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Short Commentary

Multifaceted Roles of Nursing in the Care of Patients Receiving CAR T-cell Therapy for Pediatric Refractory or Relapsed Acute Lymphoblastic Leukemia

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Abstract

Pediatric acute lymphoblastic leukemia (ALL) is the most common cancer in children. Survival rates after initial diagnosis of ALL are quite high, however survival rates for patients with refractory or relapsed ALL remain poor despite intensive chemotherapy, indicating the need for novel therapies. Treatment for pediatric refractory and relapsed ALL has undergone a dramatic change over the past twelve years due to the success of targeted immunotherapy. In particular, chimeric antigen receptor-T (CAR-T) cell therapy has shown great promise in the treatment of pediatric refractory and relapsed ALL. Due to encouraging initial results, there are increasing numbers of trials utilizing this treatment. Patients and families have been given hope with the introduction and progress of this innovative therapy. Expert nursing care is crucial for successful patient outcomes. Nurses are integral to the management, care, and monitoring of CAR-T cell patients, ensuring study guidelines are followed and providing continuity. CAR-T cell therapy has the potential to cause severe toxicities. Therefore, nurses must be educated so that they can provide safe care and effectively educate patients and families regarding the associated risks. In this article we describe the CAR-T cell process and focus on the multiple roles of the nurse along with highlighting collaborative relationships with other disciplines.

Keywords: pediatric CAR-T cell therapy, pediatric acute lymphoblastic leukemia, pediatric relapsed and refractory ALL, nursing management

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1 INTRODUCTION

Pediatric acute lymphoblastic leukemia (ALL) is the most common cause of cancer in children. It accounts for 25% of all pediatric malignancies[1]. Scientific and clinical research have yielded improvements in treatment over the past decades and have led to a survival rate of 90%[2]. Unfortunately, survival rates for those with relapsed or refractory disease are far inferior, with long term survival rates ranging from 30%-60%. Children and young adults with multiply relapsed ALL have an even more dismal prognosis[1].

2 IMMUNOTHERAPY

Prior to the past two decades, treatment modalities for pediatric cancers involved chemotherapy, radiation, and surgery[3]. Unfortunately, pediatric patients with relapsed and refractory ALL have disease that is more difficult to treat due to dose limiting toxicities and chemotherapy

resistance necessitating the development of more novel therapies[4]. Immunotherapy is one of those novel therapies.

Immunotherapy utilizes a patient's own immune system to fight cancer. Immunotherapy has shown the ability to destroy cancer cells and create long term responses[3]. Immunotherapy was voted "breakthrough of the year" by Science in 2013 and has become the 4th treatment modality in the treatment of cancer[3].

Over the last decade, a form of immunotherapy called chimeric antigen receptor T cell therapy (CAR-T), has emerged as a promising novel therapy in the treatment of pediatric refractory and relapsed ALL[4]. CAR-T cell therapy has changed the landscape for the treatment of these patients by resulting in remarkably high response rates. CAR-T cell therapy involves collecting a patient's T cells, modifying them in the lab to recognize an antigen expressed on the ALL and then infusing them back into the patient to attack and destroy the cancer cells[5]. Studies using CAR-T cell therapy have shown that it is safe, that responses can be long-lasting, and that it results in improvements in patient-reported quality of life[6]. CAR-T cells are considered a living drug since they can persist in a patient's body for prolonged disease surveillance. The first pediatric patient was successfully treated on a phase 1 clinical trial in 2012[2]. This patient remains in remission since receiving CAR-T cell therapy. In August 2017, results of CAR-T cell trials in patients with refractory and relapsed ALL led to FDA approval of the first CAR-T cell product, tisagenlecleucel, for pediatric and young adult patients with refractory and relapsed ALL. Tisagenlecleucel was the first ever gene therapy approved for this indication[1,2].

3 CAR-T CELL PROCESS

Patients and families interact with nurses at every stage of the CAR-T cell process and nurses play an integral role in each stage. The many roles of nursing within this field will be discussed in this article.

