Asia-Pacific Journal of Oncology Nursing 11 (2024) 100579

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Review

# CAR T-cell therapy in cancer: Integrating nursing perspectives for enhanced patient care

Ashna Gupta [a], Gunjan Dagar [a], Mohd Umar Rehmani [a], Chandra Prakash Prasad [a], Deepak Saini [b], Mayank Singh [a,**], Abhishek Shankar [c,*]

[a] Department of Medical Oncology (Lab), Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, Delhi, India
[b] Indian Society of Clinical Oncology, Delhi, India
[c] Department of Radiation Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, Delhi, India

ARTICLE INFO

*Keywords:*
Nursing care
Adverse effects
Chimeric antigen receptor T-cell therapy
Neoplasms/therapy

ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy represents a significant advancement in cancer treatment, particularly for hematologic malignancies. Various cancer immunotherapy strategies are presently being explored, including cytokines, cancer vaccines, immune checkpoint inhibitors, immunomodulators monoclonal antibodies, etc. The therapy has shown impressive efficacy in treating conditions such as acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma, often leading to complete remission in refractory cases.

However, the clinical application of CAR T-cell therapy is accompanied by challenges, notably severe side effects. Effective management of these adverse effects requires meticulous monitoring and prompt intervention, highlighting the critical role of nursing in this therapeutic process.

Nurses play a crucial role in patient education, monitoring, symptom management, care coordination, and psychosocial support, ensuring safe and effective treatment. As research advances and new CAR T-cell therapies are developed, the role of nursing professionals remains pivotal in optimizing patient outcomes. The continued evolution of CAR T-cell therapy promises improved outcomes, with nursing professionals integral to its success.

## Introduction

The global burden of cancer, including its incidence and mortality rates, has surged significantly. The International Agency for Research on Cancer estimated 19.97 million new cancer cases and 9.7 million deaths attributed to it worldwide in 2022.[1] Cancer mutations provide mechanisms that enable unchecked growth, prevent programmed cell death, and facilitate evasion of immune detection, among other traits.[2]

Surgical interventions, along with chemotherapy and radiotherapy, have demonstrated significant success in decreasing cancer-related deaths and improving outcomes. Nevertheless, despite their efficacy in many cases, traditional therapies such as surgery, chemotherapy, and radiotherapy are plagued by inherent variability and suboptimal effectiveness.[3] Additionally, they often lead to severe side effects due to collateral damage to healthy tissues, sometimes resulting in lengthy recovery periods Immunotherapy has emerged as one such innovative approach to lessen systemic toxicity and increase overall survival. Groundbreaking work by Thomas and Burnet laid the foundation for subsequent research confirming the prognostic significance of immune cell infiltration within tumor lesions, a discovery reaffirmed over several decades.[4] Various cancer immunotherapy strategies are presently being explored, including cytokines, cancer vaccines, immune checkpoint inhibitors, immunomodulators monoclonal antibodies, etc.[5] While several of these approaches have gained clinical approval, they each come with inherent limitations that restrict their full therapeutic potential.[6] Therefore, there is a pressing need for innovative treatments like chimeric antigen receptor (CAR) T-cell therapy to overcome these constraints. CAR T-cell therapy represents a form of adoptive cell therapy wherein a patient's peripheral T cells are genetically engineered in vitro, modifying them to recognize and attack tumor cells upon infusion back into the patient's body. An overview of the flow of CAR T-cell therapy is summarised graphically in Fig. 1.

The synthetic CAR construct typically comprises an extracellular domain derived from a single-chain variable fragment (scFv) of an

* *Corresponding author.*
** *Corresponding author.*
*E-mail addresses:* mayank.singh@aiims.edu (M. Singh), doc.abhishankar@gmail.com (A. Shankar).

https://doi.org/10.1016/j.apjon.2024.100579
Received 24 May 2024; Accepted 21 August 2024

