Developing Infrastructure

Managing patients with cancer undergoing CAR T-cell therapy

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BACKGROUND: The introduction of chimeric antigen receptor (CAR) T-cell therapy has created challenges and opportunities for nurses. Clinical nurses must be educated on new treatment modalities to recognize toxicity symptoms and to support the therapy moving forward.

OBJECTIVES: This article will discuss nursing leadership and interventions to standardize care and ensure patient safety while receiving CAR T cells.

METHODS: Using evolving experience, an interprofessional team created standards of care and identified common toxicities and best practices for their management. Electronic documentation forms were designed, which led to the development of a new research infrastructure to care for patients.

FINDINGS: The ability to safely manage patients on CAR T-cell treatments has improved. The new infrastructure supported clinicians and scientists in transforming the outcomes of diseases with bleak prognoses, which is possible only with strong nursing leadership.

KEYWORDS
chimeric antigen receptor; CAR T cell; cytokine release syndrome; clinical research

HISTORICALLY, WHEN DISCUSSING TREATMENT FOR CANCER, healthcare professionals considered chemotherapy, surgery, or radiation; however, immunotherapy has emerged as a new treatment option. Some of the earliest immunotherapies were monoclonal antibodies, designed to mimic the human immune response to treat cancer (American Cancer Society [ACS], 2016). Today, one rapidly expanding immunotherapy treatment is adoptive cellular therapy (ACT), using a patient’s T cells to combat his or her disease (ACS, 2016).

ACT involves collecting a patient’s T cells through leukapheresis, in which white blood cells are filtered out from whole blood and the rest of the blood is returned to the patient. Then, the patient’s T cells are taken to a laboratory, where a new gene is introduced into the cells using an engineered viral vector. Unlike normal viruses, viral vectors are modified so they cannot replicate; instead, they are used to efficiently transfer genetic cargo into a patient’s cells. The gene introduced in ACT is the chimeric antigen receptor (CAR), which is carried by the vector and directs T cells to attack specific cancers (Abken, 2015). A CAR T cell produces a specific receptor on its surface to target a desired tumor marker.

In the inpatient hematology unit at a National Cancer Institute–designated cancer center, Memorial Sloan Kettering Cancer Center, healthcare professionals had a sense of urgency to find new treatment options for patients with relapsed or refractory B-cell malignancies because traditional therapies had been proven to have limited effect on survival. Research revealed that cluster of differentiation 19 (CD19), a protein found on the surface of most B cells, was a viable target for CAR T cells (Davila, Kloss, Gunset, & Sadelain, 2013). In the laboratory, CAR T cells directed against CD19 could efficiently recognize and kill B-cell targets in mice with B-acute lymphocytic leukemia (ALL), curing them. The results of these studies also suggested that CAR T cells can not only eradicate tumor cells but enhance long-term tumor stabilization (Davila et al., 2013). These findings showed promise for inducing remission in patients with relapsed or refractory CD19-positive B-cell malignancies. However, safely transitioning CAR T-cell treatments from the laboratory to the patient has required significant collaboration and innovation among principal investigators (PIs), clinical nurses, nursing leadership, and hospital administration.
At the time of initial CAR T-cell clinical trials, the Memorial Sloan Kettering Cancer Center was beginning to see an increase in complex clinical trials requiring inpatient admission. Once the complexity of the CAR T-cell clinical trials was recognized, a dedicated clinical research nurse was assigned to the trials and acted as a bridge between the research team and the nursing units. The clinical research nurse and inpatient multidisciplinary team collaborated to develop an infrastructure to support these phase I clinical trials. Although the focus of this article is a phase I clinical research program, the concepts of this article can be applied in various clinical settings initiating new treatment processes.

**Preparing for the First Clinical Trials**

Prior to their first clinical trial using CD19-targeted CAR T cells, the current authors collaborated with clinicians in bone marrow transplantation to review policies for autologous T-cell infusions. Nurses discussed the infusion process and possible side effects with the PI and scientists who developed and produced CAR T cells. They agreed to infuse the cells by gravity with IV macro-tubing to avoid using IV pumps. Some were concerned that these cells were fragile and would fracture with minimal pressure. They also decided to avoid infusing through a port because the angle of the noncoring needle could potentially damage the CAR T cell.

