

# Beyond CAR T-Cell Therapy: Continued Monitoring and Management of Complications

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## Abstract

Chimeric antigen receptor (CAR) T-cell therapy has recently emerged as a groundbreaking treatment for CD19-expressing hematologic malignancies and received rapid approval by the U.S. Food & Drug Administration. Tisagenlecleucel and axicabtagene ciloleucel are now widely available at CAR T-cell therapy centers around the United States. Many patients have achieved complete response or remission despite failing multiple previous lines of therapy, but some patients endure the severe risks of cytokine release syndrome, neurotoxicity, and other immunologic effects. As more patients receive this therapy, they will present to their primary oncologists in the community setting for continued follow-up. Oncology-trained advanced practitioners must then have a working knowledge of CAR T-cell therapy, its toxicities, and follow-up care. This review presents the CAR T-cell therapy development and infusion process with associated immediate management. In addition, patient assessment and disease monitoring, relevant diagnostics, unique grading systems to CAR T-cell therapy toxicities, indications for hospitalization, infection prophylaxis, and management of nonneutropenic and neutropenic fever are presented.

**C**himeric antigen receptor (CAR) T-cell therapy is a novel treatment currently approved by the U.S. Food & Drug Administration (FDA) for CD19-expressing hematologic malignancies (acute lymphoblastic leukemia, chronic lymphocytic leukemia, and lymphoma), yet the management of toxicities, long-term follow-up, and patient monitoring remain challenges both in the inpatient and

outpatient setting. Numerous clinical trials are underway investigating the use of CAR T-cell therapy in not only CD19-targeted malignancies, but also in multiple myeloma, leukemias, and some solid tumors (Arabi, Torabi-Rahvar, Shariati, Ahmadbeigi, & Naderi, 2018; Zhao, Chen, Francisco, Zhang, & Wu, 2018).

CAR T-cell therapy is an immunotherapy manufactured from a patient's own T cells, which are geneti-

cally engineered to mount an immune response to a specific target of a malignancy, leading to cell death of the target tumor (Maus & Levine, 2016; Zhao et al., 2018). These T cells develop memory and subsequently create lasting immunity, theoretically creating a durable antitumor effect.

The treatment has proven largely effective in achieving remission and durable response for relapsed/refractory CD19-expressing hematologic malignancies, but patients are likely to develop toxicities that require intensive care under the management of a multidisciplinary team while in the hospital and subsequently as they recover (Zheng, Kros, & Li, 2018).

As the therapy expands and more patients demonstrate long-term survival outcomes, it is imperative that oncology advanced practitioners have a working knowledge of the indications, development, patient assessment, toxicities, complications, and survivorship issues of CAR T-cell therapy (Maus & Levine, 2016). This article will review these topics in the context of FDA-approved therapies.

## FDA-APPROVED THERAPIES

Two commercially available therapies, tisagenlecleucel (Kymriah) by Novartis Pharmaceuticals and axicabtagene ciloleucel (axi-cel; Yescarta) by Kite Pharma are gaining momentum as they provide treatment options for patients who have endured multiple lines of chemotherapy and radiation without remission or cure.

Tisagenlecleucel is indicated in patients up to 25 years old with B-cell acute lymphoblastic leukemia (ALL) and adults with relapsed/refractory large B-cell lymphomas after two or more lines of systemic therapy. This includes diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Novartis Pharmaceuticals Corporation, 2018).

Axi-cel is only indicated for adults with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy. This includes DLCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL from follicular lymphoma (Kite Pharma, Inc., 2019). Neither of these therapies are indicated for primary central nervous system lymphoma.

## CAR T-CELL PROCESS

### Harvesting and Manufacturing

After a patient is selected for treatment with either product, the patient must undergo T-cell harvesting through leukapheresis, much like peripheral blood stem cells are harvested for stem cell transplant. From this point, the cells are transferred to the company laboratory for manufacturing. Processing involves activation of T cells, transduction, and expansion (Maus & Levine, 2016). The cells are activated by binding to specific human leukocyte antigen complexes with tumor-associated antigens. Transduction is accomplished by using incompetent retroviral vectors that contain the gene specific to the CD19 malignancy being treated. Finally, the modified T cells undergo ex vivo expansion, then are formed into a cryopreserved suspension (Dushenkov & Jungsuwadee, 2019).

### Lymphodepleting Chemotherapy

In the week prior to the administration of the CAR T cells, patients receive lymphodepleting chemotherapy. For patients being treated for B-cell ALL with tisagenlecleucel, fludarabine is administered at 30 mg/m<sup>2</sup> intravenously for 4 days and cyclophosphamide at 500 mg/m<sup>2</sup> intravenously for 2 days with the first dose of fludarabine. The cells are then infused between 2 to 14 days after chemotherapy (Novartis Pharmaceuticals Corporation, 2018).

