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Review

Nurses' roles in CAR-T therapy for B-cell malignancies and managing associated cytokine release syndrome

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ABSTRACT

Introduction: In recent times, significant innovations have been made in cancer immunotherapy. These innovations have yielded positive outcomes, including a substantial improvement in the clinical outcomes of cancer patients, especially in the B-cell setting involving patients with B-cell malignancies.
Method: This paper explores oncology nurses' actual and expanded roles in utilizing chimeric antigen receptor T-cell (CAR-T) therapy.
Result: CAR-T therapy is an exciting innovation in cancer treatment. However, this therapy is often associated with some mild to life-threatening side effects and toxicities, including cytokine release syndrome (CRS). Unfortunately, nurses lack adequate standardized guidelines for monitoring and managing patients with CRS. This paper explains oncology nurses' actual and expanded roles in utilizing CAR-T therapy in treating B-cell malignancies based on experience and published data.
Discussion: Nurses' responsibilities for patients experiencing CAR-T toxicities with a particular focus on CRS during treatment are discussed.

Introduction

Recent advances in cell and gene therapy (CGT) are revolutionizing how certain cancers are treated. Multiple CGT clinical trials are currently being conducted, and it is estimated that over 50 CGTs will be clinically available by 2030.[1] The introduction of chimeric antigen receptor T-cell (CAR-T) therapy in managing patients with B-cell cancers exemplifies a significant advancement in CGT. CAR-T is a cellular immune-oncologic therapy that activates and redirects a patient's T cells to identify, target, and kill tumor cells. While CAR-T therapy is still relatively new, it is rapidly gaining the attention of oncology professionals and clinicians worldwide. Many of the B-cell tumors are effectively being treated with intensive chemotherapy and stem-cell transplant. However, the major challenge arises when there is a recurrent or refractory relapse of these cancers without an effective treatment for the relapse after chemotherapy or a stem-cell transplant. For patients with relapsed or refractory B-cell cancers, CAR-T therapy offers a treatment option unavailable a few years ago.[2]

The introduction of CAR-T therapy as a treatment option for cancer has been a focus of many clinical studies, especially in patients with refractory B-cell malignancies. So far, the results have been quite positive. For example, a study conducted in 2014 reported that CAR-T therapy yielded sustained remission in patients with acute lymphocytic leukemia.[3] Also, recently, Dellinger et al. reported its effectiveness in treating non-Hodgkins B-cell lymphoma.[4]

Overview of the body's T cells and T-cell activation

T cells are a component of the white blood cells that identify and annihilate illness and pathogens throughout the human body. Individual T cells have a receptor that recognizes antigens (proteins or molecules recognizable by the immune system). When the immune system identifies unfamiliar or abnormal antigens, it can work to kill them, but cancer cells sometimes have antigens that the body does not identify as deviant. Consequently, the immune system may not release the T cells to destroy malignant cells. A clear understanding of T cells' specific contributions and immunobiology is required to fully harness immunotherapies' curative potential.[5]

Regarding immunology principles, T cells are essential to the body's immune system. These T cells play a critical role in both components of active immunity, including cell-mediated and, to a lesser extent, humoral

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immunity. Generally, the T cells identify, attack, and destroy infectious agents. They are called T cells because they mature and develop in the thymus gland. A vital feature of the immune system is distinguishing self from nonself or foreign. This remarkable ability is necessary because the human body is constantly exposed to pathogens. The basis of its ability to differentiate between both is the presentation of antigens to immune cells. Once an immune cell recognizes its specific antigen, the body establishes an immune response to protect itself.

T cells also help antibody production by B cells, which are considered the effectors of antigen-specific cell-mediated immunity (CMI). CMI is essential in eliminating intracellular infections (e.g., viruses, mycobacteria, and some bacteria) and aberrantly differentiating cells (e.g., neoplasms). CMI also fights and kills allogeneic cells (graft rejection). In addition to this, CMI is involved in cellular autoimmune activities, as well as type IV allergic reactions to drugs and contact dermatitis. Interestingly, T cells trigger the activation of innate immune cells, such as phagocytic cells, to become more effective at killing other pathogens, such as fungi.

The activation of T cells involves the immunological transformation of resting T cells to become functional.[6] T-cell activation is required at multiple stages of a T-cell immune response, and complete activation involves the constant signal integration by the T cell through specialized receptor types, including the T-cell antigen receptor (TCR, signal 1), costimulatory receptors (signal 2), and cytokines (signal 3).[6] This implies that TCR signals are essential for T-cell activation. Each TCR is generated through somatic recombination and is selected to recognize linear peptide antigens when presented in the context of self–human leukocyte antigen proteins.