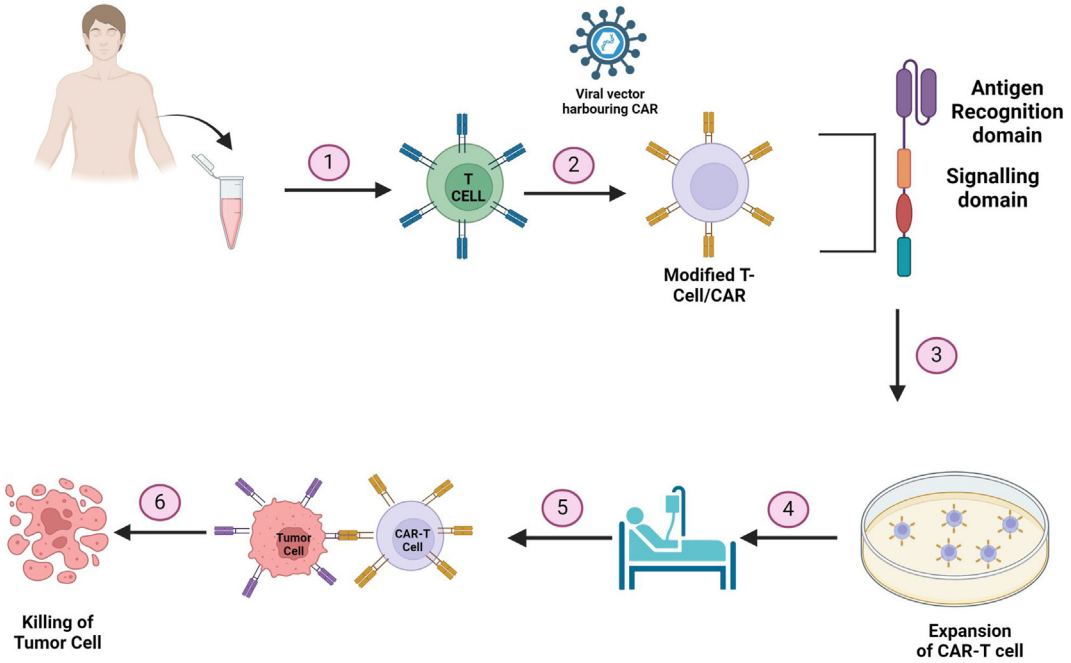


**Fig. 1.** Overview of CAR T-cell therapy. **Step 1:** Patient T-cell is isolated through a process called leukapheresis. **Step 2:** T-cell are then reprogrammed using viral vector harboring respective CAR. **Step 3:** Reengineered CAR T-cell are then expanded in lab which usually takes 3–4 weeks. **Step 4:** CAR T-cells are then infused into the patient's bloodstream, where they continue to propagate. **Step 5:** CAR T-cell binds to target antigen on tumor cell triggers signaling cascade and CAR T-cell activation. **Step 6:** Engagement of CAR T-cells with tumor cell finally leads to the death of tumor cells. CAR, chimeric antigen receptor.

antibody, along with a hinge domain and a transmembrane domain. These components work together to anchor the receptor within the cell membrane, enabling it to recognize and bind to specific antigens present in tumor cells,[7] as shown in Fig. 2 A distinguishing feature of the extracellular domain is the scFv region, resembling the variable segments of heavy (VH) and light (VL) chains of an antibody, fused via a flexible linker. The spacer serves to connect the antigen recognition segment to the transmembrane region, which is an alpha helix embedded within the cell membrane, linking the extracellular antigen-binding domain to the intracellular cytoplasmic domain.[8,9] The functional terminal of the CAR, which typically contains activation and co-stimulatory domains, is known as the intracellular domain. Within the cytoplasmic domain of CD3, the most prevalent intracellular domain component is called an ITAM (immunoreceptor tyrosine-based activation motif).[10]

Despite maintaining a similar foundational modular structure since they first developed, CAR T-cells can be categorized into five generations based on how their intracellular signalling domain is structured as shown in Fig. 3. These CARs incorporate truncated intracellular domains of cytokine receptors (such as fragments of the interleukin [IL]-2R chain) with motifs for binding transcription factors like STAT-3/5. Activation of

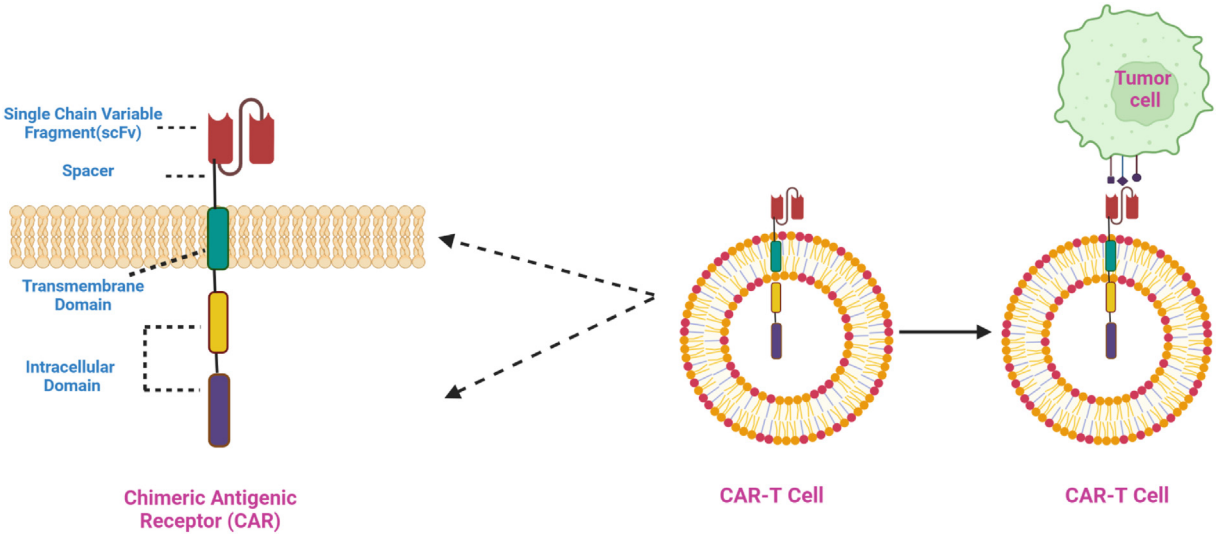


**Fig. 2.** Structure of CAR T-cell. Extracellular domain which contains a single-chain fragment of variable region antibody and a spacer domain; Transmembrane domain; An intracellular signalling domain responsible for signal transduction.

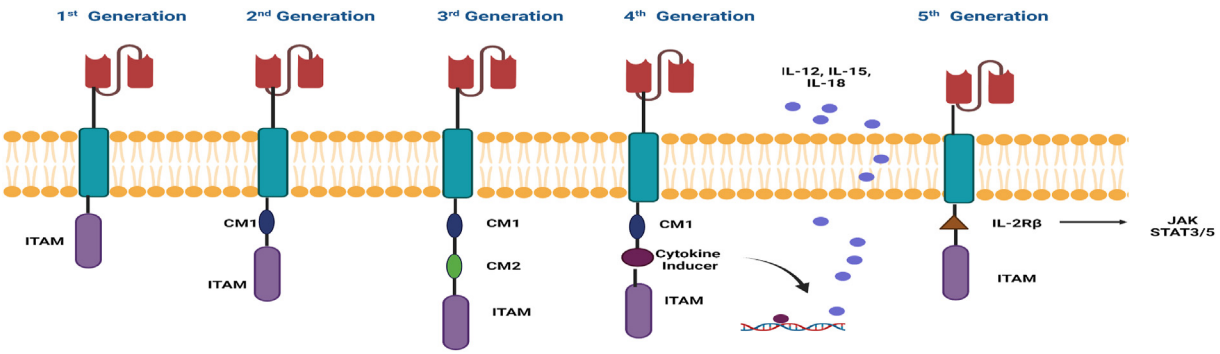


**Fig. 3. Structure of different CAR generations-** 1st generation CAR contains only ITAM motif such as CD3ζ in the intracellular domain. 2nd generation CAR include addition of one co-stimulatory molecule (CM) such as 4-1BB/CD28. 3rd generation CAR include two co-stimulatory domains. 4th generation CAR also called TRUCKs, it contains cytokine-induced domain IL-12. 5th generation CAR contain JAK-STAT activation domain which is derived from IL-2Rβ. CAR, chimeric antigen receptor; IL, interleukin; ITAM, immunoreceptor tyrosine-based activation motif.

