The Role of the Research Advanced Practice Provider in CAR T-Cell Clinical Trials

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Abstract

In recent years, chimeric antigen receptor (CAR) T-cell therapy has emerged as an effective and potentially paradigm-shifting therapy for patients with refractory lymphoma and myeloma. This novel therapy involves engineering T cells to recognize specific antigens on the surface of cancer cells. Several CAR T-cell products are approved by the US Food and Drug Administration as a result of numerous clinical trials. Due to the complexity of these studies and the high level of care required for CAR T-cell therapy patients, the role of the research advanced practice provider (APP) has become increasingly central to the success of CAR T-cell trials. This review article explores the vital role of the research APP in CAR T-cell clinical trials.

In recent years, chimeric antigen receptor (CAR) T-cell therapy has emerged as an effective therapy for patients with refractory lymphoma and myeloma. To date, six CAR T-cell therapies have been approved by the US Food and Drug Administration (FDA) for this patient population (Table 1). These approvals were the culmination of complex clinical trials over several years. At our center, CAR T-cell trials have only increased in number as various pharmaceutical companies develop novel versions of this therapy. Due to the high acuity of the patients enrolled on these trials and the level of care required, it has become increasingly common for advanced practice providers (APPs) to serve as study coordinators, a role traditionally filled by research nurses. This article will explore the important role of the research APP in CAR T-cell clinical trials.

LYMPHOMA

Non-Hodgkin lymphoma (NHL) is a heterogenous collection of hematologic malignancies with a wide array of subtypes, ranging from aggressive to indolent in nature. It accounts for 4% of all cancers (Thandra et al., 2021). Advances in targeted therapies and immunotherapy have improved overall survival outcomes

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Table 1. FDA-Approved CAR T-Cell Therapies

Manufacturer	Drug	Trade name	FDA approval	Design
Kite/Gilead	Axicabtagene ciloleucel (axi-cel)	Yescarta	• Relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy, or refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy • Relapsed/refractory follicular lymphoma after two or more lines of systemic therapy, including combination of an anti-CD20 monoclonal antibody and alkylating agent	• Target: anti-CD19 • Construct: CD28 co-stimulatory domain • Vector: retroviral
Novartis	Tisagenlecleucel (tisa-cel)	Kymriah	• Relapsed/refractory pediatric B-cell precursor acute lymphoblastic leukemia • Relapsed refractory large B-cell lymphoma after two or more lines of systemic therapy	• Target: CD19 • Construct: 4-1BB co-stimulatory domain • Vector: lentiviral
Juno/ Celgene/ Bristol Myers Squibb	Lisocabtagene maraleucel (liso-cel)	Breyanzi	• Relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy, or refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy or not eligible for hematopoietic stem cell transplantation	• Target: CD19 • Construct: 4-1BB co-stimulatory domain • Vector: lentiviral
Kite/Gilead	Brexucabtagene autoleucel (brexu-cel)	Tecartus	• Relapsed/refractory mantle cell lymphoma • Relapsed/refractory adult B-cell precursor acute lymphoblastic leukemia	• Target: CD19 • Construct: CD28 co-stimulatory domain • Vector: retroviral
Juno/ Celgene/ Bristol Myers Squibb	Idecabtagene vicleucel (ide-cel)	Abecma	• Relapsed/refractory multiple myeloma after four or more lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody	• Target: BCMA • Construct: 4-1BB co-stimulatory domain • Vector: lentiviral
Janssen Biotech, Inc.	Ciltacabtagene autoleucel (cilta-cel)	Carvykti	• Relapsed/refractory multiple myeloma after four or more lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody	• Target: BCMA • Construct: 4-1BB co-stimulatory domain • Vector: lentiviral

for these patients, but there remains an unmet need for patients with relapsed or refractory disease. Approximately two thirds of patients with diffuse large B-cell lymphoma will be cured with front-line therapy (Abramson, 2020). However, those patients who have relapsed/refractory disease will have a poor prognosis, with only 50% of patients who undergo standard therapy with autologous stem cell transplant achieving a durable response (Abramson et al., 2019). Another NHL subtype, mantle cell lymphoma, remains incurable with conventional therapies. Furthermore, approximately 20% of follicular lymphoma patients will have disease recurrence within 24 months of their initial therapy, and these patients have a poor prognosis (Abramson, 2020). CAR T-cell therapy has recently emerged as a highly effective therapy for these chemotherapy-refractory NHL patients, with a durable remission rate of 40% (Roschewski et al., 2022). Axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), lisocabtagene maraleucel (Breyanzi), and brexucabtagene autoleucel (Tecartus) are CAR T-cell therapies approved by the FDA in recent years for these lymphoma subtypes (Table 1).

MYELOMA

Multiple myeloma, which accounts for 10% of hematologic cancers (Michels & Petersen, 2017), is a plasma cell malignancy arising in the bone marrow. In recent years, the treatment landscape for this disease has broadened to a variety of modali-

ties, including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies (Anderson, 2022). While these novel agents have allowed for better disease control, myeloma remains incurable, and drug resistance and relapse remain an issue.

With the success of CAR T-cell trials in lymphoma patients, the use of CAR T-cell therapies in myeloma patients was a logical expansion. In 2021, the FDA approved idecabtagene vicleucel (Abecma) for the treatment of relapsed or refractory multiple myeloma in adult patients who had previously undergone at least four lines of therapy that included an immunomodulatory drug, a proteasome inhibitor, and a monoclonal antibody targeting CD38, adding another potent weapon in the arsenal against this disease (Anderson, 2022). In February 2022, ciltacabtagene autoleucel (Carvykti) became the second CAR T-cell therapy approved for myeloma under the same indications (FDA, 2022).