Lymphodepleting chemotherapy differs for DLBCL treated with tisagenlecleucel. Patients may receive fludarabine at 25 mg/m<sup>2</sup> intravenously for 3 days and cyclophosphamide at 250 mg/m<sup>2</sup> intravenously for 3 days concurrently with fludarabine. Alternatively, bendamustine at 90 mg/m<sup>2</sup> intravenously for 2 days may be administered if the patient has previously experienced grade 4 hemorrhagic cystitis with cyclophosphamide or resistance to cyclophosphamide in previous treatments. The T cells are infused 2 to 11 days after chemotherapy is complete (Novartis Pharmaceuticals Corporation, 2018).

Conversely, axi-cel administration is preceded by only one option for chemotherapy. Patients receive cyclophosphamide at 500 mg/m<sup>2</sup> and fludarabine at 30 mg/m<sup>2</sup> intravenously on days -5, -4, and -3 prior to cell infusion (Kite Pharma, Inc., 2019).

### Infusion and Monitoring

Patients are premedicated with acetaminophen and diphenhydramine prior to infusion, largely to prevent an adverse reaction to the preservative. Infusion may be performed in the inpatient or outpatient setting and depends on the patient's tumor burden, performance status, and the experience of the treatment center (Dushenkov & Jungsuwadee, 2019). Following infusion, patients are closely monitored for signs and symptoms of toxicity. Although protocols vary by treatment center, patient assessment generally occurs at least every 4 hours (Neelapu et al., 2018). Bedside nurses have created protocols specific to their treatment centers that enable rapid evaluation and management (Anderson & Latchford, 2019). Such protocol assessments include vital signs and neurologic exam to determine the presence and/or severity of cytokine release syndrome (CRS) or neurologic toxicity, recently termed immune effector cell-associated neurotoxicity syndrome (ICANS; Lee et al., 2019).

Beyond these two major toxicities, other adverse reactions for both products include fever, hypotension, tachycardia, fatigue, encephalopathy, headache, tremors, chills, anorexia, diarrhea, nausea, vomiting, constipation, hypoxia, febrile neutropenia, hypogammaglobulinemia, infection, cough, dizziness, acute kidney injury, edema, and cardiac arrhythmias (Kite Pharma, Inc., 2019; Novartis Pharmaceuticals Corporation, 2018). Patients are monitored daily for at least 7 days following infusion, then are to stay close to the treatment center for at least 4 weeks (Kite Pharma, Inc., 2019; Novartis Pharmaceuticals Corporation, 2018).

### TOXICITY DEFINITIONS AND RISK FACTORS

Cytokine release syndrome occurs as the CAR T cells mount an immune response against the targeted B cells. Patients present with pyrexia, hypotension, respiratory distress and hypoxia, and possibly multiorgan system failure (MOSF). One of these major toxicities is ICANS, which presents with encephalopathy, altered mental status, difficulty in both verbal and written language, confusion, delirium, agitation, somnolence, motor dysfunction, seizures, increased intracranial pressure, and papilledema. The CAR T-cell therapy-

associated TOXicity (CARTOX) Working Group noted that CRS is most likely to occur in the first 5 days following cell infusion, while ICANS occurs both during the initial 5 days and may extend beyond this time (Lee et al., 2019). Risk factors for both of these toxicities include high in vivo CAR T-cell populations, high disease burden, larger CAR T-cell dose, and high-dose lymphodepleting chemotherapy (Brudno & Kochenderfer, 2019; Wang & Han, 2018; Zhang, Song, & Liu, 2018). Both of these conditions require intensive care when severe. Treatment includes corticosteroids, tocilizumab, aggressive fluid resuscitation, vasopressor support, and antiepileptics (Lee et al., 2019).

An additional, but rare, toxicity is hemophagocytic lymphohistiocytosis (HLH), also termed macrophage-activation syndrome (MAS). With this toxicity, there is intense activation of the immune system with infiltration of lymphocytes into tissues resulting in MOSF (Lee et al., 2019). These patients may demonstrate liver failure and hepatosplenomegaly, coagulopathies, and increased ferritin (Lee et al., 2019; Namuduri & Brentjens, 2016). Other major adverse reactions include serious infection, prolonged cytopenia, and hypogammaglobulinemia, for which the patient remains at risk outside of their time as an inpatient (Kite Pharma, Inc., 2019; Novartis Pharmaceuticals Corporation, 2018).