T cells play a critical role in the specific immunity of B-cell cancers. T cells can kill tumor cells directly and inhibit their proliferation, infiltration, and metastasis.[7] T cells involved in this activity include the killing effect of cytotoxic T cells (CTLs) and helper T cells (Th). Unfortunately, tumor cells can also actively induce the production of regulatory T cells (Tregs) and other regulatory cells in the host body to resist the antitumor immune response, thereby supporting an environment suitable for tumor proliferation and growth. Many of the innovations in immuno-oncology have been triggered by the clinical success of immune checkpoint inhibitors. Unfortunately, many patients still do not benefit from checkpoint blockade or other immunotherapies, partly due to their body's inability to fully activate these antitumor T cells. Induction and activation of antigen-specific CTLs are essential strategies in immunotherapy for many cancers, including B-cell tumors.

The therapeutic mechanisms of CAR-T therapy

While conventional treatment strategies such as surgery, radiotherapy, and chemotherapy have improved the clinical outcomes for cancer patients, the challenge of providing a comprehensive treatment strategy for patients with refractory or recurrent B-cell malignancies triggered the innovation of CAR-T therapy. CAR-T therapy represents a paradigmatic shift in treating B-cell cancers. A growing number of CAR-T therapies are being developed and tested in clinical studies. Although there are essential differences between each specific therapy that can determine how they function in patients, they all share similar components. T cells mediate antitumor immune responses and are the chief target of immune checkpoint therapy, but they can also promote immune tolerance.[5] All nucleated cells express major histocompatibility complex (MHC) class I molecules, and B-cell cancer cells are no exception.[8] Because some cancer cells produce antigens that may not be readily recognizable by the T cells, scientists have strategically engineered the T cells genetically, configuring them to recognize the tumor antigens and fight the tumor. CAR-Ts are genetically manipulated and modified to have a new receptor to bind to cancer cells and destroy them. Once T cells detect the antigen peptide-MHC I complex presented by B-cell cancers, the CD8+ T cells are activated to form CTLs, thereby destroying tumor cells that present target antigens. When activated, CD8 T cells recognize antigens presented on MHC class I molecules and become cytotoxic CD8 T cells (CTLs).[8]

A study carried out in 2021 in mice, reported that CTL had a direct destructive effect on tumor cells by causing apoptosis.[9] CTLs constitute a distinct lymphocyte subpopulation and are induced by several diverse stimuli, including major histocompatibility antigens, protein antigens, viruses, and intracellular bacteria and parasites.[10] CTLs recognize peptides bound to the MHC class I molecules, and the activation and proliferation of CTLs are induced by exposure to specific antigens. Activated CTLs secrete the essential cytolytic mediators (perforin, granzyme, etc.) and induce apoptosis in target cells (tumor cells and virally infected cells). Interestingly, activated CTLs produce other cytokines such as interferon-gamma and tumor necrosis factor-alpha, which enhance antigen presentation and mediate antipathogenic effects.[10] Therefore, CAR-Ts are genetically engineered to express a synthetic receptor that binds to antigens expressed on the surface of tumor cells.[1]

The process of CAR-T therapy

CAR-T therapy has been recognized globally as a complex process that requires the expertise of clinicians with extensive experience. Producing CAR-Ts involves multiple carefully performed procedures and quality control throughout the entire protocol.[11] In this process, T cells are taken from the patient's blood via venipuncture through a tube and put into an apheresis machine, which removes the T cells and gets them ready for modifications. The device returns the remaining blood to the patient's body through a different tube. The extracted T cells are then reprogrammed in the laboratory by adding a gene for a receptor (also known as chimeric antigen receptor or CAR), which changes the T cells to target tumor cells by enabling the T cells to attach to a specific cancer cell antigen.[11] The CAR-Ts are then allowed to multiply over a while. The modified T cells (CAR-Ts) are then injected back into the patient with the expectation that they will redirect the immune response against the targeted cells, thereby leading to apoptosis. If everything works as planned, the CAR-Ts are expected to go on to proliferate in the patient's body and, with moderation from their engineered receptor, identify and kill any malignant tissues that harbor the target antigen on their surfaces.