CAR T-CELL THERAPY

CAR T cells are human T cells genetically modified to recognize a specific target antigen (Figure 1). Lymphocytes are collected via apheresis and sent to a manufacturing facility to be engineered. CAR T cells are produced by transducing a genetically altered CAR fusion protein using a lentiviral or retroviral vector into autologous cells. The result is a chimeric T cell that is capable of recognizing a specific tumor antigen (Sermer & Brentjens, 2019). Since the first iteration, each generation of CAR T-cell constructs has resulted in increasingly more efficient and durable responses (Anderson & Mehta, 2019). As demonstrated in Figure 2, the current FDA-approved CAR T cells are designed with the same general construct. In earlier generations, the construct consisted of a single-chain variable fragment antigen-recognition domain and a CD3-derived T-cell activation domain. In later generations, a costimulatory domain (i.e., CD28, 4-1BB, or both) was added (Chavez & Locke, 2018). There

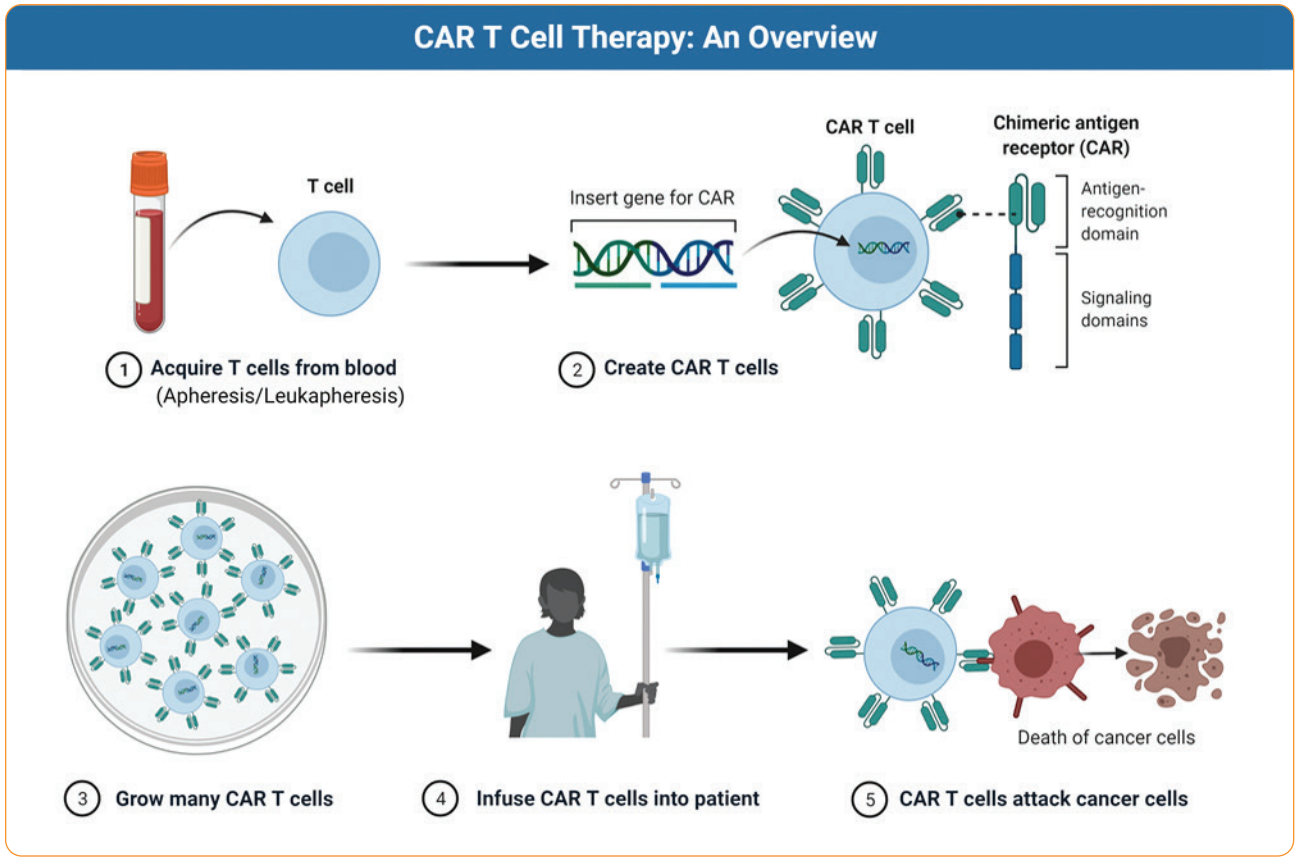

Figure 1. Overview of CAR T-cell therapy. Adapted from "CAR T Cell Therapy Overview" by BioRender.com (2022).