CAR T-cell therapy is now widely commercially available with increasing numbers of clinical trials for not only hematologic malignancies, but also solid tumors (Pettitt et al., 2018). At least 800 are underway worldwide (ClinicalTrials.gov, 2019). It is only a matter of time until patients present to primary care offices, emergency departments, and outpatient oncology clinics for follow-up following this unique immunotherapy. For this reason, it is imperative that the advanced practitioner in oncology be aware of not only the major toxicities and their sequelae, but also ongoing immunologic and neurologic side effects (Brudno & Kochenderfer, 2019; Namuduri & Brentjens, 2016; Zheng et al., 2018).

### MANAGEMENT OF COMPLICATIONS

An array of complications may arise following therapy, but major categories include CRS, neurologic side effects, and immunologic implications.

### Cytokine Release Syndrome

As discussed previously, CRS is an immune response due to the release of cytokines from the CAR T-cells, resulting in life-threatening fever, hypotension, tachycardia, respiratory distress, rash, and possible MOSF. One major cytokine noted to correlate with both CRS and neurologic toxicity was interleukin (IL)-6 (Mahmoudjafari et al., 2019). Both commercially available products provided grading scales to evaluate CRS severity, but the recently published American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading is more comprehensive. It includes grades 1 through 5, with varying severities of fever, hypotension, and hypoxia (Table 1; Lee et al., 2019).

Cytokine release syndrome primarily occurs within the first week of therapy, lasts on average 1 week, and is handled in a CAR T-cell treatment center (Mahmoudjafari et al., 2019). Patients often require intensive care unit monitoring with hemodynamic support. Treatment requires the infusion of tocilizumab, an anti-IL-6 humanized monoclonal antibody to target the IL-6 cytokines implicated in CRS. Systemic corticosteroids such as dexamethasone, methylprednisolone, or hydrocortisone are considered as second-line therapy for CRS so as not to inhibit CAR T-cell activity against the tumor (Lee et al., 2019; Mahmoudjafari et al., 2019).

### Neurologic

Neurotoxicity is chiefly an acute toxicity, but has been reported to occur over 1 year following CAR T-cell infusion and lasts on average for 1 to 2 weeks

(Mahmoudjafari et al., 2019). It is critical that providers caring for patients who have received CAR T cells be knowledgeable on this long-term adverse effect. Two published grading systems exist for ICANS: the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the CARTOX criteria. Each contains grades 1 to 4 indicating severity of adverse events such as encephalopathy, seizure, tremor, headache, altered mental status, and elevated intracranial pressure (ICP).

The CARTOX criteria contains a unique score known as the CARTOX-10, which has now been updated to the Immune Effector Cell-Associated Encephalopathy (ICE) score by the ASTCT for completeness and consistency across treatment centers (Lee et al., 2019). This scoring system can easily be implemented in a variety of settings. It assesses orientation, naming, writing, and attention (Table 2). The ASTCT ICANS Consensus Grading combines the ICE score with level of consciousness, presence of seizure, motor findings, and elevated ICP/cerebral edema (Lee et al., 2019). Workup for neurotoxicity may include CT and/or MRI, lumbar puncture, or electroencephalogram if seizure is suspected. In addition to scoring assessments, the patient should be assessed for papilledema. Just as with CRS, patients in the inpatient setting are treated with corticosteroids and tocilizumab based on severity, but corticosteroids are considered first line for this toxicity. Tocilizumab is only administered if neurotoxicity coincides with concurrent CRS. Should a patient present to an outpatient oncology office with any

**Table 1. American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine Release Syndrome Consensus Grading**

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever (temperature $\geq 38^{\circ}\text{C}$ )	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Death
<i>With</i>					
Hypotension	None	Not requiring vasopressors	One vasopressor with or without vasopressin	Multiple vasopressors (excludes vasopressin)	Death
<i>And/or</i>					
Hypoxia	None	Low-flow nasal cannula <sup>a</sup> or blow-by	High-flow nasal cannula <sup>a</sup> , facemask, nonrebreather mask, or Venturi mask	Positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	Death

*Note.* BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure.

<sup>a</sup>Low-flow nasal cannula:  $\leq 6$  L/min; high-flow nasal cannula: oxygen  $> 6$  L/min. Information from Lee et al. (2019).



neurologic changes suspicious for ICANS, the patient should be directed to the appropriate CAR T-cell specialized center. Seizure prophylaxis may be provided using levetiracetam (Mahmoudjafari et al., 2019).