Side effects and other clinical issues associated with CAR-T therapy

While it has been established that CAR-T therapy has revolutionized the treatment of certain cancers, including B-cell cancers, serious side effects and relapse remain significant barriers to compliance and long-term survival.[12] The widespread implementation of CAR-T therapy is encumbered by several obstacles, including antigenic evasion, uneven intratumoral infiltration in solid cancers, cytokine release syndrome (CRS), neurotoxicity, logistical implementation, and a financial burden.[13] As in all other cancer treatments, CAR T therapies have been associated with unique adverse effects, including CRS and neurologic events (also known as immune effector cell–associated neurotoxicity syndrome [ICANS]),[14] with CRS generally occurring in the first week after CAR-T infusion and ICANS occurring in the second week after infusion.[15] In addition, cytopenia,[14] and infections[16] have been reported among people undergoing CAR-T therapy experiencing CRS.

Cytokine release syndrome

After the administration of CAR-T therapy, it usually would recognize the tumor antigens and fight to destroy them.[17] However, the CAR-T cells may further release massive amounts of perforin/granzymes and cytokines, including interferon-gamma and tumor necrosis factor-alpha, resulting in tumor pyroptosis.[18] Pyroptosis is a type of programmed cell death that differs from apoptosis[19] and is characterized by cellular swelling, lysis, subsequent cell content, and proinflammatory factor release. Generally, the difference in cell death, either through apoptosis or pyroptosis, depends mainly on the magnitude of gasdermin expression because low levels of gasdermin are commonly associated with apoptosis. In contrast, high levels trigger the switching from apoptosis to pyroptosis. In CRS, CAR-Ts release a large amount of perforin/granzymes

to induce massive gasdermin release, surpassing their self-repair capability and leading to pyroptosis.[17] It is believed that pyroptosis of the target cell represents the onset of CRS.[18] CRS is known to represent one of the most frequent serious adverse effects of CAR-T therapy. In other words, CRS happens when the body's immune system exaggerates its response to the CAR-T, resulting in an acute systemic inflammation syndrome characterized by high circulating levels of many cytokines, including interleukin-6 and interferon γ and the presence of fever and multisystem organ failure.[16]

Generally, the severity of CRS presentation varies widely and ranges from mild flu-like symptoms, fever, fatigue, headache, rash, arthralgia, and myalgia to severe life-threatening symptoms and exaggerated inflammatory responses such as hypoxia, tachypnea, tachycardia, hypotension, arrhythmia, vascular leakage, disseminated intravascular coagulation, and multiorgan failure (Fig. 1). Although the confirmation of CRS cannot be established or ruled out exclusively by laboratory studies, they can be utilized to monitor the pattern of organ dysfunction. The laboratory results of these patients are expected to show elevated creatinine, rising liver enzyme levels, cytopenia, and abnormal coagulation parameters, including high C-reactive protein, a hallmark of ongoing inflammation. It is interesting to know that most of the symptoms associated with CRS, especially the mild ones, are reversible, whereas 0–9.1% of patients may progress to fatal cases.[7]

Roles of the nurse in CAR-T therapy and caring for patients experiencing CRS

Nurses are an integral component of the healthcare system whose expertise and clinical opinions are vital in all aspects of patient care. Oncology nurses have the training and expertise to care for patients undergoing cancer treatments. Therefore, nurses must be strategically involved in all decision-making phases regarding CAR-T therapy use in managing cancer patients. Ensuring that cancer nurses receive the essential education needed to effectively manage patients on new cellular therapies cannot be underestimated. While it has been established that CAR-T therapy has revolutionized the treatment of certain cancers, including B-cell cancers, there are specific clinical issues that nurses must pay attention to for improved outcomes and patient safety.

Nurses are involved in the administration, management, and assessment of the complications of CAR-T therapy. The nurse clinician ensures that the facility has established protocols and that the therapy schedules are well established. Nurses are often required to perform both leukapheresis and eventually do the CAR-T infusion. In some cases, nurses with different specializations may be required. For example, some facilities require the dialysis nurse to perform leukapheresis, whereas the oncology nurse delivers the CAR-T therapy.