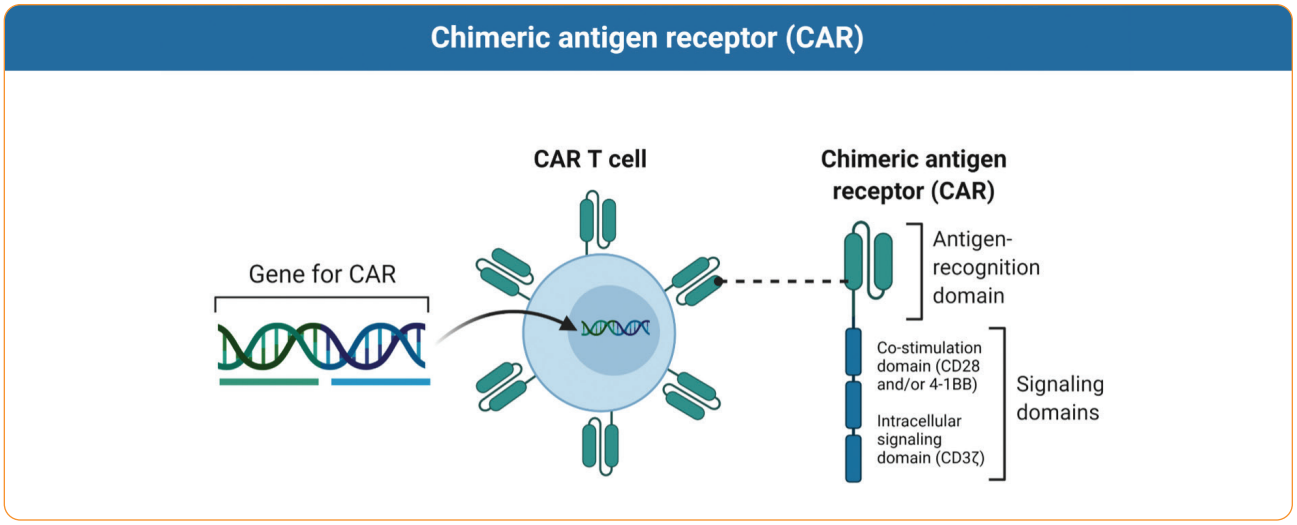

Figure 2. Overview of CAR T-cell constructs. Adapted from "Chimeric Antigen Receptor (CAR)" by BioRender.com (2022).

are also various allogeneic CAR T-cell products currently being studied in clinical trials. These CAR T-cell products are derived from healthy donors and may confer an advantage because the product is readily available.

Production to Cell Infusion

For the currently approved CAR T-cell products, the method of production and administration can vary among institutions as well as specific CAR T-cell products, but in general, the process includes T-cell apheresis and activation followed by CAR transduction, expansion of the CAR T cells, and quality control measures before the final product is released for infusion. The patient first undergoes leukapheresis/apheresis at the treating site for collection of peripheral blood mononuclear cells. The collection is shipped to a manufacturing site where the T cells are separated and activated before undergoing transduction of the CAR DNA. The cells are then expanded ex vivo, purified, and checked for quality and sterility. The final product is cryopreserved and shipped to the treating site when the patient is ready to proceed with therapy. Typical turnaround times from cell collection to shipment of the final CAR T-cell product can vary from 2 to 4 weeks, depending on the specific cell product (Anderson & Mehta, 2019; Abramson et al., 2019).

While the patient is waiting for their cells to be manufactured, the patient may undergo bridging therapy if deemed appropriate for disease control. Bridging therapy may include standard-of-care chemotherapies, targeted therapies, corticosteroids, or radiation therapy. To allow room for T-cell expansion, the patient undergoes a conditioning/lymphodepleting chemotherapy (LDC) regimen, typically consisting of fludarabine and cyclophosphamide (Locke et al., 2017). There is typically a 2- to 4-day break between LDC and CAR T-cell infusion (Anderson & Mehta, 2019).

At our center, most patients can undergo LDC in the outpatient setting unless they are deemed to have a high risk of toxic effects due to comorbidities or high tumor burden. Certain CAR T-cell products, such as tisagenlecleucel and lisocabtagene maraleucel, can be infused in the outpatient setting with daily clinical assessments for 7 to 10 days after infusion (Neelapu et al., 2017). Other CAR T-cell products, such as axicabtagene ciloleucel, are usually infused in the inpatient setting followed by at least a 7-day inpatient observation due to a higher risk of toxicities that requires close monitoring (Neelapu et al., 2017). Many CAR T-cell products that are under investigation in clinical trials may require inpatient administration. All patients should be closely monitored for toxicities for the first 30 days following infusion. Approximately 1 month following CAR T-cell infusion, PET and/or CT scans are conducted to assess treatment response. Patients are then followed up monthly—or more frequently if needed—for up to 3 months. Patients who remain in remission can continue to

be followed with serial surveillance scans after the 3-month timepoint as deemed appropriate. All patients are typically followed up on for survival and potential complications such as secondary malignancies for up to 15 years after treatment.

COMMON TOXICITIES

Some toxicities are unique to CAR T-cell therapy. Many of these effects are reversible if addressed early; thus, recognition and appropriate treatment of these CAR T-cell–related toxicities are imperative.

Cytokine Release Syndrome

Cytokine release syndrome (CRS) is the most common acute CAR T-cell–related toxicity (Neelapu, 2019). It is a systemic inflammatory response triggered by cytokines released by CAR T cells. This cytokine release likely activates other immune cells such as macrophages to release more cytokines. Patients with CRS may present with a wide range of symptoms ranging from mild fever, myalgias, rigors, and fatigue, to multiorgan dysfunction that can result in death (Neelapu, 2019). Cytokine release syndrome is often reversible and self-limited if managed properly.

