary throughout the risk period for CRS (Neelapu et al., 2018). Monitoring levels of C-reactive protein and ferritin is helpful as these can provide insight into the grade of CRS (Brudno & Kochenderfer, 2016; Neelapu et al., 2018; Wang & Han, 2018). There have been cases of hemophagocytic lymphohistiocytosis during high-grade CRS; a severely elevated ferritin level may be concerning for hemophagocytic lymphohistiocytosis and would warrant further workup (Neelapu et al., 2017).

Neurologic events may be biphasic, with onset of the first phase occurring simultaneously with CRS symptoms, usually within the first 5 days after CAR T-cell therapy (Neelapu et al., 2018). These events can occur with or without CRS, and just because a patient has had CRS does not mean that he/she will have neurologic events. The common initial presentation of neurotoxicity is very subtle—it may be a slowness to respond, flat affect, mild confusion, headache, or tremor. This can progress to aphasia, disorientation, confusion, and inability to complete instrumental activities of daily living and even activities of daily living. Patients may demonstrate seizure activity, somnolence, agitation, and may progress further still to obtundation and/or an inability to protect the airway (Neelapu et al., 2018). There

have been several cases reported of cerebral edema in patients who have received anti-CD19 CAR T-cell therapy. Neurologic events are generally reversible, but cerebral edema is a rare fatal AE that progresses quickly, may lead to patient death, and is a medical emergency (Neelapu et al., 2018). Assessment for cerebral edema should always be performed with the onset and worsening of neurologic events. A thorough neurologic assessment should be completed daily by the providers and at least once per shift for nursing, with increasing frequency in the setting of neurotoxicity (Neelapu et al., 2018).

Staff in the intensive care units (both medical and neurological) should be knowledgeable about AEs associated with CAR T-cell therapy, particularly CRS and neurologic events, because patients may be transferred to their unit with both conditions. For further details on the grading and management of CRS and neurologic events, please review the second article in this supplement (Adkins, 2019).

Discharge

All nonhematologic AEs should improve to grade ≤ 1 before consideration is given to discharge. Hematologic AEs due to lymphodepleting chemotherapy may linger beyond the resolution of CRS and neurologic events and, if they can be monitored and managed in the outpatient setting, should not prohibit discharge. Some patients become profoundly deconditioned and require an inpatient rehabilitation center to bridge them to discharge home. Others may require in-home physical therapy and/or nursing services.

Per the Risk Evaluation and Mitigation Strategies (REMS) programs for FDA-approved CAR T-cell therapies, patients who have received a commercial CAR T-cell therapy must be advised to stay within 2 hours of the treating institution for the first 30 days after the infusion, because there is a chance for late onset or recurrence of CRS and/or neurologic events (Kite Pharma Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). Institutional requirements may also dictate that a caregiver stay with the patient at all times during that 30-day period. Patients are instructed not to drive for 60 days after the infusion, given the risk for late-onset neurologic events (Kite Pharma

Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). Patients and their caregivers should keep the CAR T-cell therapy identification card with them at all times in the event of an emergency. Discharge instructions should include a list of signs and symptoms to be aware of that could be associated with CRS or neurologic events.

Outpatient Follow-Up

Patients who have received CAR T-cell therapy products commercially or through many clinical trials are required by the FDA to be assessed daily for the first 7 days after the infusion (Kite Pharma Inc., 2017; Novartis Pharmaceuticals Corporation, 2018a). Institutional guidelines or clinical trial study protocols may require that patients be admitted for this period, but it is not a REMS program requirement for commercial CAR T-cell therapy.

When follow-up for 7 days post infusion is on an outpatient basis, advanced practitioners and other providers should be knowledgeable about AE assessment and management and have a plan in place to treat in the outpatient setting, if needed, and expedite patient admission for further management. Beyond this high-risk window and/or after discharge, monitoring is dictated by the clinical needs and preference of the medical team. Often, patients continue to have a poor appetite and may need intravenous fluids. Many of them have thrombocytopenia and/or anemia requiring blood product transfusion (Locke et al., 2019; Schuster et al., 2019). Although there is no standard follow-up of disease response, often the first assessment (positron emission tomography/computed tomography) is conducted at 1 month after infusion.

Transition of Care

During the first month after infusion, the patient's local/primary oncologist should be notified of his/her CAR T-cell therapy experience and recovery. Patient care should be transitioned from the treating institution to the patient's primary oncologist. Over the long term, patients will begin to be followed by their primary oncologist more often and less often by the treating institution. This schedule will vary among institutional guidelines/recommendations. It is important that the transition of care is smooth and that communication is kept open. Local oncologists should be educated on acute AEs of CAR

T-cell therapy, steroid use, and long-term effects of treatment (i.e., hypogammaglobulinemia). They should know the point of contact at the treating institution and have a thorough understanding of when and how to contact the oncologist who treated the patient with CAR T-cell therapy.

CONCLUSION

CAR T-cell technology is revolutionary, boosting a patient's own immune system to fight cancer. CAR T-cell therapy helps T cells to overcome some of the mechanisms that cancer has developed for evading the immune system. The two commercially available anti-CD19 CAR T-cell therapies, as well as some currently in clinical trials, have consistently demonstrated effective, long-lasting responses to a single treatment. Providing access to this innovative treatment will require institutions to establish workflows that guide health-care providers and patients through each step of the process. Despite logistical hurdles of implementing a CAR T-cell therapy program, this is an exciting time in cancer treatment. Close collaboration between patients, caregivers, and the multidisciplinary team is essential for positive patient outcomes and successful implementation of this potentially curative therapy. ●

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