To prepare the clinical staff on the unit, the PI held educational in-services to provide a basic overview of the clinical trial, indication for CAR T-cell therapy, product handling, administration, and potential toxicities. This information guided the development of a CAR T-cell nursing infusion plan of care to be used before each infusion (see Figure 1).

Nursing preparation for the management of patients receiving CAR T cells included identification and designation of one inpatient unit on which to manage patients. All patients on CAR T-cell clinical trials were admitted for CAR T-cell infusion and monitored by the inpatient leukemia staff, which consisted of clinical nurses of mixed skill levels, varying from novice to expert, who embraced the challenges of the unknown in this clinical trial.

Multiple steps must be taken before infusion (see Figure 2). Prior to patient admission, the CAR T-cell production and quality testing is completed in the Cell Therapy and Cell Engineering Facility (CTCEF). This process takes about four weeks, and then the cells are frozen until the day of infusion. When the CAR T cells are ready to be reinfused, the patient’s disease is restaged for CAR T-cell dosing and, if still clinically appropriate, he or she is scheduled for inpatient admission. The initial treatment involves a conditioning chemotherapy, which is necessary to enhance the efficacy of the CAR T cells (Davila et al., 2013). Currently, no standard conditioning regimen exists; the treatment varies with each clinical trial. CAR T cells are infused two to seven days after the patient has completed conditioning therapy. On the day of infusion, patients receive IV hydration and premedication with acetaminophen (Tylenol®) and diphenhydramine (Benadryl®). Because CAR T cells are frozen with the cryoprotective agent dimethyl sulfoxide, which is associated with adverse reactions ranging from mild to serious, including anaphylaxis (Shu, Heimfeld, & Gao, 2013), premedication is recommended to decrease the likelihood of adverse reactions. The method of administration for the CAR T-cell treatments can vary from IV infusion to IV push according to clinical trial requirements.

**Toxicity Management**

As the volume of patients treated with CAR T cells increased, side effects were observed, including fevers and neurologic toxicities. The most common acute toxicity related to CAR T cells was identified as cytokine release syndrome (CRS), a constellation of symptoms related to a systemic inflammatory reaction to the treatment.

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**FIGURE 1.**

**NURSING CARE PLAN PRIOR TO INFUSION OF CAR T CELLS**

- **PROVIDE PATIENT AND CAREGIVER EDUCATION.**
  - Written and verbal education on CAR T-cell treatment
  - Written and verbal education on signs and symptoms of cytokine release syndrome
  - Electronically document education on Patient Education Documentation Form.

- **ENSURE EMERGENCY EQUIPMENT IS AVAILABLE.**
  - Code cart is on the unit
  - Hypersensitivity kit is at patient bedside

- **INITIATE IV HYDRATION.**
  - Fluid type and rate per clinical trial or as ordered by the provider
  - Document per standard nursing process

- **ADMINISTER PREMEDICATIONS.**
  - Administer oral acetaminophen and IV diphenhydramine 30 minutes before treatment with dosing per clinical trial or as ordered by the provider
  - Document per standard nursing policy

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CAR—chimeric antigen receptor
According to Brudno and Kochenderfer (2016), these included the following:

- Temperature of 100.4°F (38°C) or higher
- Chills and rigors
- Tachycardia
- Hypotension
- Hypoxia
- Generalized body edema
- Headache
- Rash
- Nausea
- Generalized body weakness
- Increased C-reactive protein

Usually, the symptoms patients experience undergoing CAR T-cell therapy are indicative of CRS, and are similar to the symptoms seen with rituximab (Rituxan®). Alternatively, when patients are treated with CAR T cells, CRS can develop over time as the cells proliferate and target cancer cells, causing a delayed release of cytokines.

Neurologic toxicities can develop in some patients in addition to or independent of CRS after CAR T-cell infusion, and can present as subtly as mild confusion, disorientation, aphasia, and tremors to somnolence, a decreased level of consciousness, and/or seizures. Neurologic side effects are treated based on their severity, avoiding interventions that may affect the efficacy and persistence of CAR T cells, such as higher doses of steroids. In addition, collaboration with the neurology service and intensive care unit staff was invaluable in managing more severe presentations of these side effects. Why some patients developed these neurologic toxicities after CAR T-cell infusion remains unclear, and data continue to be gathered to better understand this phenomenon (Davila, Sauter, & Brentjens, 2015). Many clinicians are developing algorithms for the management and grading of CRS.