Since the inception of CAR T-cell therapy, multiple CRS grading systems have been used across trials and institutions, necessitating the creation of a standardized grading and management system. The most readily accepted guidelines for grading and management of CRS were developed by the American Society for Transplantation and Cellular Therapy (ASTCT), although some clinical trials may still use previous grading systems (Lee et al., 2019). According to the ASTCT guidelines, fever (≥ 38°C) is the hallmark presenting symptom and is required for the diagnosis of CRS (Lee et al., 2019). The clinical presentation of CRS can overlap with those of infection, tumor lysis syndrome, and disseminated intravascular coagulation, and patients should undergo appropriate workup, including empiric antibiotics and supportive care with antipyretics, intravenous (IV) fluids, and vasopressors if needed (Anderson, 2019). Daily monitoring of inflammatory markers such as C-reactive protein (CRP) and ferritin levels can be useful in identifying CRS onset and resolution. Grading of CRS should occur at least twice daily and additionally with any status change. At our center, treatment of CRS is based on the severity of grade as outlined in Table 2, although if there are study-specific guidelines, those are followed instead. Serum interleukin 6 (IL-6) levels have been shown to correlate with CRS severity (Neelapu, 2019). For persistent or higher-grade CRS, the administration of an IL-6 antibody such as tocilizumab and/or corticosteroids is warranted (Neelapu, 2019).

Cytokine release syndrome usually occurs within 1 to 2 weeks following cell infusion, although median onset times can vary among CAR T-cell products due to differences in their constructs (Brudno & Kochenderfer, 2019). Patients treated with 4-1BB-costimulated CAR T cells often experience later CRS onset compared to patients treated with CD28-costimulated CAR T cells because CD28-costimulated CAR T cells undergo more rapid expansion than slower-growing but more persistent 4-1BB-costimulated CAR T cells (Neelapu, 2019).

Immune Effector Cell–Associated Neurotoxicity Syndrome

CAR T-cell–related neurotoxicity was previously thought to be part of the CRS spectrum; however, it is now considered a distinct but related entity. Immune effector cell–associated neurotoxicity syndrome (ICANS) is the second most common acute CAR T-cell therapy–related toxicity after CRS (Neelapu, 2019). The exact mechanism of ICANS is not fully understood but is believed to be driven in part by excessive cytokine release in a manner similar to CRS (Neelapu, 2019). It can manifest in a variety of clinical presentations, including mild encephalopathy, delirium, focal neurologic deficits, aphasia, seizures, cerebral edema, and death. It can be mild and self-limited or severe and lethal; however, most patients recover without sequalae. Immune effector cell–associated neurotoxicity syndrome can develop concurrently with CRS but more often occurs after CRS resolution.

Like CRS, ICANS can be reversible and self-limited if identified early and managed properly (Neelapu, 2019). However, ICANS grading and management is distinct from that of CRS. Immune effector cell–associated neurotoxicity syndrome grading has also been standardized according to ASTCT guidelines (Lee et al., 2019). Grading in-

Table 2. Management of Cytokine Release Syndrome

	Diagnostic workup	Supportive care	Therapies
Grade 1	• Fever workup (assess for infection) • Cardiac telemetry and pulse oximetry	• Acetaminophen and hypothermia blanket • Ibuprofen if fever not controlled with above • Empiric broad-spectrum antibiotics • Consider filgrastim products for neutropenia • IV fluids	• Consider tocilizumab for 1 dose for persistent fever lasting more than 3 days
Grade 2	• Fever workup if not already done • Cardiac telemetry and pulse oximetry	• IV fluid boluses for hypotension • For hypoxia, use supplemental oxygen as needed and monitor closely • Continue symptomatic management of fever as in grade 1 CRS	• Administer tocilizumab for 1 dose and consider dexamethasone 4–10 mg IV for 1 dose; reassess in 6 hr or earlier if indicated • Tocilizumab can be repeated every 8 hr for up to 3 doses in a 24-hr period
Grade 3	• Fever workup if not already done • Cardiac telemetry and pulse oximetry • Obtain echo if not already done for hypotension	• Transfer to ICU • For hypotension, IV boluses and vasopressors as needed • For hypoxia, supplemental oxygen according to oxygen needs • Continue symptomatic management of fever as in grade 1 CRS	Hypotension: • Tocilizumab as in grade 2 if not given already and: » If on one vasopressor: add dexamethasone 10 mg IV every 6 hr » If on two vasopressors: dexamethasone 20 mg IV every 6 hr • Once CRS improves to grade 1 or less, taper/stop steroids as appropriate Hypoxia: • Tocilizumab as in grade 2 and dexamethasone 10 mg IV every 6 hr as in grade 2 if not given already • If no improvement within 24 hr or rapid progression of pulmonary infiltrates or sharp increase in FiO2 needs, increase dexamethasone to 20 mg IV every 6 hr • Once CRS improves to grade 1 or less, taper/stop steroids as appropriate
Grade 4	• Fever workup if not already done • Cardiac telemetry • Obtain echo if not already done for hypotension • For hypoxia, monitor oxygen saturation while on mechanical ventilation	• Transfer to ICU • IV fluid boluses as needed as in grade 2 CRS • Vasopressors as in grade 3 CRS • Positive pressure ventilation as needed • Continue symptomatic management of fever as in grade 1 CRS	• Tocilizumab as in grade 2 and methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by rapid taper as appropriate • If hypotension and/or hypoxia are refractory > 24 hr or patient is rapidly deteriorating, consider additional therapies (e.g., siltuximab, anakinra, cyclophosphamide), safety switches (e.g., i-caspase-9 or EGFRt-positive products)

Note. Adapted from MD Anderson Cancer Center Department of Clinical Effectiveness (2020). echo = echocardiogram; ICU = intensive care unit; IV = intravenous; FiO2 = fraction of inspired oxygen; EGFRt = truncated EGFR.

cludes daily assessments using the immune effector cell–associated encephalopathy (ICE) scoring system (Lee et al., 2019). Corticosteroids remain the mainstay of ICANS treatment (Table 3). At our institution, most patients receiving CAR T-cell therapy are also started on prophylactic antiseizure medications such as levetiracetam for the first 30 days following cell infusion. If there are study-specific guidelines for ICANS management, these will be followed instead.