A patient's first visit to the CAR-T cell institution involves meeting with the CAR-T cell team. This is usually a two-to-three-day visit and includes meeting with the nurse practitioner, nurse navigator, clinic nurse, social worker, and physician. During this visit a consent meeting is held to review the therapy and potential side effects. Patients and families are given written CAR-T cell educational materials, suggested websites, a map of the hospital, and numbers to call if needed. This visit generally includes T cell collection, which requires placing an apheresis catheter in Interventional Radiology, usually under general anesthesia. Following central line placement, patients go to the apheresis unit where the T cells are collected. Apheresis nurses are integral in teaching about the collection process. Once the T cells are collected the apheresis catheter is removed. The product is then transported to the cell therapy lab to prepare the product for processing. The T cells are delivered to the manufacturing facility. Once the T cells are manufactured into CAR-T cells, they are returned to the cell therapy lab who is then responsible for preparing the CAR-T cells for infusion.

Following the visit for CAR-T cell consent and T cell collection, the patients return home while awaiting CAR-T cell manufacturing. During this time, patients receive bridging chemotherapy at their local institution. Once the cells are manufactured, patients and their families return to the CAR-T cell institution. This length of stay is much longer, usually five-to-six weeks. Due to the possibility of side effects post infusion, patients are required to stay locally during this period.

During the first week of their stay, patients receive lymphodepleting chemotherapy to prepare for the CAR-T cell infusion. They then undergo disease evaluation including a bone marrow aspirate, biopsy, and lumbar puncture to assess pre infusion disease burden. The CAR-T cell infusion occurs the week following chemotherapy. Patients receive premedication with acetaminophen and diphenhydramine prior to infusion of the CAR-T cells. The CAR-T cells are infused over a few minutes. At our institution the infusion occurs in the outpatient clinic. Patients are observed for an hour after the infusion and, if there are no complications, can then return to their local lodging. During the next month, they are seen frequently in our outpatient clinic to monitor for side effects and adverse events. Four weeks following the CAR-T cell infusion, patients undergo another bone marrow aspirate, biopsy, and lumbar puncture to evaluate disease response and then can return home.

It takes the combined efforts of a multidisciplinary team to successfully guide patients through the entire CAR-T cell process. These patients and families have complex needs and experience a lot of stress and anxiety. Most patients leave their home institution and travel far distances to receive CAR-T cell therapy. A multidisciplinary team approach enables the provision of safe and seamless care to guide them through the CAR-T cell process. At our institution, this team includes both clinical and research members. Clinical team members include intake coordinators, nurse navigators, insurance specialists, social workers, psychologists, research nurses, inpatient nurses, outpatient nurses, nurse practitioners, physicians, child life specialists, physical therapists, occupational therapists, and nutritionists. A program manager, clinical research coordinators, data coordinators, and research nurses comprise our research team. Staff must be specially trained to provide this therapy and have access to resources and intensive monitoring.

4 NURSING IMPLICATIONS

Due to the striking response rates and the durable

remissions that have been achieved, CAR-T cell therapy is now being trialed in other hematologic malignancies and in solid tumors. This exciting therapy is providing hope for many patients and families. Along with this clincians comes the need for patient, family, and staff education. Nurses are at the forefront through their roles as clinician, supporters, educators, leaders, collaborators, and experts in the care of these patients. Nurses are expected to provide safe, high-quality care which requires continued education.

Relapsed or refractory disease is an enormous stress on the patient and family. Adding to this stress is having to travel to a new center for treatment. Patients and families experience financial, social, and emotional stressors. Caregivers often must take leave from work. Patients often come with one caregiver while the other caregiver is at home with siblings. When patients and families travel to the treating center, they are leaving their local social support network and beginning therapy in a new institution with unfamiliar staff and procedures leading to feeling disconnected and isolated. Another major stressor is the worry regarding if this therapy will be successful. Nurses are in a prime position to help patients and families. Nurses are usually the first ones to hear these concerns, often through the intake process and at the initial visit to the treating institution. They are able to intervene when it is apparent that increased psychosocial support is needed. Nurses can screen and refer families for further support and assistance. Nurses collaborate with psychosocial staff including social workers, psychologists, and child life specialists. They work closely with patients and families through providing guidance regarding institutional processes. They provide consistency for patients and families and establish relationships of trust and comfort.

Additional stressors include language barriers and cultural beliefs. Nurses strive to provide family centered and culturally sensitive care. Visits are completed in a patient's native language through the use of interpreters and translated educational materials are provided. Culturally sensitive care fosters a relationship of trust between patients, families, and staff.

5 NURSING EDUCATION

Comprehensive care for patients receiving CAR-T cell therapy requires nurses knowledgeable in the management of hematologic malignancies and immunotherapy principles. Nursing education is an integral part of a successful program.