this receptor by the antigen triggers TCR signalling (via the CD3ζ domains), co-stimulatory signalling (via the CD28 domain), and cytokine signalling (JAK–STAT3/5), thereby providing all three synergistic signals necessary for complete T cell activation and proliferation physiologically.[5,11]

## Indication of CAR T-cell

Over the past few years, the clinical utilization of CAR T-cells has experienced significant success in treating various hematological malignancies. In 2017, the Food and Drug Administration (FDA) approved CAR T-cell therapy to address diffuse large B-cell lymphoma (axicabtagene ciloleucel) and relapsed or refractory (R/R) acute lymphoblastic lymphoma (tisagenlecleucel). These developments and discoveries highlight the important benefits of CAR T-cell therapy and support its continued advancement.

### *Haematological malignancies*

CAR T-cells are predominantly employed in hematological malignancies such as acute lymphoblastic leukemia (ALL), distinguished by the rapid proliferation of immature cells within the bone marrow. Tisagenlecleucel and Axicabtagene ciloleucel, approved by the FDA in 2017 and the European Medicines Agency (EMA) in 2018, are CAR T-cells designed to target the CD19 antigen found in the B cell lineage.[12] Initial attempts showed that more than half of patients who received early CD19-targeted CAR T-cell therapy for relapsed or refractory (R/R) with B-cell ALL (B-ALL) experienced relapse. Nevertheless, CAR-T cell therapy in conjunction with allogeneic stem cell transplantation (SCT) may improve patient survival.[13]

Patients diagnosed with B-ALL often experience a relapse following CD19-targeted immunotherapy, necessitating the exploration of new alternative strategies. CAR-T cells targeting CD4 show promising results against CD4-positive T-cell lymphoma models both in vivo and in vitro, indicating their potential as effective therapeutic targets.[14,15] The cell marker CD72 is associated with poor prognosis in patients diagnosed with B-ALL. Synthetic CD72-specific nanobodies integrated into CARs have shown robust activity against B-cell malignancy models, presenting novel avenues for treatment approaches.[16] Positive outcomes have been observed in clinical trials assessing multitargeted CAR T-cell therapy against ALL. These treatments include single-designed CAR T-cells that target both CD19 and CD22, as well as a combination of CAR T-cells with anti-CD20 and anti-CD19 to target each antigen separately.

### *Multiple myeloma*

Multiple myeloma is a type of cancer that originates from plasma cells and can produce excessive amounts of immunoglobulin, leading to tissue damage. B-cell maturation antigen (BCMA) represents a crucial therapeutic target for multiple myeloma (MM). Various BCMA-targeted therapies have shown promising outcomes in treating MM.[17] The National Cancer Institute conducted the first human trial of BCMA-CAR T-cells in MM in 2016, involving the treatment of 12 patients with BCMA-CAR-T cell therapy. Nevertheless, in two cases, patients encountered toxicities associated with cytokine release, and symptoms like hypotension, fever, and dyspnoea.[18] Other antigens present on the surface of plasma cells besides BCMA may serve as novel targets for CAR T-cell recognition. When compared to BCMA or CS1 alone. CAR-T therapy, BCMA-CS1 bispecific CAR T-cells showed a better tumor cell clearance ability.

In 2021, the FDA approved to idecabtagene vicleucel for treating patients with MM. This marks the first FDA-approved cell therapy for MM.[19] In 2022, U.S. FDA authorized CARVYKTI™ (ciltacabtagene autoleucel), as a BCMA-directed CAR-T immunotherapy for managing patients with relapsed or refractory multiple myeloma. Targeting the CD38 antigen in MM patients using CAR T-cells with intracellular regions composed of 4-1BB and CD-28 holds promise to stimulate T cell proliferation and enhance anti-tumor function significantly. This approach could offer a new avenue for MM therapy.[20]

### *Non-Hodgkin lymphoma*

Non-Hodgkin lymphoma (NHL) is a type of cancer that originates from the lymphoid tissues, involving B cell precursors, T cell precursors, mature T cells, and mature B cells. Axi-Cel, a $CD19^{+}$ CAR T-cell treatment, demonstrates a notable impact in patients with refractory large B-cell lymphoma.[21] Patients who underwent CAR T-cell therapy with Axi-Cel exhibited high levels of good response. CD22 is expressed in both progenitor and differentiated B cells and is notably abundant in leukemia and B-cell lymphomas. Treatment with anti-CD22 therapy yielded promising outcomes, with 4 out of 9 patients achieving negative minimal residual disease (MRD) and complete remission.[22] CAR T-cell therapy in B-Cell NHL can lead to various adverse reactions, and patient prognosis is not as favourable as in ALL. The lower response rate may be attributed to the physical barriers posed by the tumor-inhibitory microenvironment.[23] While the therapeutic efficacy of CAR T-cells in NHL is remarkable, single-targeted CAR T-cell therapy still faces limitations. A primary concern is an immune escape from tumor cells resulting from target antigen loss. Multi-targeted CAR T-cell therapy may offer improved therapeutic outcomes by addressing this challenge.