Nevertheless, the nurse's role spans the whole course of this therapy, from the screening of patients to discharge and follow-up visits. Nurses

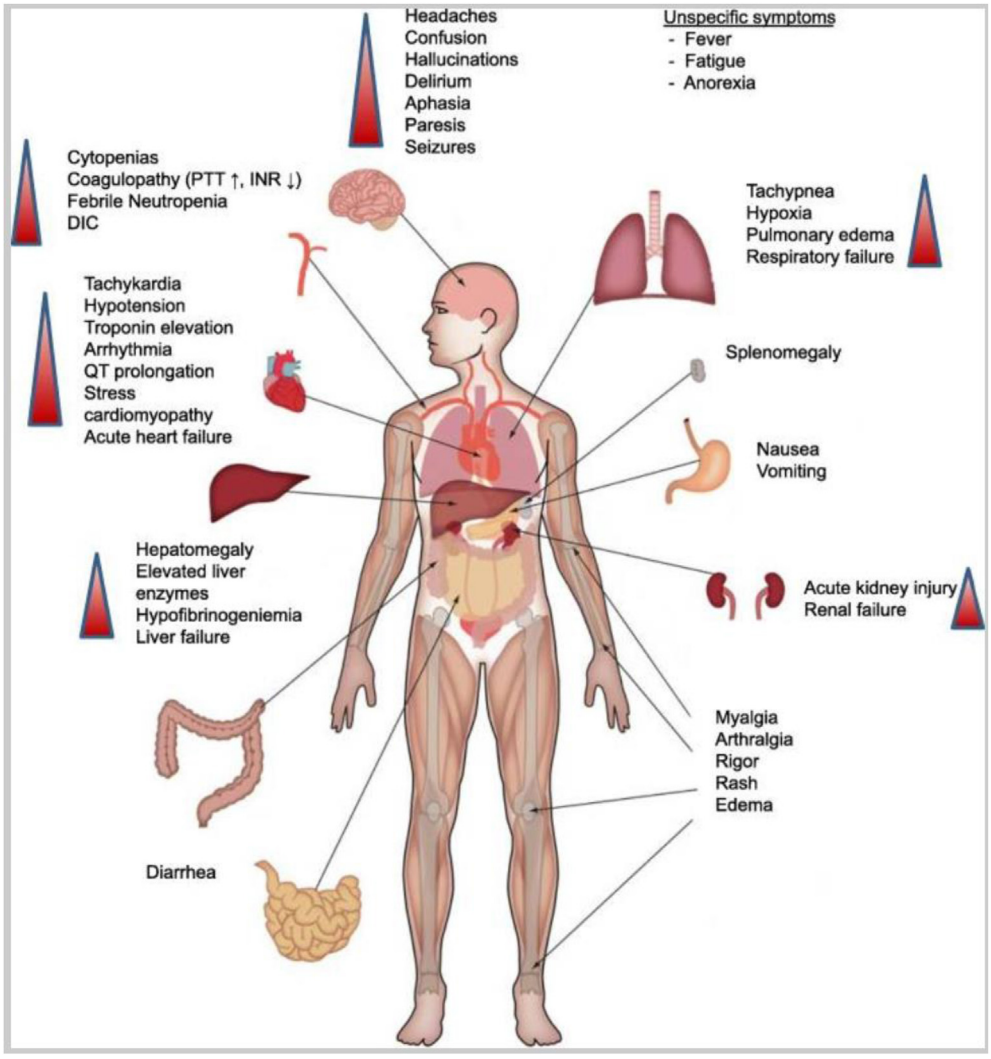

Fig. 1. Clinical presentations of CRS. Adopted from Shimabukuro-Vornhagen et al. (2018).[16] CRS, cytokine release syndrome; PTT, partial thromboplastin time; INR, international normalized ratio.

identify the patient, determine the availability of resources, and actively involve patients and family members in drafting out a working plan to make sure that the patient stays through the whole course of therapy, from the implementation of apheresis (specifically leukapheresis) to the T-cell re-engineering phase. During this period, the nurse continues to ensure that the patient's disease is under control. Typically, this is when patients undergo cytoreduction/bridging therapy and lymphodepletion chemotherapy, usually in the outpatient setting, before they are admitted to the hospital for the CAR-T infusion.

Interestingly, some institutions also provide CAR-T therapy in the clinic on an outpatient basis, raising concerns about the training needs of the outpatient nurses to handle the complexities associated with this treatment effectively. Caring for acutely ill patients, ensuring early recognition of treatment-related side effects, and activating a quick hospitalization response when indicated require an active and comprehensive triage infrastructure. The triage nurses within the outpatient facilities often take calls from the patients. The outpatient nurse should be trained to multitask, make quick decisions, and perform assessments on incoming patients to evaluate their symptoms, sort patients into priority groups, and coordinate their referrals to appropriate treatment areas.