Older adults who have received CAR T-cell therapy are particularly vulnerable to neurologic adverse events, as they are already at risk for delirium due to hospitalization, infection, and general overall stress to the body. Careful assessment for low-grade ICANS should be implemented in this population. Subtle changes in behavior or memory often present similarly to delirium in the older population and should be treated as side effects of CAR T-cell therapy rather than an effect of hospitalization.

### Immunologic

As previously discussed, CAR T-cells target CD19 B cells of both DLBCL and B-cell ALL. Consequently, an on-target/off-tumor effect of B-cell aplasia occurs (Zheng et al., 2018). B cells do recover, but this recovery can take upward of 3 years (Brudno & Kochenderfer, 2019; Neelapu et al., 2018). This further impairs the patient's immunity in cumulative effect with chemotherapy-induced neutropenia. As a result of B-cell aplasia, immunoglobulin production is decreased leading to low levels. Hypogammaglobulinemia places the patient at risk for opportunistic infections and must be addressed (Namuduri & Brentjens, 2016). Therefore, it is recommended that IgG levels are monitored so that replacement can be provided. Intravenous immunoglobulin infusion practices vary, as Barmettler and Price (2015) cite administration for IgG levels anywhere from 96 to 755 mg/dL. A reasonable threshold would be to infuse IgG for levels below 500 mg/dL (Brudno & Kochenderfer, 2019).

Cytopenia is common following lymphodepleting chemotherapy, compounding the risk for infection with B-cell aplasia and hypogammaglobulinemia. Close monitoring and transfusion support are required. Neelapu (2019) reported that severe cytopenias occurred 30 days following CAR T-cell therapy and are likely due to ongoing CAR T-cell effects. Growth factor may be used to support patients in recovery, and prophylactic antimicrobials are recommended to prevent bacterial, viral, and

**Table 2. Immune Effector Cell–Associated Encephalopathy (ICE) Assessment Tool for Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)**

	Points
<b>Orientation:</b> To year, month, city, hospital	4
<b>Naming:</b> Ability to name 3 objects (e.g., point to clock, pen, button)	3
<b>Follow commands:</b> Ability to follow simple commands (e.g., “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1
<b>Writing:</b> Ability to write a standard sentence	1
<b>Attention:</b> Ability to count backwards from 100 by 10	1

*Note.* Scoring: 10, no impairment; 7–9, grade 1 ICANS; 3–6, grade 2 ICANS; 0–2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS. Information from Lee et al. (2019).

fungal infections. Antimicrobial prophylaxis is indicated for patients with an absolute neutrophil count of  $< 1,000/\mu\text{L}$ ; recommended medications are antibiotics including fluoroquinolone, antifungals such as an oral triazole, and antivirals such as acyclovir (Taplitz et al., 2018). It is likely the patient received fludarabine and is at risk for *Pneumocystis jirovecii* pneumonia, and should therefore receive trimethoprim-sulfamethoxazole for 1 year (Neelapu, 2019; Taplitz et al., 2018)

Finally, febrile episodes are common following therapy. The patient may or may not be neutropenic during the fever and should be treated accordingly. Initial workup includes a thorough history and review of symptoms to identify possible causes, two sets of blood cultures (one from a central line and one peripheral, or two peripheral), a urine culture, and chest x-ray at minimum.

Due to combined B-cell aplasia and cytopenia, additional testing should be considered, including sputum Gram stain and culture, lumbar puncture, CT scan, and stool testing as indicated (Cantwell & Perkins, 2018). If the patient is neutropenic (absolute neutrophil count  $< 500/\mu\text{L}$ ), hospitalization is indicated in this population due to the high risk of morbidity and mortality associated with fever, bacteremia, and sepsis (Pherwani, Ghayad, Holle, & Karpiuk, 2015). If the need for hospitalization is in question, the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index Score is utilized to identify if a patient is high or low risk

and has been validated in the hematologic population (Taj et al., 2017). Many patients in this population are likely to be high risk and should be sent to a CAR T-cell treatment center for broad spectrum intravenous antibiotics and further management.

For those who are deemed low risk, outpatient management can be safely performed with close follow-up. Following infectious workup, a review of previous antimicrobial therapy and renal and hepatic function is performed prior to initiating therapy. Patients should be prescribed ciprofloxacin at 500 mg po every 8 hours with amoxicillin-clavulanate at 500 mg po every 8 hours (or clindamycin at 600 mg po every 8 hours with penicillin allergy). Careful coordination of follow-up via office visit or telephone, along with collaboration with the caregiver at home to perform symptom monitoring, is imperative (Pherwani et al., 2015; Taplitz et al., 2018).