Standards were created to guide nursing care of patients exhibiting the most prevalent and challenging toxicities (see Figure 3). A multidisciplinary team made up of the PI, nursing leadership, and clinical nurses collaborated to devise phase I CAR T-cell standards of care by carefully carrying out interventions and evaluating the results. For example, they learned that aggressive interventions for severe or life-threatening side effects could be used without compromising the efficacy of the T cells. This was accomplished through use of immunosuppressive medications, such as steroids or tocilizumab (Actemra®), a medication traditionally used to treat autoimmune diseases like rheumatoid arthritis.

### Emerging Challenges

Researchers also learned valuable lessons related to dosing and long-term side effects as more patients were treated. Once a CAR T cell connects to its target, it expands and proliferates, potentially increasing the intensity of the side-effect profile (Davila et al., 2014). Ultimately, early studies revealed that the more diseases a patient had, the lower dose of CAR T cells he or she needed. Conversely, patients with a lower disease burden require higher doses of T cells (Davila et al., 2014). In addition, the dose of CAR T cells each patient requires is dependent on his or her conditioning chemotherapy and disease subtype (Park, Geyer, & Brentjens, 2016). Researchers concluded that, although CD19 CAR T-cell therapy is effective in eradicating disease in patients with B-ALL and chronic lymphocytic leukemia, it could induce long-term B-cell aplasia, or failure of this type of white blood cell, in some patients. B-cell aplasia can be diagnosed by the presence of hypogammaglobulinemia, which can put patients at an increased risk for infection. Hypogammaglobulinemia can be treated with IV immunoglobulin; however, this temporary measure does not mitigate the potential long-term consequences of immunosuppression, such as life-threatening infection requiring prolonged antimicrobial therapy (Davila et al., 2013).

### Establishing Standards of Care

Ongoing clinical nurse education regarding the range and intensity of side effects of CAR T-cell therapy was essential for the team. Clinical nurses needed to recognize the urgency of prompt reporting of signs and symptoms of related toxicities. The team worked to develop electronic nursing care plans for CAR T-cell infusion and standard management of side effects for these complex patients. The nursing leadership worked to capture the acuity level of care provided to adjust staffing levels to meet patient and staff needs. In addition, the inpatient nursing leadership developed a formalized infrastructure to support safe administration and the management of postinfusion toxicities.
Nursing Education
Continuous nursing education was conducted with all staff on the designated unit by the service clinical nurse specialist and nurse practitioners. Content focused on the indications for CAR T-cell therapy, product handling, administration, and potential toxicities. Overviews of the current clinical trials involving this therapy were also included. This content was transitioned into a CAR T-cell therapy education module included in the required program for all hematology nurses to ensure sustainability of the learning content for new hires.

Documentation
Too often, nursing documentation forms drive the care nurses provide. In this case, once the nursing workflow and the side effects of this therapy were better understood, new electronic documentation forms for nursing care plans, clinical care, and patient education were developed through the collaboration of clinical nurses at the bedside and nurses who specialize in informatics. Using existing electronic nursing documentation forms and processes as a template ensured ease of use and decreased development time. The documentation ensured patient safety before, during, and after CAR T-cell infusion, therefore optimizing patient outcomes (see Figure 4). In addition, an electronic vital sign parameter was created in the healthcare record of these patients, providing source documentation of clinical parameters for the research team and alerting clinicians of any deviation from the expected range.

New Infrastructure
In 2006, Memorial Sloan Kettering Cancer Center began the first phase I CAR T-cell clinical trial for hematologic malignancies, and now, 11 years later, its portfolio has grown 10-fold in various disease services because of essential changes to its infrastructure. In 2014, the institution recognized the increasing number of clinical trials using CAR T-cell therapy and the level of expertise required to safely care for these patients. As a result, the Cellular Therapeutics Center (CTC) was developed to unite the researchers and clinicians conducting CAR T-cell clinical trials. The CTC is a team, not a physical location, that cares for this unique population. The invaluable role that the clinical and advanced practice nurses played in the success of the early phase I trials was recognized by their inclusion in the CTC, which now includes a medical director, PIs, a clinical research nurse coordinator, a dedicated research nurse, and research study assistants, all who cross the care continuum. The CTC would not exist without the CTCEF, the laboratory that produces CAR T cells, which consists of researchers and scientists who develop, validate, and implement procedures critical to gene transfer–related clinical research at the institution. The nursing administration also formally designated an outpatient clinic for the care and follow-up of this patient population, in addition to the inpatient unit.