Onset of ICANS can be delayed and can occur several days to weeks after CAR T-cell infusion (Brudno & Kochenderfer, 2019). Due to the potential of delayed onset, we recommend patients

Table 3. Management of Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

	Diagnostic workup	Supportive care	Therapies
Grade 1	• Imaging of the brain (CT can be done if MRI not feasible) • Neurology consultation • ICE score assessment every 6 hr or as clinically indicated • EEG • Consider diagnostic lumbar puncture if other causes of encephalopathy suspected	• Aspiration precaution, IV hydration • Withhold oral intake and assess swallowing; convert oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause CNS depression • May use low doses of lorazepam or haloperidol for agitation with careful monitoring	• Dexamethasone 10 mg IV for 1 dose and reassess in 6 hr or earlier as needed • If associated with concurrent CRS, add tocilizumab
Grade 2	• Neurologic workup as in grade 1 ICANS	• Supportive care as in grade 1 ICANS	• Dexamethasone 10 mg IV every 12 hr • Once ICANS improves to grade 1 or less, taper/stop steroids as appropriate • If associated with concurrent CRS, add tocilizumab
Grade 3	• Neurologic workup as in grade 1 ICANS • Consider repeat imaging every 2–3 days for persistent grade 3 or higher encephalopathy • Consider diagnostic lumbar puncture if grade 3 encephalopathy persists for 2 or more days	• Supportive care as in grade 1 ICANS • Consider transfer to ICU for encephalopathy • Transfer to ICU for seizure or focal cerebral edema • Treat seizures as appropriate • If there are new abnormal findings on brain imaging not related to primary malignancy, control hypertension and correct any uremia and/or coagulopathy	• For encephalopathy: dexamethasone 10 mg IV every 6 hr. If grade 3 encephalopathy persists for > 24 hr, increase to 20 mg IV every 6 hr • For seizures: dexamethasone 20 mg IV every 6 hr • For focal edema (brain stem/thalamus): methylprednisolone 1,000 mg/day in divided doses IV for 3 days followed by taper. For other areas: methylprednisolone 1,000 mg/day in divided doses for 1 day, followed by taper • Once ICANS improves to grade 1 or less, taper/stop steroids as appropriate • If associated with concurrent CRS, add tocilizumab
Grade 4	• Neurologic workup as in grade 1 ICANS • Repeat neuroimaging and lumbar puncture as in grade 3 ICANS • MRI of spine if motor weakness	• Transfer to ICU • Supportive care as in grade 1 ICANS • Consider mechanical ventilation for encephalopathy and/or depressed level of consciousness; manage as per grade 3 ICANS • Treat seizures as appropriate • Treat diffuse cerebral edema or raised intracranial pressure as appropriate	• Methylprednisolone 1,000 mg/day in divided doses for 3 days followed by taper • Once ICANS improves to grade 1 or less, taper/stop steroids as appropriate • If associated with concurrent CRS, add tocilizumab • If grade 4 ICANS is refractory for > 24 hr or if patient is deteriorating rapidly, consider additional therapies (e.g., siltuximab, anakinra, cyclophosphamide), safety switches (e.g., i-caspase-9 or EGFRt-positive products)

Note. Adapted from MD Anderson Cancer Center Department of Clinical Effectiveness (2020). CNS = central nervous system; echo = echocardiogram; EEG = electroencephalogram; ICE = immune effector cell–associated encephalopathy; ICU = intensive care unit; IV = intravenous; EGFRt = truncated EGFR.

stay within close proximity to the treating site or hospital, have a caregiver present with them at all times, and abstain from driving or operating heavy machinery for 8 weeks following their cell infusion.

Cytopenias, B-Cell Aplasia, and Hypogammaglobulinemia

A common effect of CAR T-cell therapy is B-cell aplasia and hypogammaglobulinemia due to the destruction of nonmalignant B cells (Neelapu,

2019). Fludarabine, which is part of many lymphodepleting regimens used before CAR T-cell administration, can also contribute to prolonged cytopenia. All of these factors can predispose CAR T-cell therapy patients to infection. At our institution, all CAR T-cell patients are placed on antimicrobial prophylaxis. Patients who develop frequent or prolonged infections in the setting of hypogammaglobulinemia may also receive IV immunoglobulin G infusions. Patients who experience persistent and profound cytopenias may require workup for infections such as cytomegalovirus, human herpesvirus 6, and herpes simplex virus reactivation, and secondary malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) may need to be ruled out through bone marrow aspiration or biopsy.

JOURNEY OF A PATIENT AND THE ROLE OF THE RESEARCH APP IN A CAR T-CELL TRIAL

Several open CAR T-cell studies are currently enrolling lymphoma or myeloma patients at our institution. A critical component of running such a high number of studies is the use of research APPs. Research APPs serve as navigators for patients throughout their participation in a study. The following outlines the process our patients undergo as participants of a CAR T-cell clinical trial and the role of the research APP at each step.