## ASSESSMENT OF THE PATIENT WHO HAS RECEIVED CAR T-CELL THERAPY

### Disease Status

Following treatment, patients and family members await news if the tumor has responded to therapy. Depending on the tumor burden and expansion of T cells, the rapidity of response varies. Evaluation of disease status is performed using PET scan and bone marrow biopsy with peripheral flow cytometry (Beaupierre et al., 2019). Disease response is described as partial response (PR) or complete response (CR) for patients with lymphoma (Locke et al., 2019), minimal residual disease (MRD)-positive or MRD-negative complete remission (Park et al., 2018), or metabolically active tumor response (Shah et al., 2018).

### Physical Exam

The provider must be meticulous during the physical exam due to the wide array of toxicity and side effects caused by CAR T-cell therapy, in addition to the fact that there is little known about the long-term effects. It should be preceded by a thorough history that includes the chemotherapy and infusion time frame, as well as a detailed review of systems and focus on signs and symptoms of infection.

The neurologic exam must be comprehensive and include assessment of orientation, executive functioning, communication, and motor status.

Cognitive testing is most important in evaluating for any lingering neurotoxicity and is used to grade ICANS (Brudno & Kochenderfer, 2019; Lee et al., 2019). Although a tool like the Mini-Mental Status Exam (MMSE) may be used (as this was utilized during the ZUMA-1 trial evaluating axicel as a treatment option for B-cell lymphoma; Whittington et al., 2019), experts in CAR T-cell therapy have developed specific grading systems that are still applicable during follow-up. The CARTOX-10/ICE neurologic toxicity grading is a 10-point system that evaluates orientation and alertness, object naming, writing, and counting (Brudno & Kochenderfer, 2019; Lee et al., 2019). Further neurologic assessment should evaluate coordination, gait, motor changes, vision disturbances, and sensation.

Cardiovascular examination evaluates fluid status, orthostatic hypotension, and signs of arrhythmia. Although the majority of adverse cardiovascular events occur during the immediate treatment phase, patients may present with lingering side effects of end-organ damage as a result of on-target/off-tumor toxicity and unknown long-term effects of CAR T-cell therapy (Zhao et al., 2018). The cumulative effects of previous chemotherapy must also be taken into consideration (Zheng et al., 2018). In addition, signs and symptoms of thromboembolic events including deep vein thrombosis and pulmonary embolism should be noted due to the inflammatory effects of therapy and likely immobility during hospitalization. Similarly, pulmonary assessment should include sequelae of CRS or infection that may have occurred during CAR T-cell therapy. Auscultation and percussion for adventitious or absence of lung sounds is paramount for detecting signs or symptoms of pneumonia, bronchiolitis, or pleural effusion. The provider should take note of oxygenation, exertional dyspnea, and overall conditioning.

Gastrointestinal and genitourinary assessment includes a review of current functioning, such as continence, diarrhea or constipation, nausea or vomiting, dysuria, and blood in stool or urine. For patients with DLBCL in the abdomen, cases of gastrointestinal perforation have been reported as a consequence of both CAR T-cell therapy (Hu et al., 2018) and chemotherapy (Tatar et al., 2017), and therefore must be monitored for both dur-

ing and after treatment. In addition, patients may have received broad spectrum antibiotics during CAR T-cell treatment, placing them at risk for *Clostridium difficile* infection in the setting of lymphodepleting chemotherapy.

Finally, a thorough examination of the skin for signs of infection, wounds or breakdown, sensitivities, and central line status is necessary. Patients who were severely deconditioned during treatment may present with pressure injury. During inspection of the integumentary system, it is imperative to examine the lymph nodes as well, especially for those patients with DLBCL.

### Laboratory and Diagnostic Testing

Standard lab work, including a comprehensive metabolic panel, complete blood count with differential, magnesium, phosphorus, prothrombin time, partial thromboplastin time, and international normalized ratio should be collected on all patients following CAR T-cell therapy. Notable abnormalities included anemia, neutropenia, thrombocytopenia, electrolyte derangement, and prolonged clotting times. Other unique labs to order are D-dimer, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH), uric acid, lactate, creatinine phosphokinase (CPK), and ferritin (Brudno & Kochenderfer, 2019; Lee et al., 2019). These inflammatory markers are indicators of lingering risk for CRS, tumor lysis, or immune processes such as HLH. Although late occurrence of such toxicity is rare, there is so little known about the long-term effects of this therapy that a thorough review of all relevant laboratory parameter is imperative. Finally, immunoglobulin levels are monitored for hypogammaglobulinemia, a common complication.