Oncology nurses are involved with CAR-T cell patients from initial referral through long term follow up. Nurses work collaboratively in various roles to meet the needs of this complex population of patients. One of the most important nursing roles is that of educator. Nurses are responsible for educating other nurses within their institution and those from referring institutions. A major aspect of the nursing role is to also provide education and anticipatory guidance for patients and families. They often have excellent questions regarding this therapy. Therefore, nurses must be educated and consistently updated regarding CAR-T cell therapy. At our institution, we offer bi-annual nursing education days that include CAR-T cell therapy specific information including implications, assessments and monitoring, possible infusion reactions, and long-term side effects. Additional focused education includes CAR-T cell therapy treatment timelines, cellular infusion procedures, and management of unique side effects, such as cytokine release syndrome (CRS) and neurotoxicity. Nurses caring for patients receiving CAR-T cell therapy products are required to complete annual knowledge assessments offered through our institution's online education platform.

As CAR-T cell therapy evolves, programs can best serve nursing staff by establishing continuing education, offering periodic competency assessment, and providing updates about evidence-based care delivery. Implementation of these education requirements may vary based on the primary role of the nurse and location of practice (inpatient or outpatient). In centers with combined bone marrow transplant (BMT) and CAR-T cell therapy programs, it is important to collaborate to ensure consistency in staff practice. Centers must also develop policies and procedures for product infusion and patient assessment if not already in place. Organizational practices for managing patient care should have consistent policies and procedures across BMT and CAR-T cell therapy programs to support safe and effective care for patients and the safe administration of the CAR-T cell product[7].

6 NURSING ROLES

6.1 Nurse Navigator

Nurse navigators are integral to the overall coordination and logistics of CAR-T cell therapy care. As they are often the first point of contact for the referring clinician, the nurse navigator must be knowledgeable about the available CAR-T cell products and clinical trials. The nurse navigator must possess a deep understanding of each trial's inclusion and exclusion criteria to compile the documents needed for eligibility determination. During the referral process, the nurse navigator acts as a liaison between the referring team and the receiving team to obtain clinical updates and to gather documents such as treatment summaries, labs, echocardiograms, and radiology reports[8]. The nurse navigator also works closely with the financial and insurance authorization teams to obtain insurance approval for CAR-T cell therapy and related care.

In addition to their interactions with the referring team, the nurse navigator communicates directly with patients and families to answer questions, provide updates, and coordinate logistics for the initial consent

and T cell collection visit[9]. The nurse navigator connects patients and families to social workers for assistance with housing, transportation, and caregiver resources. Direct communication with patients and families continues beyond the referral and intake process. Throughout the entirety of the CAR-T cell therapy treatment and follow up period, the nurse navigator continues to support patients and families by coordinating appointments, fielding clinical concerns, and providing a consistent contact for logistical questions.

6.2 Research Nurse

To have a successfully functioning CAR-T cell therapy service, resources are necessary to help manage the regulatory requirements[10]. Research nurses help fulfill this role. They are involved in the operational aspects of CAR-T cell therapy clinical trials and ensure that study protocol guidelines are followed correctly[9]. They also review medical records for adverse events and treatment toxicities. They gather the clinical data needed to make adverse event logs and to file Serious Adverse Event reports to the Food and Drug Administration (FDA). Research nurses are in close contact with the primary investigators of each trial to discuss trial data and safety outcomes and to participate in regulatory activities.

6.3 Outpatient Nurse

Outpatient oncology clinic nurses are involved in many aspects of the care of a CAR-T cell therapy patient. Perhaps most importantly, at an institution where most of the treatment is referral based, outpatient nurses help patients and families navigate the daily clinic experience in a new and unfamiliar setting by providing a consistent presence at the bedside[8]. During their 5-week stay for treatment, patients and families become accustomed to seeing the faces of familiar nurses which helps to alleviate the stress of being in a new place.

In addition to building rapport with patients and families, outpatient nurses perform numerous essential nursing tasks. During lymphodepleting chemotherapy week, they administer the chemotherapy which necessitates a knowledge of administration standards of practice and anticipated side effects[10].