Cytoreduction/bridging therapy and lymphodepletion chemotherapy are widely used to stabilize or debulk disease between leukapheresis and CAR-T administration.[20] Because some patients often have highly aggressive B-cell malignancies and can decline to the point where it may no longer be safe to administer the manufactured CAR-Ts, waiting for the CAR-T therapy to be manufactured, can be extremely challenging. While the CAR-T therapy is being manufactured, a bridging therapy can be administered to prevent uncontrolled progression of the underlying disease, palliate symptoms, debulk the primary tumor, and preserve the functional status of the patients before the CAR-T is infused. However, lymphodepletion chemotherapy, often given after the bridging therapy and before the CAR-T infusion, helps create a favorable immune environment for CAR-Ts, improving their expansion, persistence, clinical activity, and overall effectiveness while reducing the potential for anti-CAR immune responses. Adequate considerations should be made in ensuring that the patient has a low burden of disease due to the risk of tumor lysis syndrome during chemotherapy and an increased risk of CRS and treatment failure. A recent study found that pre-CAR-T bulky disease was associated with CAR-T therapy failure.[21] Because the manufacturing process of CAR-T can take several weeks to complete, some patients may require bridging therapy in the period between apheresis and infusion. Therefore, tumor lysis prophylaxis may also need to be considered.[2]

Nurses play a pivotal role in educating patients regarding the therapy, including identifying CAR-T therapy's side effects and adverse events. The education provided by the nurse must also involve the patient's family and significant others in what to expect before, during, and after the therapy. The nurse must provide adequate and correct information regarding the importance of and expectations during lymphodepletion chemotherapy. The nurse will verify if consent has been signed to indicate that the patient has understood the information given by the provider. Patients should be allowed to ask questions at any point during the CAR-T therapy.

The leukapheresis period is usually a frightening time for the patients and family. This is the period when the highly skilled apheresis nurse uses the apheresis machine to remove patients' T-cell components of their white blood cells. Nurses must have open communication with patients, assess their pain and anxiety levels, and provide all the support the patient needs. This includes spending significant time with the patient and providing educational and psychological support. Since one nurse cannot effectively achieve all these, it is crucial that all team members understand the clinical expectations, collaborate well, and work together as a unit to give the best outcomes for the patients.

As the first line of contact, oncology nurses are often the first to observe signs and symptoms of adverse events and acute changes in a patient's status. Understanding what to watch for can improve patient outcomes and assist nurses to deliver safe, effective care. The nurse is responsible for monitoring how the patient tolerates the infusion and ensuring that the infusion goes well. Patients undergoing CAR-T therapy must be closely monitored frequently for cardiovascular function and temperature. The first sign of CRS is usually fever. Hospitals must have established protocols to help respond to patients with different degrees of fever and take some proactive actions if the patients fully manifest CRS. While the CAR-T infusion takes place on day zero (0), the symptoms of CRS may start between day one (1) and day five (5).[16] Nurses should continue to monitor laboratory values associated with the CRS, especially the complete blood count and *c-reactive protein*. Because CRS inflammation is often reversible, treatment and nursing care aim to control symptoms without interfering with the T cells' ability to identify and kill malignant cells. First-line interventions, such as antipyretics, pain medications, antiemetics, vasopressor support, and oxygen therapy, are often supportive.[22] In severe cases, especially in the presence of multiorgan system failure, renal dosing of medications, total parenteral nutrition, oxygen support, and intubation may be required.

Critical assessment by the nurse also includes observing for neurological symptoms such as problems with speech, somnolence, confusion, and other manifestations that may signify neurological toxicity. CAR-related encephalopathy syndrome is characterized by typical manifestations such as toxic encephalopathy with early signs of diminished attention, language disturbance, and impaired handwriting. Other important presentations include confusion, disorientation, agitation, aphasia, somnolence, and tremors. Therefore, nurses may take a sample of the patient's handwriting before, during, and after CAR-T infusion to detect neurological deterioration. While nurses need to know the symptoms of CRS and ICANS, it is even more vital to understand how to grade these symptoms as interventions are often based on the grade of toxicity according to recommendations by the American Society for Transplantation and Cellular Therapy[23] and other nursing-based guidelines.[22] The nurse at the patient's bedside must notify the provider of the changes in the patient's condition from the beginning of pretreatment screening to discharge. Nurses must have a clear communication pathway with the provider regarding whether an intervention is needed at that point and who will be providing the interventions to mitigate further complications. This communication pathway keeps patients safe and prevents their conditions from getting to a critical point. In addition, nurses serve as patient advocates by ensuring the facility has experienced personnel that can effectively manage CRS.