Screening and Enrollment

The first step in enrolling a patient on a clinical trial is the screening process. The research APP will screen the patient based on the study's specific eligibility criteria. If the patient is potentially eligible, the research APP will assist the treating physician in the consent process. The research APP, along with the treating physician, will discuss the study and review the informed consent document with the patient. Patients are given ample time to have their questions or concerns answered prior to signing the consent document. Once the patient has consented to enrollment on the study, they will undergo screening tests as required by the study to determine eligibility. These may include laboratory tests, imaging scans, diagnostic/research biopsies, and cardiac workup. The research APP is central to this process as they will order these tests and ensure all screening requirements are met. They will communicate the screening results with the study sponsor to obtain official approval of enrollment.

During this time, the research APP is also communicating with our financial clearance department to ensure the patient is approved by their insurance to participate in the study. If further information is required by the patient's insurance, the research APP will provide this.

Leukapheresis and CAR T-Cell Manufacturing

Once the patient's eligibility is officially confirmed, they can proceed with leukapheresis of their cells. The research APP will coordinate scheduling of the procedure and courier pick-up of the cell collection with our Apheresis Clinic, Cell Therapy Lab, and the study sponsor. The research APP will also counsel the patient on holding anticoagulant therapy in case an apheresis catheter is needed and order any necessary laboratory and other testing prior to the procedure. Communication with the research APP regarding the status of the cells throughout the manufacturing process is critical in determining when or if the patient can proceed with LDC and CAR T-cell infusion. If the patient is receiving bridging therapy following leukapheresis, the research APP may coordinate this with the treating team to ensure they are adhering to appropriate regimens and washout periods per study guidelines and assist with ordering the chosen bridging therapy.

Lymphodepleting Chemotherapy and CAR T-Cell Infusion

Once the patient's CAR T cells have met the viability and quality standards, the research APP will be notified of the earliest available delivery date. The APP will coordinate the patient's return to start LDC and CAR T-cell infusion and schedule the delivery of the cells. Before starting LDC, the patient should undergo appropriate laboratory tests, including COVID-19 testing. If the patient received bridging therapy, they may also need new baseline imaging, including a CT scan of the head without contrast if the patient does not have recent brain imaging. The patient is assessed by their treating physician before the start of LDC, and the research APP also ensures the patient continues to meet the criteria for treatment.

Once cleared, the patient will undergo an LDC regimen. Depending on the study design, the type of LDC agents and schedule may vary; however, the regimen typically consists of fludarabine and cyclophosphamide for 3 days followed by a break of at least 2 days before the CAR T cells are infused. After the break following LDC, the CAR T cells can be administered. Depending on the type of CAR T-cell product and study design, inpatient administration may be warranted. At our institution, CAR T-cell therapy patients are admitted only to our Lymphoma/Myeloma Unit, where nursing staff are experienced in caring for these high acuity patients. For some CAR T-cell products, outpatient administration may be acceptable. Our institution has a dedicated outpatient CAR T-cell unit where patients can receive CAR T-cell infusions and post–CAR T-cell outpatient care such as IV hydration or transfusion support in the days immediately following their infusion or CAR T-cell admission.

The research APP's role is critical during this time period, as they will write and co-sign orders for the LDC and cell infusion, collection of laboratory samples or biopsies required for research, and general admission. The research APP also coordinates cell delivery with the Cell Therapy Lab and the cell infusion with the nursing staff. They will record any adverse events as required by the study for source documentation. The research APP may also manage toxicities from LDC to post–cell infusion, and order interventions as appropriate (antiemetics, IV hydration, pain medications, medications to control hypersensitivity reactions, growth factor support, etc.).

Post-Treatment Period

The patient should be monitored closely for the first 30 days following their cell infusion. Each CAR T-cell study has its own guidelines regarding toxicity management, supportive care, and prophylactic regimens, and they may not necessarily follow the established ASTCT guidelines for CRS or ICANS. An important part of the research APP's role is to ensure the study guidelines are followed by communicating clearly and frequently with the involved medical staff within the inpatient and/or outpatient setting. This requires ongoing and open conversations between the research APP, principal investigator (PI), sponsor, and outpatient/inpatient providers. Research APPs will communicate these guidelines via orders within the treatment plan, alerts placed on the patient's chart, emails, and/or phone calls.

The research APP monitors the patient post treatment for concerning toxicities such as infection, CRS, and ICANS, especially in the first 30 days. They will consult with the treating team and/or PI if needed and assist with any recommended interventions such as diagnostic workup, supportive care measures, or coordinating care with consulting services such as the Emergency Center, Cardiology, Neurology, or Infectious Disease. This is especially evident once the patient is monitored in the outpatient setting, as the research APP is often the main point of contact for the patient.

The study may require the patient to be followed up at certain points during this period (e.g., weekly or twice a week) for physical examinations and laboratory tests for clinical and research purposes. Approximately 30 days following the cell infusion, the patient will undergo imaging, usually with PET/CT, to assess disease response. The patient may then be required to be followed up at specific intervals for their respective study. The research APP will order these assessments accordingly and ensure compliance with the study schedule. Patients on CAR T-cell trials are typically followed up for at least 2 years following treatment. Once the patient has reached their "end of study" visit, they will often roll over to a long-term follow-up study, which may continue for up to 15 years. While the patient is on the study, the research APP may also assist the primary treating team by conducting physical exams as part of the study or outside of study-mandated timepoints and ordering supportive care or diagnostic tests that fall outside the purview of the study but are part of the patient's overall clinical management. The research APP may also assist with ensuring the patient is adhering to infection prophylaxis. Patients typically receive the regimens outlined in Table 4, unless a study has different guidelines. The research APP will ensure the patient continues to follow these regimens as applicable and consult with the treating physician and/or PI as needed.