Any decision to perform radiographic imaging or invasive diagnostic testing is based on patient presentation at the time of evaluation. Signs and symptoms of respiratory distress lend to performing CT scanning over a routine chest radiograph, as these patients are at higher risk for complex infections, pleural effusions, and respiratory end-organ damage. Similar precautions should be taken for any neurologic, cardiovascular, gastrointestinal, or genitourinary complications. For example, a patient presenting with acute confusion should not only be ruled out for stroke or infection but also

CAR T-cell invasion of the central nervous system. Such a case would not only require a CT scan of the brain, but likely MRI and lumbar puncture.

Studies have also measured circulating CAR T-cells, which tend to peak early in treatment but have also been present for as long as 20 months, as cited in Zhang and colleagues (2018). Another study in refractory advanced DLBCL noted significant increases in total T cells 1 to 2 months post infusion (Wang et al., 2014). It remains unclear if higher levels of cells are associated with better overall survival. It is, however, correlated with more severe toxicities. Noting this may provide insight into anticipating any complications.

### Caregiver Involvement

Patients are required to have a 24-hour caregiver when enrolled for CAR T-cell therapy. This individual is crucial to the comprehensive evaluation of the CAR T-cell patient. Even while hospitalized, patient caregivers may be the first to note a subtle change in behavior that may indicate neurologic toxicity. Caregivers provide transport to appointments, assistance with medications, and monitoring for signs and symptoms of infection. While performing a history and review of systems with the patient, the provider should incorporate input from the caregiver. This individual may also require support or respite, for which social services referrals are warranted.

### Patient-Reported Outcomes

Clinical trials have reported rates of toxicity and disease response, but few include patient-reported outcomes. Factors such as physical functioning, financial toxicity, socioemotional status, role function, and pain should not be neglected (Chakraborty et al., 2019). Despite numerous grading systems for CAR T-cell specific toxicities, none exist to evaluate for patient-reported outcomes following this therapy. Both tisagenlecleucel and axi-cel are indicated for relapsed/refractory disease that has been heavily pretreated with chemotherapy, radiation, and other immunotherapies. Patients are likely to already suffer from functional deficits, psychological stress, and chronic symptom management issues.

Performance status is often already scored prior to and during therapy using the Eastern Cooperative Oncology Group (ECOG) Performance

Status score (ECOG-ACRIN, 2019). This focuses on self-care ability and both functional and essential activities of daily living, but neglects other important patient-reported outcomes. Four core items were outlined by the National Cancer Institute and Symptom Management and Health-Related Quality of Life steering committee: general health status, physically unhealthy days, mentally unhealthy days, and activity limitation days (Yin, Njai, Barker, Siegel, & Liao, 2016). The National Comprehensive Cancer Network Distress Thermometer covers these domains and is an excellent tool that uses a validated 0 to 10 Likert scale to assess patient “practical problems,” “family problems,” “emotional problems,” “spiritual/religious concerns,” and “physical problems” (NCCN, 2019). Assessment tools specifically for the oncology population include the Functional Assessment of Cancer Therapy–General and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. Both of these are considerably comprehensive with multiple functional domains, symptom scores, and even chemotherapy-specific questions (Chakraborty et al., 2019). Although no standardized recommendations exist at this time about which tool to use, the oncology provider should include such an assessment in routine follow-up, as patients not only hope for a cure, but optimal quality of life.

## CONCLUSIONS AND IMPLICATIONS

Chimeric antigen receptor therapy is a groundbreaking treatment for CD19-expressing hematologic malignancies and has received rapid approval by the FDA. While significant positive outcomes of overall survival and remission have been achieved with both tisagenlecleucel and axicel, they carry major toxicity risks, including CRS and ICANS, which may lead to long-term sequelae. Little research exists on continuing effects of CAR T-cell therapy, and this article highlights this challenge. From what studies are available, patients may present with lingering CRS, neurologic, and immunologic complications. It is imperative that the advanced practitioner in oncology maintain an updated and working knowledge on how to manage these patients as an increasing number of individuals have access to a revolutionary yet hazardous therapy. ●