Many CAR-T cell products can be infused in the outpatient setting which aids in the reduction of healthcare costs, optimizes resource utilization, and increases patient and family satisfaction and convenience[6]. As such, outpatient clinic nurses play an integral role on CAR-T cell infusion day. They participate in the confirmatory pre-infusion product check that occurs between the physician and cell therapy lab. They premedicate patients with acetaminophen and diphenhydramine prior to infusion to prevent reactions due to the cryopreservative in the CAR T cell product. They obtain vital signs before, during, and after the CAR-T cell infusion and remain at the bedside monitoring for potential infusion reactions[9]. Providers rely on nurses to notify them with any changes in vital signs or overall patient condition[11]. Once the observation period is over, the nurse reviews clear instructions with the patient and family regarding reasons to call and follow up information.

During the month of monitoring post-infusion, clinic nurses are responsible for accessing ports, drawing labs, giving transfusions, and administering supportive care infusions. They perform frequent assessments and monitoring for symptoms of CRS and neurotoxicity and are expected to rapidly escalate care as needed[12]. In addition, outpatient nurses monitor phone calls and triage patient and family questions. Patients need to have a reliable and consistent contact for questions and for reporting symptoms. Outpatient nurses are a bridge between the patient/family and the clinicians which makes them fundamental to the CAR-T cell therapy team.

6.4 Inpatient Nurse

Inpatient nurses play a key role in providing anticipatory guidance to families. This guidance should include the adverse effects of the specific drugs and treatment modalities in addition to potential side effects that might occur. Patients are monitored closely for signs of CRS which is the most common toxicity associated with CAR-T cell therapy. CRS is a systemic inflammatory response involving elevated cytokines that occurs with immune system activation. Fever is the hallmark sign, and symptoms can mimic those of an infection. Inpatient nurses need to be educated on recognizing signs as well as management. Mild CRS includes fevers, myalgias, headaches, nausea, and pain. Severe CRS includes hypotension, capillary leak, hypoxia, respiratory distress, coagulopathies, and organ toxicities such as cardiac, renal, and liver dysfunction[10]. A critical component of effective monitoring and management is the nurse's awareness of the period during which to expect CRS development. It is recommended to anticipate onset within the first week post-CAR-T cell infusion. Nurses must be able to identify signs of severe CRS early to facilitate the appropriate interventions.

There is a distinct neurologic toxicity called immune effector cell associated neurotoxicity syndrome (ICANS) that can include confusion, difficulty finding words, impaired fine motor skills, seizures, cerebral edema, and encephalitis[12]. In addition to CRS symptoms, nurses need to be educated on how to carefully assess patients for neurologic toxicities. The nurse's role in the care of patients at risk for neurotoxicity after CAR-T cell therapy includes frequent assessments, symptom management, coordination of care, and timely escalation of care for patients experiencing sequelae of therapy. If signs and symptoms are recognized, neurologic assessment should occur more frequently to identify further neurologic deterioration.

In most cases, symptoms are transient and don't result in long-term deficits as the inflammatory state is generally self-limited[13]. With prompt recognition and appropriate supportive interventions, the acute symptoms of ICANS are reversible in nearly all patients.

At our institution, we work very closely with our colleagues in the intensive care unit (ICU) and emergency department. We share important information about the care of our CAR-T cell patients through our unit-based nursing experts. When patients are admitted to the hospital for post CAR-T cell infusion complications, our oncology unit-based clinical nurse experts reach out to the experts on the unit caring for the patients. We help to coordinate care, review side effects of chemotherapy, provide anticipatory guidance surrounding common post-infusion complications, and offer our expertise for educating and supporting patients and their families. Early collaboration with the ICU is essential for patients developing severe CRS and ICANS. Nurse practitioners and nurses play a central role in identifying early signs of severe CRS and consulting the critical assessment team to facilitate the safe transfer of patients to the ICU if needed. Another means of collaborating with our colleagues in the ICUs is by making our high-risk patients "medical watchers". By identifying these patients as watchers, our critical care outreach team, which consists of an ICU physician, ICU nurse, and respiratory therapist, is made aware of the patients who are at potential risk for clinical deterioration. They round on these patients twice per day and will follow their clinical status from afar. This offers both teams an opportunity for ongoing collaboration, early detection, and a smoother transfer of care should the patients become acutely and/or critically ill[10].

6.5 Nurse Practitioner

Nurse practitioners are integral to the functioning of the CAR-T cell therapy team. They are relied upon to build rapport with patients and families, provide continuity of care, assess for and manage side effects, and provide anticipatory guidance and education[5].