### *Mantle cell lymphoma*

Mantle cell lymphoma (MCL) is a subtype of NHL arising from mature B-cells. It is characterized by a translocation involving the cyclin D1 gene (CCND1), resulting in the overexpression of Cyclin D1 protein. CAR T-cell therapies have shown effectiveness in treating high-risk MCL. Recently in May 2024, the FDA approved Breyanzi® (lisocabtagene maraleucel; liso-

cel), a CD19-directed CAR T-cell therapy for adult patients with relapsed or refractory MCL. This approval applies to patients who have undergone at least two prior lines of systemic therapy, including treatment with a Bruton tyrosine kinase (BTK) inhibitor.[24] Brexucabtagene autoleucel (Tecartus®) is another FDA-approved CAR T-cell therapy for adult patients diagnosed with relapsed or refractory MCL. This approval was grounded in the outcomes of the ZUMA-2 phase 2 multicenter clinical trial, which assessed the effectiveness and safety of Tecartus® in R/RMCL patients, who had previously failed treatments, including anti-CD20 antibody therapy, and a Bruton's tyrosine kinase inhibitor.[25] While CD-19-specific CAR T-cells have demonstrated clinical efficacy in aggressive B-cell lymphomas, long-term disease control has proven elusive for many patients.[26] Consequently, there exists an unmet need for strategies to enhance the therapeutic effectiveness of CAR-T cell therapies. Promising clinical outcomes have been observed with third-generation CAR T-cells that target CD20 in B-cell NHL (B-NHL).[27]

*Follicular lymphoma*

Follicular lymphoma (FL) is a slow-growing B-cell lymphoproliferative disorder originating from transformed follicular center B cells. It is typified by diffuse lymphadenopathy, bone marrow infiltration, and often, splenomegaly. There have been notable advancements in the treatment of FL over the past two decades. The effectiveness of CAR T-cells was initially shown in a heavily treated patient with advanced-stag FL in 2010, and this was subsequently supported by a small series of cases.[28,29]

In 2021, axicabtagene ciloleucel (axi-cel) received approval for treating patients with R/R FL who have undergone two or more lines of systemic therapy. This approval was based on findings from the ZUMA-5 study, a phase II multicenter international trial conducted as a single-arm study. In this phase 2 trial, 124 patients with FL and 16 with marginal zone lymphoma were enrolled. Of the 80 evaluable FL patients, 94% demonstrated a response, with 79% achieving complete remission (CR). After a follow-up period of 31 months, the progression-free survival (PFS) rate at 18 months was 65.6%, and the overall survival (OS) rate was 88%.[30,31]

Likewise, tisagenlecleucel was given accelerated approval by the FDA in May 2022 for a similar indication. Tisa-cel has also been studied in high-risk FL. The phase II ELARA trial assessed the safety and efficacy of Tisa-Cel in 97 patients with R/R FL who had received two or more prior treatments or relapsed after autologous hematopoietic stem cell transplantation. The overall response rate was 86%, with a complete response rate of 69%.[32] Recently in May, 2024, the FDA granted new approval based on results from the single-arm phase 2 TRANSCEND-FL trial, which included adults with R/R FL. Participants had previously received two or more lines of systemic therapy. The efficacy analysis involved 94 patients with positron emission computed tomography (PET)-positive disease at baseline or after bridging therapy. Following lymphodepletion chemotherapy, patients received a single infusion of lisocabtagene maraleucel within 2–7 days. The researchers observed an overall response rate (ORR) of 95.7% however the median duration of response was not reached after a median follow-up of 16.8 months.[33] Clinical trials focused on hematological/solid malignancies have demonstrated that CAR T-cell therapy can induce remission in patients who have undergone multiple unsuccessful cancer treatments over several years.[34] Additionally, this therapy can prevent cancer progression, extend patients' lifespans, and, in some cases, make them eligible for treatments like stem cell transplantation. However, a significant limitation is the potential for relapse, which may be driven by antigen escape and the limited persistence of CAR T-cells.[35]

## Side effects

Despite the considerable advancements observed in clinical trials of CAR T-cell therapy, the presence of adverse reactions during treatment has also impacted its effectiveness. The side effects experienced during CAR T-cell treatment can trigger various responses across different bodily systems. However, it's worth noting that the majority of these toxicities and side effects are reversible, provided patients receive timely and appropriate interventions. One of the most prevalent toxicities observed in CAR T-cell therapy is the “on-target off-tumor” effect, whereby the same target antigen is expressed on normal cells, prompting the CAR T-cells to inadvertently target healthy tissues, consequently inducing adverse effects.[36]

*Antigen escape*

The emergence of antigen escape following the infusion of modified CAR T-cells is becoming a significant concern. Tumor cells evade killing by promoting mutations in the genes coding for antigens, resulting in the downregulation of alternative antigen expression that lacks the epitopes targeted by CAR T-cells.[37] For instance, even though 70% to 90% of patients with relapsed or refractory ALL exhibit long-lasting responses to CD19-targeted CAR T-cell therapy, recent follow-up data indicate the emergence of a prevalent disease resistance mechanism. This includes the downregulation or loss of CD19 antigen in 30% to 70% of patients experiencing disease recurrence post-treatment.[38] Similarly, it has been noted that individuals with multiple myeloma receiving treatment with BCM-targeted CAR T-cells have downregulated or lost BCMA expression.[39]

To overcome this challenge, one strategy involves designing T cells with multiple CARs to target multiple tumor-associated antigens (TAAs). This approach suggests that evading the therapy would necessitate mutations in multiple genes instead of just one. Various engineering techniques are being explored, such as tandem CAR T-cells, bicistronic CAR T-cells, and co-administered CAR T-cells.[40,41]

*Immunosuppressive microenvironment*

Within the tumor microenvironment (TME), various cell types contribute to immunosuppression and infiltrate solid tumors. These include regulatory T cells (Tregs), TAMs, and myeloid-derived suppressor cells (MDSCs).