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## References

- Anderson, K., & Latchford, T. (2019). Associated toxicities: Assessment and management related to CAR T-cell therapy. *Clinical Journal of Oncology Nursing*, 23(2), 13–19. <https://doi.org/10.1188/19CJON.S1.13-19>
- Arabi, F., Torabi-Rahvar, M., Shariati, A., Ahmadbeigi, N., & Naderi, M. (2018). Antigenic targets of CAR T cell therapy. A retrospective view on clinical trials. *Experimental Cell Research*, 369(1), 1–10. <https://doi.org/10.1016/j.yexcr.2018.05.009>
- Barmettler, S., & Price, C. (2015). Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab—for how long? *Journal of Allergy and Clinical Immunology*, 136(5), 1407–1409. <https://doi.org/10.1016/j.jaci.2015.06.035>
- Beaupierre, A., Lundberg, R., Marrero, L., Jain, M., Wang, T., & Alencar, M. C. (2019). Management across settings: An ambulatory and community perspective for patients undergoing CAR T-cell therapy in multiple care settings. *Clinical Journal of Oncology Nursing*, 23(2), 27–34. <https://doi.org/10.1188/19CJON.S1.27-34>
- Brudno, J. N., & Kochenderfer, J. N. (2019). Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Reviews*, 34, 45–55. <https://doi.org/10.1016/j.blre.2018.11.002>
- Cantwell, L., & Perkins, J. (2018). Infectious disease emergencies in oncology patients. *Emergency Medicine Clinics of North America*, 36(4), 795–810. <https://doi.org/10.1016/j.emc.2018.06.009>
- Chakraborty, R., Sidana, S., Shah, G. L., Scordo, M., Hamilton, B. K., & Majhail, N. S. (2019). Patient-reported outcomes with chimeric antigen receptor T cell therapy: Challenges and opportunities. *Biology of Blood and Marrow Transplantation*, 25(5), e155–e162. <https://doi.org/10.1016/j.bbmt.2018.11.025>
- ClinicalTrials.gov. (2019). Search of: CAR-T. Retrieved from <https://clinicaltrials.gov/ct2/results?cond=&term=CAR-T&cntry=&state=&city=&dist=>
- Dushenkov, A., & Jungsuwadee, P. (2019). Chimeric antigen receptor T-cell therapy: Foundational science and clinical knowledge for pharmacy practice. *Journal of Oncology Pharmacy Practice*, 25(5), 1217–1225. <https://doi.org/10.1177/1078155219836480>
- ECOG-ACRIN. (2019). ECOG performance status. Retrieved from <https://ecog-acrin.org/>
- Hu, Y., Wang, J., Pu, C., Zhao, K., Cui, Q., Wei, G.,...Huang, H. (2018). Delayed terminal ileal perforation in a relapsed/refractory B-Cell lymphoma patient with rapid remission following Chimeric Antigen Receptor T-Cell Therapy. *Cancer Research and Treatment*, 50(4), 1462–1466. <https://doi.org/10.4143/crt.2017.473>
- Kite Pharma, Inc. (2019). Yescarta (axicabtagene-ciloleucel)