Many patients receive CAR-T cell therapy at referral centers away from their primary oncology team. It is challenging for patients and families to cope with the stress of their child's disease state and the need to travel far from home for care. Given their accessibility, nurse practitioners are in a unique position to provide guidance and support to these newly arrived patients and families[5]. The consistent presence of the nurse practitioner, combined with their clinical assessment and symptom management skills, allows for the development of trust and credibility between the patients/families and their new medical team[10]. The relationship created between nurse practitioner and patient is especially important in a primarily nurse practitioner-run clinic where the physicians rotate on and off service on a weekly basis.

Nurse practitioners are invaluable for their ability to provide continuity and coordination of care. They possess a global overview of the CAR-T cell therapy process and are relied upon for organizational, planning, and scheduling questions. They interact with interdisciplinary teams such as interventional radiology, apheresis, and anesthesia to get patients scheduled for apheresis line placements and collections. They refer patients to social work, psychology, child life, physical therapy, occupational therapy, and nutrition.

Inpatient and outpatient nurse practitioners communicate with each other when patients are admitted and discharged to share pertinent information regarding transitioning the patient's care. Outside of their institution, nurse practitioners help to maintain open communication with a patient's primary oncology clinicians who remain an integral part of their care team. Nurse practitioners provide referring teams with weekly updates. Routine communication is essential for identifying unique care needs and relaying clinical course. This exchange allows for a smooth transition and seamless follow up upon return home.

Another crucial responsibility of nurse practitioners is to monitor for adverse events such as CRS and ICANS and to assist in the clinical management of these side effects[10]. An in depth understanding of risk factors allows nurse practitioners to identify those at high risk for side effects and be prepared to escalate care as needed[12]. Nurse practitioners collaborate closely with physicians to identify signs and symptoms of CRS and ICANS and provide the necessary interventions for these patients.

Finally, one of the most important roles of the nurse practitioner is that of educator. Education is a continuous process throughout the CAR-T cell therapy course. The CAR-T cell journey is one of great uncertainty. It is new and different than what many of these families have experienced in the past. By providing consistent, continuous anticipatory guidance throughout the entire CAR-T cell process, nurse practitioners help to set realistic expectations, thus decreasing anxiety and stress[10]. Not only do nurse practitioners provide anticipatory guidance to patients and families, but they also act as a resource to their own multidisciplinary team members and to those of the referring institution[10]. Nurse practitioners publish articles, present posters, and lecture at conferences to help spread knowledge of CAR-T cell therapy. By presenting and publishing, nurse practitioners enable future nurses to learn about and understand this therapy so that they, in turn, can provide safe, effective, and supportive care to this population of patients.

7 CONCLUSION

CAR-T cell therapy is an exciting and innovative therapy

that has changed the treatment landscape and provided hope to pediatric patients with relapsed and refractory ALL. The progress and success that has occurred with this therapy has led to more trials for refractory and relapsed ALL, other hematologic malignancies, and solid tumors. CAR-T cell therapy comes with a distinct set of toxicities and challenges. Currently there is more experience with CAR-T cell therapy in hematologic malignancies whereas CAR-T cell therapy for solid tumors, such as neuroblastoma or brain tumors, is still fairly novel. Patients may experience different adverse events and toxicities with treatment for these malignancies. This indicates the need for additional and ongoing education for nurses to ensure that this therapy is safe and successful. Some institutions are comfortable delivering CAR-T cell therapy in the outpatient setting and this has been done effectively. As this becomes more widely used, institutions may need to develop processes to transition from inpatient delivery to the outpatient setting. Nurses will be fundamental to this process change.

Nurses play an essential role in the CAR-T cell process through involvement in patient/family education, symptom monitoring, research, psychosocial support, continuity, and care coordination. With newer CAR-T cell trials on the horizon there will be continued opportunities for further education and research and nurses will remain at the forefront in the years to come.

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Conflicts of Interest
The authors have no conflicts of interest to declare.

Data Availability
No additional data are available.

Author Contribution
Callahan C, Haas L, Smith LT and Stewart MF conceptualized this commentary and contributed the original draft preparation, writing, reviewing, editing, and revision of the manuscript.

Abbreviation List
ALL: Acute lymphoblastic leukemia
BMT: Bone marrow transplant
CAR-T: Chimeric antigen receptor-T cell
CRS: Cytokine release syndrome
FDA: Food and Drug Administration
ICANS: Immune effector cell associated neurotoxicity syndrome
ICU: Intensive care unit

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