Indeed, both infiltrating immune cells and tumor cells play crucial roles in fostering an environment supportive of tumor growth. They contribute to the secretion of chemokines, tumor-supporting growth factors, and cytokines. Additionally, the decline in antitumor immunity is facilitated by immune checkpoint proteins like CTLA-4 or PD-1, which exert inhibitory effects on immune responses, further promoting tumor progression.[42] One of the primary reasons for the lack of response or suboptimal response to CAR T-cell therapy is often attributed to inadequate T cell expansion and short-term T cell. It is believed that the fusion of CAR T-cells with checkpoint blockade and immunotherapy will be the next revolutionary approach in immunotherapy, this approach offers critical components to enhance robust immune responses. In a single-center study at the Children's Hospital of Pennsylvania, a combination therapy involving PD-1 blockade alongside CD19 CAR T-cell therapy was administered to 14 children with heavily pretreated B-ALL. The results showed enhanced persistence of CAR T-cells and improved outcomes in haematological malignancy.[43] Recently, there have been advancements in engineering CAR T-cells to confer robust resistance against immunosuppressive factors present in the TME, such as signals mediated by transforming growth factor-beta (TGF-β).[44] Moreover, CAR T-cell engineering encompasses the incorporation of immunostimulatory signals, like stimulatory cytokines, which can enhance cell proliferation, survival, and antitumor activity. This approach aims to counteract the suppressive influence of the TME.[45]

*Toxicities associated with CAR T-cell*

T-cell therapy represents a revolutionary advancement in cancer treatment, but its application has been constrained by the presence of toxicities and resulting fatalities. The primary acute toxicity associated with CAR T-cell therapy is cytokine release syndrome (CRS). The

cytokines implicated in CRS are typically generated either by the infused CAR T-cells themselves or by immune cells, such as macrophages, in response to CAR T-cell activity. CRS is typically associated with symptoms such as high fever, hypotension, and hypoxia often accompanied by multi-organ toxicities.[46] Among patients with leukemia undergoing CAR T-cell therapy, 78% to 93% experienced any grade of CRS, while in lymphoma patients, this percentage ranged from 37% to 93%. Notably, in patients treated with tisagenlecleucel for R/R B-ALL, 46% encountered CRS of $\geq$ Grade 3 severity. For diffuse large B-cell lymphoma patients treated with axicabtagene ciloleucel and tisagenlecleucel, the incidence of $\geq$ Grade 3 CRS was 13% to 18%, respectively.[47,48] Supportive therapy in the management of CRS involves the use of antipyretics, intravenous fluids, blood components transfusion, vasopressors, monoclonal antibodies (tocilizumab) that block the IL-6 receptor, and steroids in cases of high-grade CRS.[49] Immune effector cell-associated neurotoxicity syndrome (ICANS), is another prevalent toxicity following CAR T-cell therapy and is linked with treatment-related morbidity.

It is marked by tremors, difficulty with speech, seizures, or changes in mental status. ICANS can present in two phases: the first phase usually presents with a high fever and other CRS symptoms within the initial 5 days following cellular immunotherapy. The second phase typically emerges after CRS symptoms and fever have subsided, often occurring more than 5 days after cell infusion.[50] Generally, ICANS is diagnosed clinically; CSF and brain MRI evaluation are rarely beneficial but they serve to exclude other conditions like CNS infection. The management of ICANS depends on concurrent CRS and the severity score of ICANS. Supportive care suffices for grade 1 ICANS, while grade $\geq$ 2 ICANS typically requires dexamethasone with a rapid taper. In severe and unresponsive cases, treatments such as anakinra (an IL-1 receptor antagonist) or chemotherapy aimed at eliminating the CAR T-cells have been employed.[51]

Despite the numerous challenges still encountered by adoptive CAR T-cell therapies, exciting projects are driving innovative efforts to enhance their efficacy, safety, and applicability. Various distinct strategies aim to address different problematic aspects of CAR T-cell treatments. Some focus on utilizing low-affinity CARs to minimize on-target off-tumor toxicity,[52] while additional approaches target tumor-supporting cells such as TAMs, MDSCs, and Tregs.[53]

## *Nursing perspectives in CAR T-cell therapy*

*Education and counseling.* Education and counseling by nurses play a pivotal role in the comprehensive care of patients undergoing CAR T-cell therapy, an innovative treatment modality in cancer management. Nurses can educate patients and their caregivers about the therapy's principles, potential side effects, and the importance of adherence to follow-up care protocols. They can also provide crucial information regarding pre-procedural preparations, such as leukapheresis, and post-infusion monitoring for complications like cytokine release syndrome and neurotoxicity[54]

Nurses offer emotional support and facilitate informed decision-making throughout the treatment journey by addressing concerns, managing expectations, and promoting coping strategies.[55] Effective communication and patient advocacy by nurses enhance treatment outcomes and quality of life for individuals undergoing CAR T-cell therapy.

*Monitoring and assessment.* Monitoring and assessment of side effects by nurses are critical components of the care provided to patients undergoing CAR T-cell therapy. Trained oncology nurses can vigilantly observe and evaluate potential adverse events associated with therapy, ensuring early detection and prompt intervention to optimize patient outcomes.

One of the primary side effects CRS, characterized by fever, hypotension, and potentially life-threatening systemic inflammatory responses can be picked up by the nurses. Nurses can also employ standardized assessment tools to assess CRS severity and guide treatment decisions, including the administration of tocilizumab or corticosteroids to mitigate symptoms.[56]

Neurotoxicity is another significant concern, manifested by confusion, delirium, and seizures. Nurses can conduct frequent neurological assessments to identify early signs, monitor for changes in mental status, and collaborate closely with health care teams to implement appropriate management strategies, such as supportive care and neurologic interventions.[57] Additionally, due to immunosuppression, patients are at high risk for infections. Nurses monitor for infection signs and administer prophylactic antibiotics as prescribed.[58]

*Symptom management.* Nurses play a crucial role in symptom management for patients undergoing CAR T-cell therapy, ensuring comprehensive care and support throughout the treatment process. Symptom management involves addressing both expected and unexpected adverse effects of therapy, enhancing patient comfort, and optimizing treatment outcomes.