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FIGURE 3.
STANDARDS OF CARE FOR PATIENTS UNDERGOING CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

- CYTOKINE RELEASE SYNDROME
  - Educate patient and caregiver on signs and symptoms.
  - Take vital signs every four hours and as needed.
  - Weigh patient daily.
  - Record intake and output every four hours.
  - Implement interventions to manage rigors and fevers.
  - Monitor for signs of tumor lysis syndrome.

- NEUROLOGIC TOXICITIES
  - Maintain seizure precautions.
  - Assess neurologic status every shift and as needed.
  - Initiate neurologic checks as ordered.
probable side effects. A plan of care is established with the patient and their caregivers prior to admission. The CTC nurse provides the inpatient medical team and nursing staff with a handout of the patient’s history, treatment plan, and schedule, which expedites the initiation of treatment upon arrival. Patients are followed in the inpatient and outpatient settings by the CTC nurses for continuity. Monitoring patients from initial contact through treatment and follow-up has improved the collection of research data and improved the continuity and quality of patient care.

Nurses continue to work with individual study teams to develop improved guidelines for patient management, inclusion of consult services into CAR T-cell research, and collection of research data through strong collaboration with physician counterparts. This has been achieved partly through establishing strong communication pathways between nurses, administrators, and medical researchers, and facilitated through shared electronic calendars, standardized research email blasts, and weekly CTC multidisciplinary rounds.

**Future Directions**

Ten years after the first phase I CAR T-cell trial in this organization, great advancements in the care of these patients have been made, and yet much is unknown. As clinical trials with CAR T cells expand beyond B-cell malignancies expressing CD19, new targets are identified in solid tumors, such as breast, lung, and ovarian cancers. In addition, as these novel CAR T-cell constructs are explored, researchers and healthcare professionals once again are faced with the potential for new and different side effects. Some trials are now evaluating the delivery of T cells to tumor sites via intrapleural and intraperitoneal catheters. “Suicide switches” have been imbedded in newer CAR T-cell designs to enable researchers to turn off CAR T cells in the event of unintended or life-threatening toxicities (Bonifant, Jackson, Brentjens, & Curran, 2016). In addition, although patients with hematologic malignancies typically spend three to four weeks in the hospital, patients with solid tumors frequently return home in a matter of days, shifting the assessment and management of these complex toxicities to the outpatient setting for the first time. Many lessons have been learned and new knowledge applied since the initial use of CAR T-cell therapy. These lessons will aid in overcoming new challenges in the future.

**Conclusion**

Although the introduction of CAR T-cell therapy has created new and unanticipated challenges in the clinical setting, it has also created an opportunity for nurses to show their essential value by ensuring patient safety and moving the science forward. Clinical bedside nurses must be educated on new treatment modalities to ensure proficiency in recognizing symptoms representative of toxicities. Similarly, ensuring communication systems are in place for rapid reporting of symptoms and early initiation of management interventions is essential. Both traditional and clinical leadership have been essential to the success of CAR T-cell therapy.

Nursing leaders and hospital administrators are responsible for ensuring that both physical space and appropriate staffing are available to support the advancing needs of staff and patients in this complex healthcare environment. With the tremendous growth in CAR T-cell clinical trials, a nursing infrastructure is essential. Organizational support was evidenced by the development of the CTC and dedicated phase I inpatient unit. This support aligns with the overarching goal to ensure patient access to clinical care and research to improve patient outcomes.

From the beginning of the phase I CAR T-cell clinical trials, nurses have collaborated with the interdisciplinary team to contribute scientific knowledge, critical thinking skills, and care coordination to move research into practice. The current authors’ professional practice model, relationship-based care, is the basis of nursing standards developed for the care of patients receiving CAR T-cell therapy. The creation of a seamless infrastructure has been invaluable to clinicians and scientists who, through CAR T-cell therapy, aim to transform the outcomes of patients with bleak prognoses. The nurses of the CTC and dedicated inpatient unit clearly exhibit the vision of nurses to strive for excellence and leadership in patient care, education, and research in the hopes of moving CAR T-cell therapies through the stages of the clinical development to become the standard of care.

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