On discharge, the nurse makes sure that the patient and family have received all the education they need to be safe at home and how to report symptoms. Some hospitals may have protocols to have patients with CRS symptoms bypass the emergency department and be managed by a specialized team of clinicians. Patients who are fever-free for at least 24 h, have required transfusions twice weekly or fewer, and can maintain adequate hydration can be discharged after admission for CAR-T therapy toxicity. Physical therapists should screen patients with severe CRS; if deconditioning is severe, they may require rehabilitation in an inpatient setting. If patients remain neutropenic at discharge, prophylactic oral levofloxacin may be given. According to Smith and Venella,[24] nurses in the outpatient team collaborate with referring providers to ensure patients have an adequate supply of homecare equipment and medications, and family caregivers are provided education and information resources on the significance of adhering to infection prevention measures and when to call about new signs and symptoms.[24]

While nurses are highly involved in the clinical management of patients undergoing CAR-T therapy, they also assess for social and economic challenges these patients may have. For example, some socioeconomic issues and financial difficulties may lead to treatment delay.[20] There is no doubt that the total cost of CAR-T therapy, including the cost of inpatient hospitalization and treatment of

complications that may arise, can be expensive, especially for uninsured patients.[25] With CAR-T therapy, a myriad of complex financial issues may impact patients, their families, and caregivers, which has been regarded as financial toxicity.[26] Nurses continue to play an essential role in helping patients and families prevent or manage CAR-T therapy's financial toxicity by ensuring they have access to critical information about treatment-related rights and resources. With this information, patients can make informed decisions about their work, finances, and insurance coverage, which are three essential contributors to the financial toxicity of a cancer diagnosis. The entire course of CAR-T treatment may have significant short- and long-term effects on employment and income for patients and caregivers. Nurses can assist uninsured patients in enrolling in an insurance program or provide access to information to help the already insured patient make necessary changes to their insurance coverage to lower the out-of-pocket cost, thereby increasing the chances of full treatment compliance. Providing relevant resources for information about federal and state employment rights and benefits can be extremely helpful for patients whose employment is affected by cancer and CAR-T therapy.

While CAR-T therapy remains a promising treatment option for some refractory B-cell cancers, there is reported evidence that some patients experience treatment failure. Nurses are increasingly involved in confirming CAR-T persistence and monitoring for antigen loss, which is necessary for predicting relapse and instituting relapse prevention strategies. However, antigen-negative relapses are extremely difficult to manage, and even the antigen-positive relapse may not respond to CAR-T reinfusion.[27] These pose additional physical, emotional, psychological, and financial burdens on patients, families, and, sometimes, the nurses.[28] The nurses must maintain open communication and allow patients to express their fears and worries. Beyond this, the nurse continues collaborating with other clinical team members to discuss alternative treatment options with the patient if needed.

Conclusions and recommendations

Significant progress has been achieved in therapeutic interventions for B-cell malignancies. CAR-T therapy is among the most promising treatment modalities for refractory and recurrent B-cell cancers. However, as with any new treatment, managing patients undergoing CAR-T therapy has a unique set of challenges. The optimal care of patients undergoing CAR-T therapy requires a multidisciplinary team approach, which includes nursing expertise. Nurses are critical to the patient pathway and are involved in patient education, coordination, monitoring, escalation, and treatment. The essential roles of nursing in caring for a patient undergoing CAR-T therapy are monitoring the patient for abnormalities in vital signs and communicating changes effectively to the provider to enable prompt decision-making. The clinical nurse must continue to seek education on new approaches to CAR-T therapy and identify symptoms of adverse events and toxicities.

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CRediT author statement

Chinomso Nwozichi: Conceptualization, literature search, drafting of the manuscript, manuscript editing and revision. Ayodeji Ogunmuyiwa: Literature review, manuscript drafting and refining and revisions. Margaret Ojewale: Literature review, manuscript drafting and refining and revisions. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

All authors have no conflicts of interest to declare. The corresponding author, Dr. Chinomso Nwozichi, is a member of the editorial board of the *Asia-Pacific Journal of Oncology Nursing*. The article underwent the journal's standard review procedures, with peer review conducted independently of Dr. Nwozichi and their research groups.

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Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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