Some CAR T-cell therapy patients may also require assessments outside of study-mandated timepoints, such as for monitoring of lab abnormalities. These repeated assessments may need to

Table 4. Concomitant Medications in CAR T-Cell Therapy

Indication	Drug(s)	Duration	Considerations	Alternatives
Viral prophylaxis (herpes zoster)	• Valacyclovir 500 to 1,000 mg orally daily	• Start on cell infusion day and continue for at least 1 year	• May stop after 1 year if CD4 count is > 200 cells/mL • Adjust dose for renal function	• Acyclovir 400 to 800 mg orally twice daily
Viral prophylaxis (hepatitis B)	• Entecavir 0.5 mg orally daily	• Start 2 weeks prior to cell infusion; stop 12–24 months post infusion	• Adjust dose for renal function • Monitor HBV titer once a month while on prophylaxis and monthly for 1 year after stopping • Consult ID if entecavir cannot be given or PCR undetectable	• Tenofovir disoproxil fumarate 300 mg orally daily, OR • Tenofovir alafenamide 25 mg orally daily
Bacterial prophylaxis (neutropenia with ANC < 1.0 K/μL that is expected to last ≥ 7 days)	• Levofloxacin 500 mg orally or IV daily	• Start cell infusion day and continue until ANC > 0.5 K/mL for 3 consecutive days without growth factor support	• Consult ID if allergic to quinolones or cephalosporins • Adjust dose for renal function	• Cefpodoxime 200 mg orally twice daily, OR • Ciprofloxacin 500 mg orally twice daily
Bacterial prophylaxis (*Pneumocystis jiroveci*)	• Pentamidine (inhaled) 300 mg flat dose every 28 days, OR • Pentamidine (IV) 4 mg/kg (max dose 300 mg) every 21 days • Once counts recover, switch to trimethoprim/sulfamethoxazole, (800/160 mg) orally every M, W, F, or orally twice daily for 2 consecutive days per week or 1 (400/80 mg) daily	• Start within 1 week of cell infusion and continue for at least 1 year	• All patients should receive PJP prophylaxis for at least 1 year post cell infusion, preferably with pentamidine until blood counts recover and then with trimethoprim/sulfamethoxazole or alternative • Monitor blood counts; if cytopenia develops, consider switching to alternative • May stop after 1 year if CD4 count is > 200 cells/mL	• Dapsone 100 mg orally daily or 50 mg orally every 12 hr, OR • Atovaquone 1,500 mg orally daily
Fungal prophylaxis (high-risk)	• Posaconazole 300 mg IV/orally daily	• Start day of cell infusion or when high-risk criteria are met, continue for at least 1 month after steroid completion. Do not stop if ANC is less than 1 K/mL.	• High risk includes patients with leukemia, recent allogeneic stem cell transplant, prior history of mold infection, neutropenia ≥ 14 days, or patients with grade 3 or 4 CRS/ICANS or who received ≥ 3 days of steroids	• Caspofungin 50 mg IV daily
Fungal prophylaxis (low-risk)	• Fluconazole 200–400 mg orally/IV daily	• Start day of cell infusion and continue until ANC > 0.5 K/mL for 3 consecutive days without growth factor support	• For patients who don't meet high-risk criteria for fungal infection • Adjust for renal function	• Caspofungin 50 mg IV daily
Hypogamma-globulinemia	• IVIG replacement as appropriate	• Consider in patients who develop hypogammaglobulinemia and recurrent infections		

Note. ANC = absolute neutrophil count; ICANS = immune effector cell–associated neurotoxicity syndrome; IV = intravenously; IVIG = intravenous immunoglobulin G; PCR = polymerase chain reaction test; ID= Infectious Disease; PJP = *Pneumocystis jiroveci* pneumonia.

Continued on following page

Table 4. Concomitant Medications in CAR T-Cell Therapy (cont.)

Indication	Drug(s)	Duration	Considerations	Alternatives
Seizure prophylaxis	• Levetiracetam 500 mg or 750 mg orally twice daily	• Start on cell infusion day and continue for 30 days post infusion, then once daily for 3 days, then stop	• Patients who experience seizures following cell infusion may need to continue beyond 30 days or increase dose as appropriate	
Neutropenia	• Filgrastim or equivalent biosimilar	• Consider for neutropenia if not contraindicated for cell product		

Note. ANC = absolute neutrophil count; ICANS = immune effector cell–associated neurotoxicity syndrome; IV = intravenously; IVIG = intravenous immunoglobulin G; PCR = polymerase chain reaction test; ID= Infectious Disease; PJP = *Pneumocystis jiroveci* pneumonia.

be continued several weeks to months after their cell infusion, as persistent or delayed pancytopenia can occur. Research APPs will often ensure these assessments are continued as needed. Many of our patients are also not local to our area and desire to continue assessments such as lab monitoring with their local oncologist, and to return to our institution only for study-mandated visits. The research APP will coordinate this care with the local oncologist, monitoring local lab results and providing guidance to the local care team. Often, it is the research APP who is the initial provider to review lab results and can notify the treating team and PI of concerning results. This may be especially important in infection prophylaxis/management, management of hypogammaglobulinemia, and concerns for therapy-related MDS or AML that necessitate immediate workup.