Nurses educate patients and caregivers about potential symptoms associated with CAR T-cell therapy along with guiding recognizing early signs, the importance of monitoring, and when to seek immediate medical attention.[59]

Nurses also implement standardized protocols for symptom assessment, utilizing validated scales and clinical guidelines to monitor symptom severity and progression.[56] They provide ongoing emotional support, coordinate pain management interventions, and promote patient advocacy throughout the treatment journey.

*Co-ordination of care.* In CAR T-cell therapy, nurses play a pivotal role in coordinating care across various phases of treatment to ensure seamless and effective patient management. Their coordination efforts encompass multidisciplinary collaboration, patient education, and advocacy to optimize therapeutic outcomes and patient safety.

Nurses facilitate communication and collaboration among health care providers, including oncologists, hematologists, pharmacists, and other specialists involved in the care team. They ensure that treatment plans are communicated, understood, and executed, minimizing errors and enhancing continuity of care.[57]

Nurses also serve as central points of contact for patients and caregivers, providing comprehensive education on treatment protocols, potential side effects, and the importance of adherence to follow-up appointments.[60] They coordinate scheduling for pre-treatment evaluations, leukapheresis, infusion procedures, and post-treatment monitoring, ensuring timely interventions and continuity of care.

*Patient advocacy.* Nurses play a critical role in patient advocacy in CAR T-cell therapy, ensuring that patients' voices are heard and their rights are upheld throughout the treatment process. This advocacy can start with patient and family education with comprehensive information about CAR T-cell therapy, including its benefits, risks, and potential side effects. This will empower patients to make informed decisions about their care.[56]

Nurses act as intermediaries between patients and the multidisciplinary health care team, ensuring that patients' concerns and preferences are communicated and addressed. They facilitate discussions on treatment options, aligning medical recommendations with the patient's values and goals.[61] Nurses also offer emotional support, helping patients cope with the psychological and emotional challenges of CAR T-cell therapy. They advocate for resources such as psychological counseling and support groups, recognizing the holistic needs of patients.[59]

Nurses' roles are very crucial in monitoring for complications or adverse effects, and advocating for timely interventions and modifications to the treatment plan as necessary. This proactive approach always helps to enhance patient safety and improves treatment outcomes.[62]

*Documentation and communication.* Nurses play an essential role in documentation and communication in CAR T-cell therapy, crucial for ensuring patient safety, continuity of care, and optimal treatment outcomes. Accurate documentation of patient assessments, interventions, and outcomes is crucial for continuity of care. Nurses maintain detailed records that inform the ongoing treatment plan and support effective communication among the health care team. Clear and concise communication with patients and their families ensures that they are informed and engaged in their care.[63] Accurate documentation begins with recording detailed patient histories, including previous treatments, comorbidities, and baseline assessments. This comprehensive information forms the foundation for individualized care plans.[55]

Nurses have an important role in communications related to the identification of adverse events to the patients and caregivers and are advised to make a call, in case of any adverse events.[64] Nurses educate patients and their families about what to expect during and after therapy, fostering an open line of communication. This empowers patients to report symptoms promptly, leading to timely management of side effects.[62]

Operations management can help to improve communication and collaboration among health care providers including nurses, leading to better coordination and continuity of care for cancer patients.[65]

## Conclusions

CAR T-cell therapy is an innovative cancer treatment, particularly for hematologic malignancies. Despite its potential, the therapy poses challenges, including severe side effects like cytokine release syndrome and neurotoxicity. Nurses play a crucial role in patient education, monitoring, symptom management, care coordination, and psychosocial support, ensuring safe and effective treatment. The continued evolution of CAR T-cell therapy promises improved outcomes, with nursing professionals integral to its success.

## Ethics statement

Not required.

## Funding

This study received no external funding.

## CRediT authorship contribution statement

Ashna Gupta, Mayank Singh, and Abhishek Shankar: Conceptualization, Methodology, Formal Analysis, and Writing. Gunjan Dagar, Mohd Umar Rehmani, Chandra Prakash Prasad and Deepak Saini: Writing and revised draft preparation.

All authors had full access to all the data in the study, and the corresponding authors had final responsibility for the decision to submit for publication. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Declaration of competing interest

The authors declare no conflict of interest.

## Data availability statement

Not applicable.