- package insert. Retrieved from <https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf>
- Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N.,...Neelapu, S. S. (2019). ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biology of Blood and Marrow Transplantation*, 25(4), 625–638. <https://doi.org/10.1016/j.bbmt.2018.12.758>
- Locke, F. L., Ghobadi, A., Jacobson, C. A., Miklos, D. B., Lekakis, L. J., Oluwole, O. O.,...Neelapu, S. S. (2019). Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1–2 trial. *Lancet Oncology*, 20(1), 31–42. [https://doi.org/10.1016/S1470-2045\(18\)30864-7](https://doi.org/10.1016/S1470-2045(18)30864-7)
- Mahmoudjafari, Z., Hawks, K. G., Hsieh, A. A., Plesca, D., Gatwood, K. S., & Culos, K. A. (2019). American Society for Blood and Marrow Transplantation pharmacy special interest group survey on chimeric antigen receptor T cell therapy administrative, logistic, and toxicity management practices in the United States. *Biology of Blood and Marrow Transplantation*, 25(1), 26–33. <https://doi.org/10.1016/j.bbmt.2018.09.024>
- Maus, M. V., & Levine, B. L. (2016). Chimeric antigen receptor T-cell therapy for the community oncologist. *The Oncologist*, 21(5), 608–617. <https://doi.org/10.1634/theoncologist.2015-0421>
- Namuduri, M., & Brentjens, R. J. (2016). Medical management of side effects related to CAR T cell therapy in hematologic malignancies. *Expert Reviews in Hematology*, 9(6), 511–513. <https://doi.org/10.1080/17474086.2016.1183479>
- National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Distress management. V1.2020. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/distress.pdf](https://www.nccn.org/professionals/physician_gls/pdf/distress.pdf)
- Neelapu, S. S. (2019). Managing the toxicities of CAR T-cell therapy. *Hematological Oncology*, 37(suppl 1), 48–52. <https://doi.org/10.1002/hon.2595>
- Neelapu, S. S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F. L.,...Shpall, E. J. (2018). Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. *Nature Reviews Clinical Oncology*, 15(1), 47–62. <https://doi.org/10.1038/nrclinonc.2017.148>
- Novartis Pharmaceuticals Corporation. (2018). Kymriah (tisagenlecleucel) package insert. Retrieved from <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf>
- Park, J. H., Rivière, I., Gonen, M., Wang, X., Sénéchal, B., Curran, K. J.,...Sadelain, M. (2018). Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *New England Journal of Medicine*, 378(5), 449–459. <https://doi.org/10.1056/NEJMoa1709919>
- Pettitt, D., Arshad, Z., Smith, J., Stanic, T., Holländer, G., & Brindley, D. (2018). CAR-T Cells: A systematic review and mixed methods analysis of the clinical trial landscape. *Molecular Therapeutics*, 26(2), 342–353. <https://doi.org/10.1016/j.jymthe.2017.10.019>
- Pherwani, N., Ghayad, J. M., Holle, L. M., & Karpiuk, E. L. (2015). Outpatient management of febrile neutropenia associated with cancer chemotherapy: Risk stratification and treatment review. *American Journal of Health-System Pharmacy*, 72(8), 619–631. <https://doi.org/10.2146/ajhp140194>
- Shah, N. N., Nagle, S. J., Torigian, D. A., Farwell, M. D., Hwang, W. T., Frey, N.,...Svoboda, J. (2018). Early positron emission tomography/computed tomography as a predictor of response after CTL019 chimeric antigen receptor T-cell therapy in B-cell non-Hodgkin lymphomas. *Cytotherapy*, 20(12), 1415–1418. <https://doi.org/10.1016/j.jcyt.2018.10.003>
- Taj, M., Nadeem, M., Maqsood, S., Shah, T., Farzana, T., & Shamsi, T. S. (2017). Validation of MASCC Score for risk stratification in patients of hematological disorders with febrile neutropenia. *Indian Journal of Hematology and Blood Transfusion*, 33(3), 355–360. <https://doi.org/10.1007/s12288-016-0730-7>
- Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Gleason, C., Hawley, D. K.,...Flowers, C. R. (2018). Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *Journal of Clinical Oncology*, 36(30), 3043–3054. <https://doi.org/10.1200/jco.18.00374>
- Tatar, C., Yavas, M., Akkus, O., Tapkan, B., Batikan, O. K., Bayrak, S., & Arikan, S. (2017). Intestinal perforation that developed after chemotherapy in a patient diagnosed with non-Hodgkin lymphoma: A case report and review of literature. *International Journal of Surgery Case Reports*, 39, 321–323. <https://doi.org/10.1016/j.ijscr.2017.08.058>
- Wang, Z., & Han, W. (2018). Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomarker Research*, 6, article number: 4. <https://doi.org/10.1186/s40364-018-0116-0>
- Wang, Y., Zhang, W. Y., Han, Q. W., Liu, Y., Dai, H. R., Guo, Y. L.,...Han, W. D. (2014). Effective response and delayed toxicities of refractory advanced diffuse large B-cell lymphoma treated by CD20-directed chimeric antigen receptor-modified T cells. *Clinical Immunology*, 155(2), 160–175. <https://doi.org/10.1016/j.clim.2014.10.002>
- Whittington, M. D., McQueen, R. B., Ollendorf, D. A., Kumar, V. M., Chapman, R. H., Tice, J. A.,...Campbell, J. D. (2019). Long-term survival and cost-effectiveness associated with axicabtagene ciloleucel vs chemotherapy for treatment of b-cell lymphoma. *JAMA Network Open*, 2(2), e190035. <https://doi.org/10.1001/jamanetworkopen.2019.0035>
- Yin, S., Njai, R., Barker, L., Siegel, P. Z., & Liao, Y. (2016). Summarizing health-related quality of life (HRQOL): Development and testing of a one-factor model. *Population Health Metrics*, 14, 22. <https://doi.org/10.1186/s12963-016-0091-3>
- Zhang, L. N., Song, Y., & Liu, D. (2018). CD19 CAR-T cell therapy for relapsed/refractory acute lymphoblastic leukemia: factors affecting toxicities and long-term efficacies. *Journal of Hematology & Oncology*, 11(1), article number: 41. <https://doi.org/10.1186/s13045-018-0593-5>
- Zhao, Z., Chen, Y., Francisco, N. M., Zhang, Y., & Wu, M. (2018). The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. *Acta Pharmaceutica Sinica B*, 8(4), 539–551. <https://doi.org/10.1016/j.apsb.2018.03.001>
- Zheng, P. P., Kros, J. M., & Li, J. (2018). Approved CAR T cell therapies: Ice bucket challenges on glaring safety risks and long-term impacts. *Drug Discovery Today*, 23(6), 1175–1182. <https://doi.org/10.1016/j.drudis.2018.02.012>