Other Contributions of Research APPs

Outside of the patient care research APPs provide to their study patients, they also serve a vital role in activation, conduct, and closeout of CAR T-cell studies. Prior to a study's official activation, research APPs at our institution ensure several tasks have been completed. They design treatment orders in collaboration with our electronic health record team, ensuring these orders are accurate and will result in proper and safe treatment administration. They review research lab orders and research biopsy order templates. They may review study budgets to ensure accuracy of charges to the sponsor vs. patients' insurance. They will also provide in-service training to applicable nursing staff prior to the first infusion and work with our Cell Therapy Lab to ensure all guidelines for storage and handling of the cellular product are understood. When the study is ready to be activated, a Site Initiation Visit (SIV) is conducted, which is typically the final meeting that occurs between the sponsor, monitors, PI, research staff, and relevant site staff (e.g., nursing, Cell Therapy Lab, Pharmacy, data coordinators, regulatory staff) prior to study activation. During the SIV, the sponsor and monitor review the study design, guidelines, management and reporting of adverse events, data entry requirements, investigational product administration, and site/PI responsibilities. The research APP plays a critical role during the SIV,

as they are familiar with every aspect of the study and often bring important issues to the attention of the sponsor and other attendees. After the SIV, they will determine if all requirements to activate the study have been met prior to requesting institutional review board (IRB) activation.

While the study is active, the research APP will work with regulatory staff to ensure any amendments to the study are submitted to our IRB. They submit annual reviews to our IRB. They will also submit initial and follow-up reports as required for the study for any serious adverse events. They may also review any safety reports distributed to all participating sites by the sponsor and consult with the principal investigator if these safety events need to be reported to our IRB. They will assist the study's data coordinator with providing source documentation for data entry, answering queries, and processing and shipment of research biopsy specimens. The research APP will also work closely with members of the sponsor team, including medical monitors, data scientists, and monitors or auditors.

When a study is ready to be permanently closed, the research APP may assist with closeout tasks such as resolving data queries and assisting with audits, and ensuring any final tasks are completed.

Research APPs and Research Nurses/ Clinical Research Coordinators

The role of the study coordinator has been traditionally filled by research nurses or clinical research coordinators/clinical study coordinators. However, given the complexity of cellular therapy trials, our institution has found a distinctive advantage of utilizing APPs in this role. At our institution, we serve in the hybrid role of a practicing APP and study coordinator. Many of our APPs come into the research role with prior clinical experience as inpatient or ambulatory APPs, while others were previously research nurses. Regardless of prior experience, all new research APPs go through an onboarding process where they are trained by an experienced research APP, and they also train in the ambulatory and inpatient setting with our non-research APPs. This provides a well-rounded orientation in both the clinical and research aspects of the role. Research APPs also continue to make a positive impact even outside their main role. Some continue to work with their PI in the clinic, also seeing non-trial patients and balancing non-clinic days with their research duties. Other research APPs volunteer to work in the inpatient service on weekends and holidays. Many of our research APPs have also provided training to our non-research APPs regarding CAR T-cell therapies (standard of care and study-specific) due to the extensive experience they have gained from closely working with CAR T-cell study patients. Former research APPs are also currently running our outpatient CAR T-cell program, further expanding their influence.

Given the higher scope of practice and breadth of knowledge APPs possess, they can adequately manage patients throughout their participation in a CAR T-cell study, especially regarding toxicities and supportive care. Given the central role of the study coordinator, the research APP serves as the main point of contact for the patient and their caregiver throughout their participation in the study. Because they are often the first point of contact, the research APP can recognize concerning signs or symptoms such as fever, pain, and lab abnormalities, and initiate early intervention. As APPs are still able to practice within the full scope of their license, they are able to order labs, diagnostic imaging, infusions, and medications as needed to ensure their patients are being safely and properly managed within the guidelines of the study.

At our institution, the attending physician or PI is consulted prior to the administration of drugs for CRS or ICANS management such as tocilizumab or corticosteroids. However, for other supportive care measures such as growth factor, transfusion, or electrolyte support, and infectious disease workup, experienced research APPs are able to initiate these interventions without needing to first consult the PI or they directly coordinate care with the help of the non-research inpatient/outpatient team overseeing the patient's care at the time. This is a distinct advantage over research nurses, who often need physician or APP oversight to initiate these interventions. Research nurses and clinical study coordinators are also unable to sign orders for treatments, infusions, or medications, further limiting their ability to effectively manage these patients when time is often critical. Our inpatient/outpatient nursing staff often contact the study coordinator first with questions or

concerns, and research APPs are able to give verbal or written orders directly, which can save crucial time.

The clinical study coordinator/research nurse is often the focal contact between the patient and the rest of their care team. From the initial conversation to introduce the study to the end of their participation, the patient relies heavily on communication with their research APP. Not only can they rely on the research APP for study-related guidance, but they can also rely on them for their expert clinical knowledge and coordination of care with the rest of their medical team. As evidenced by the success of our institution's research CAR T-cell program, research APPs have demonstrated they can function both autonomously and as a key member of the study patient's care team.

CONCLUSIONS

The contribution of research APPs in CAR T-cell clinical research is unquestionable. Because research APPs serve dual roles as study coordinators and APPs, their scope of practice and clinical knowledge allow for more efficient screening and management of this special patient population. They are a vital point of contact for their patients, colleagues, PIs, and study sponsor staff. The knowledge that research APPs gain through close management of CAR T-cell patients enables them to teach their colleagues in the inpatient/outpatient settings regarding toxicities of specific CAR T-cell products and their management. The unique role of the research APP is crucial to a robust and successful CAR T-cell clinical trial program at any institution.

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