## Declaration of generative AI and AI-assisted technologies in the writing process

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

## References

1. *Global Cancer Observatory: Cancer Today*. Lyon, France: International Agency for Research on Cancer; 2022. Available from: https://gco.iarc.fr/today. Accessed May 21, 2024.
2. Salk JJ, Fox EJ, Loeb LA. Mutational heterogeneity in human cancers: origin and consequences. *Annu Rev Pathol*. 2010;5:51–75. https://doi.org/10.1146/annurev-pathol-121808-102113. PMID: 19743960; PMCID: PMC3375045.
3. Arruebo M, Vilaboa N, Sáez-Gutierrez B, et al. Assessment of the evolution of cancer treatment therapies. *Cancers*. 2011 Aug 12;3(3):3279–3330. https://doi.org/10.3390/cancers3033279. PMID: 24212956; PMCID: PMC3759197.
4. Burnet FM. Immunological surveillance in neoplasia. *Transplant Rev*. 1971;7:3–25. https://doi.org/10.1111/j.1600-065x.1971.tb00461.x. PMID: 5146537.
5. Chakraborty A, Dutta P, Saha D, et al. Chimeric antigen receptor CAR-T therapy on the move: current applications and future possibilities. *Curr Tissue Microenviron Rep*. 2023;4:29–40.
6. orman AJ, Peggs KS, Allison JP. Checkpoint blockade in cancer immunotherapy. *Adv Immunol*. 2006;90:297–339. https://doi.org/10.1016/S0065-2776(06)90008-X. PMID: 16730267; PMCID: PMC1951510.).
7. Dagar G, Gupta A, Masoodi T, et al. Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments. *J Transl Med*. 2023;21:449. https://doi.org/10.1186/s12967-023-04292-3.
8. Bird RE, Hardman KD, Jacobson JW, et al. Single-chain antigen-binding proteins. *Science*. 1988 Oct 21;242(4877):423–426. https://doi.org/10.1126/science.3140379. Erratum in: Science 1989 Apr 28;244(4903):409. PMID: 3140379.
9. Huston JS, Levinson D, Mudgett-Hunter M, et al. Protein engineering of antibody binding sites: recovery of specific activity in an anti-digoxin single-chain Fv analogue produced in Escherichia coli. *Proc Natl Acad Sci U S A*. 1988 Aug;85(16):5879–5883. https://doi.org/10.1073/pnas.85.16.5879. PMID: 3045807; PMCID: PMC281868.
10. Chmielewski M, Hombach AA, Abken H. Of CARs and TRUCKs: chimeric antigen receptor (CAR) T cells engineered with an inducible cytokine to modulate the tumor stroma. *Immunol Rev*. 2014 Jan;257(1):83–90. https://doi.org/10.1111/imr.12125. PMID: 24329791.
11. Kagoya Y, Tanaka S, Guo T, et al. A novel chimeric antigen receptor containing a JAK–STAT signaling domain mediates superior antitumor effects. *Nat Med*. 2018;24:352–359. https://doi.org/10.1038/nm.4478.
12. Umut Ö, Gottschlich A, Endres S, Kobold S. CAR T cell therapy in solid tumors: a short review. *Memo*. 2021;14(2):143–149. https://doi.org/10.1007/s12254-021-00703-7.
13. Martino M, Alati C, Canale FA, Musuraca G, Martinelli G, Cerchione C. A review of clinical outcomes of CAR T-cell therapies for B-acute lymphoblastic leukemia. *Int J Mol Sci*. 2021;22:2150. https://doi.org/10.3390/ijms220421.
14. Pinz K, Liu H, Golightly M, et al. Preclinical targeting of human T-cell malignancies using CD4-specific chimeric antigen receptor (CAR)-engineered T cells. *Leukemia*. 2016;30:701–707. https://doi.org/10.1038/leu.2015.311.
15. Sahlolbei M, Ahmadieh-Yazdi A, Rostamipoor M, et al. *Recent Updates on Chimeric Antigen Receptor T-Cell Approaches in Cancer Immunotherapy*. IntechOpen; 2024. https://doi.org/10.5772/intechopen.1005116.
16. Nix MA, Mandal K, Geng H, et al. Surface proteomics reveals CD72 as a target for in vitro-evolved nanobody-based CAR-T cells in KMT2A/MLL1-rearranged B-ALL. *Cancer Discov*. 2021;11:2032–2049.
17. Sheykhhasan M, Ahmadieh-Yazdi A, Vicidomini R, et al. CAR T therapies in multiple myeloma: unleashing the future. *Cancer Gene Ther*. 2024 May;31(5):667–686. https://doi.org/10.1038/s41417-024-00750-2. Epub 2024 Mar 4. PMID: 38438559; PMCID: PMC11101341.
18. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood*. 2016;128:1688–1700.
19. Ferment B, Arnulf B. CAR-T cells immunotherapy in multiple myeloma: present and future. *Bull Cancer*. 2021;108(10 suppl l):S65–S72. https://doi.org/10.1016/j.bulcan.2021.09.005.
20. rent E, Poels R, Ruiter R, et al. Combined CD28 and 4-1BB costimulation potentiates affinity-tuned chimeric antigen receptor-engineered T cells. *Clin Cancer Res*. 2019;25:4014–4025. https://doi.org/10.1158/1078-0432.CCR-18-2559.
21. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N*.
22. Stetler-Stevenson M, Shah NN, Yuan CM, et al. Clinical activity and persistence of anti-CD22 chimeric antigen receptor in children and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL). *Blood*. 2015;126.
23. Yin Z, Zhang Y, Wang X. Advances in chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma. *Biomark Res*. 2021;9:58.
24. Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. *JCO*. 2024;42:1146–1157. https://doi.org/10.1200/JCO.23.02214.
25. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020 Apr 2;382(14):1331–1342. https://doi.org/10.1056/NEJMoa1914347. PMID: 32242358; PMCID: PMC7731441.
26. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023 Jun;20(6):359–371. https://doi.org/10.1038/s41571-023-00754-1.
27. Till BG, Jensen MC, Wang J, et al. CD20-specific adoptive immunotherapy for lymphoma using a chimeric antigen receptor with both CD28 and 4-1BB domains: pilot clinical trial results. *Blood*. 2012 Apr 26;119(17):3940–3950. https://doi.org/

10.1182/blood-2011-10-387969. Epub 2012 Feb 3. PMID: 22308288; PMCID: PMC3350361.
28. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017 Dec 28;377(26):2545–2554. https://doi.org/10.1056/NEJMoa1708566. Epub 2017 Dec 10. PMID: 29226764; PMCID: PMC5788566.
29. Hirayama AV, Gauthier J, Hay KA, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. *Blood*. 2019 Aug 15; 134(7):636–640. https://doi.org/10.1182/blood.2019000905. PMID: 31648294; PMCID: PMC6695558.
30. Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood*. 2024 Feb 8;143(6):496–506. https://doi.org/10.1182/blood.2023021243. PMID: 37879047; PMCID: PMC10934297.
31. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022 Jan;23(1):91–103. https://doi.org/10.1016/S1470-2045(21)00591-X. Epub 2021 Dec 8. PMID: 34895487.
32. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med*. 2022 Feb;28(2): 325–332. https://doi.org/10.1038/s41591-021-01622-0. Epub 2021 Dec 17. PMID: 34921238.
33. A Study to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects With Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (NHL). ClinicalTrials.gov identifier: NCT04245839. Updated August 2021. Accessed July 20, 2024. https://clinicaltrials.gov/study/NCT04245839.
34. De Marco RC, Monzo HJ, Ojala PM. CAR T cell therapy: a versatile living drug. *Int J Mol Sci*. 2023 Mar 27;24(7):6300. https://doi.org/10.3390/ijms24076300. PMID: 37047272; PMCID: PMC10094630.
35. Song MK, Park BB, Uhm JE. Resistance mechanisms to CAR T-cell therapy and overcoming strategy in B-cell hematologic malignancies. *Int J Mol Sci*. 2019 Oct 10; 20(20):5010. https://doi.org/10.3390/ijms20205010. PMID: 31658644; PMCID: PMC6834308.
36. Mishra AK, Gupta A, Dagar G, et al. CAR-T-Cell therapy in multiple myeloma: B-cell maturation antigen (BCMA) and beyond. *Vaccines (Basel)*. 2023 Nov 16;11(11):1721.
37. Majzner RG, Mackall CL. Tumor antigen escape from car T-cell therapy. *Cancer Discov*. 2018;8:1219–1226. https://doi.org/10.1158/2159-8290.
38. Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood*. 2015;125: 4017–4023. https://doi.org/10.1182/blood-2014-12-580068.
39. Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. *J Clin Invest*. 2019;129:2210–2221. https://doi.org/10.1172/JCI126397.
40. Hegde M, Corder A, Chow KK, et al. Combinational targeting offsets antigen escape and enhances effector functions of adoptively transferred T cells in glioblastoma. *Mol Ther*. 2013;21:2087–2101. https://doi.org/10.1038/mt.2013.185.
41. ackson HJ, Brentjens RJ. Overcoming antigen escape with CAR T-cell therapy. *Cancer Discov*. 2015;5:1238–1240. https://doi.org/10.1158/2159-8290.CD-15-1275.
42. Yin Y, Boesteanu AC, Binder ZA, et al. Checkpoint blockade reverses anergy in IL-13Rα2 humanized scFv-based CAR T cells to treat murine and canine gliomas. *Mol Ther Oncolytics*. 2018;11:20–38.
43. Li AM, Hucks GE, Dinofia AM, et al. Checkpoint inhibitors augment CD19-directed chimeric antigen receptor (CAR) T cell therapy in relapsed B-cell acute lymphoblastic leukemia. *Blood*. 2018;132:556. https://doi.org/10.1182/blood-2018-99-112572.
44. Kloss CC, Lee J, Zhang A, et al. *Dominant-Negative TGF-β Receptor Enhances PSMA-Targeted Human CAR T Cell Proliferation and Augments Prostate Cancer Eradication*. 2018.
45. hmielewski M, Hombach AA, Abken H. Of CARs and TRUCKs: chimeric antigen receptor (CAR) T cells engineered with an inducible cytokine to modulate the tumor stroma. *Immunol Rev*. 2014;257:83–90.
46. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016;127:3321–3330. https://doi.org/10.1182/BLOOD-2016-04-703751.
47. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531–2544. https://doi.org/10.1056/NEJMoa1707447.
48. aude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–448. https://doi.org/10.1056/NEJMoa1709866.
49. Zhang C, Durer S, Thandra KC, Kasi A. Chimeric Antigen Receptor T-Cell Therapy. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2022 Oct 3, 2024 Jan–. PMID: 30725979.
50. Castaneda-Puglianini O, Chavez JC. Assessing and management of neurotoxicity after CAR-T therapy in diffuse large B-cell lymphoma. *J Blood Med*. 2021 Aug 24;12:775–783. https://doi.org/10.2147/JBM.S281247. PMID: 34466048; PMCID: PMC8403007.
51. Rees JH. Management of immune effector cell-associated neurotoxicity syndrome (ICANS). In: Kröger N, Gribben J, Chabannon C, Yakoub-Agha I, Einsele H, eds. *The EBMT/EHA CAR-T Cell Handbook*. Cham (CH): Springer; 2022. ISBN 978-3-030-94352-).
52. Drent E, Themeli M, Poels R, et al. A rational strategy for reducing on-target off-tumor effects of CD38-chimeric antigen receptors by affinity optimization. *Mol Ther*. 2017 Aug 2;25(8):1946–1958. https://doi.org/10.1016/j.ymthe.2017.04.024. Epub 2017 May 13. PMID: 28506593; PMCID: PMC5542711.
53. Rodriguez-Garcia A, Palazon A, Noguera-Ortega E, Powell Jr DJ, Guedan S. CAR-T cells Hit the tumor microenvironment: strategies to overcome tumor escape. *Front Immunol*. 2020 Jun 17;11:1109. https://doi.org/10.3389/fimmu.2020.01109. PMID: 32625204; PMCID: PMC7311654.
54. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet*. 2015;385(9967):517–528.
55. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531–2544.
56. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.
57. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47–62.
58. Castro I, Ruiz J, Tasias M, Montero M, Salavert M. Central nervous system infections in immunocompromised patients. *Rev Esp Quimioter*. 2018 Sep;31(1):56–61.
59. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31–42.
60. Dahlawi HH, Al Obaidellah MM, Rashid NA, et al. Defining physician-nurse efforts toward collaboration as perceived by medical students. *Healthcare (Basel)*. 2023 Jul 3;11(13):1919.
61. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531–2544.
62. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov*. 2017;7(12):1404–1419.
63. Mathioudakis A, Rousalova I, Gagnat AA, Saad N, Hardavella G. How to keep good clinical records. *Breathe*. 2016 Dec;12(4):369–373.
64. Shankar A, Wallbridge IG, Yau C, et al. Development of management strategies for immune-related adverse effects of immunotherapies used in oncological treatment. *Asia Pac J Oncol Nurs*. 2021 Dec 25;9(1):7–11. https://doi.org/10.1016/j.apjon.2021.12.007.
65. Gautam P, Shankar A. Operations management interventions in cancer care delivery in LMICs: the way forward. *Asian Pac J Cancer Prev*. 2023 Jan 1;24(1):1–7. https://doi.org/10.31557/APJCP.2023.24.1.1. PMID: 36708545; PMCID: PMC10152871.