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CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY - NARRATIVE REVIEW ON MECHANISMS, CLINICAL APPLICATIONS, ADVERSE EFFECTS, SUPPORTIVE CARE, AND FUTURE DIRECTIONS

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ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide despite continuous advances in diagnosis and treatment. Conventional treatment modalities, including surgery, chemotherapy, radiotherapy, and targeted therapies, have significantly improved survival in many malignancies. However, treatment resistance, disease relapse, and therapy-related toxicities continue to limit long-term clinical outcomes. These challenges have driven the development of immunotherapeutic approaches that harness the body's immune system to recognize and eliminate malignant cells.

Among the available immunotherapies, chimeric antigen receptor T-cell (CAR-T) therapy has emerged as one of the most important advances in cancer treatment. CAR-T therapy involves the genetic modification of autologous or allogeneic T lymphocytes to express synthetic receptors capable of recognizing tumor-associated antigens independently of major histocompatibility complex (MHC) presentation. Following reinfusion, these engineered cells selectively target tumor cells, proliferate, release inflammatory cytokines, and induce tumor cell death through multiple cytotoxic mechanisms.

CAR-T therapy has produced remarkable clinical responses in patients with relapsed or refractory hematological malignancies. Currently approved indications include B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and multiple myeloma. In addition, several clinical trials are evaluating its potential role in other hematological cancers and solid tumors.

Despite its impressive therapeutic efficacy, CAR-T therapy is associated with important limitations, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, prolonged cytopenias, infections, manufacturing complexity, high treatment costs, and reduced effectiveness against solid tumors.[5,9,13,21] Ongoing research is focused on improving CAR design, developing allogeneic and gene-edited CAR-T products, optimizing manufacturing strategies, and exploring combination therapies to enhance efficacy while minimizing toxicity.[25,26,27,28]

This narrative review summarizes the evolution of CAR-T cell therapy, its structural components, mechanism of action, manufacturing process, approved clinical indications, adverse effects, supportive care strategies, current challenges, and emerging future directions. [2,7,28]

Keywords: CAR-T Cell Therapy, Immunotherapy, Malignancies, Major Histocompatibility Complex

1 INTRODUCTION

Cancer continues to pose a major global health challenge and remains one of the leading causes of illness and death worldwide. Although considerable progress has been achieved in early diagnosis, surgical techniques, radiotherapy, chemotherapy, targeted therapies, and supportive care, many patients continue to experience disease progression, recurrence, or treatment failure. Furthermore, conventional anticancer therapies often lack tumor specificity, resulting in damage to healthy tissues and significant treatment-related toxicities. The emergence of drug resistance further limits the long-term effectiveness of these therapeutic approaches, particularly in advanced-stage malignancies. [3,7,24]

A deeper understanding of tumor biology and host immune responses has led to the development of cancer immunotherapy, an approach that enhances or modifies the immune system to identify and eliminate malignant cells. Unlike conventional therapies that directly target tumor cells, immunotherapy aims to restore or strengthen the body's natural immune surveillance mechanisms. Several immunotherapeutic strategies have entered clinical practice, including immune checkpoint inhibitors, monoclonal antibodies, cancer vaccines, cytokine-based therapies, and adoptive cell therapies. [3,7,10]

Among these approaches, adoptive cell therapy has attracted considerable attention because of its ability to generate highly specific and durable antitumor immune responses. In this strategy, immune cells are isolated from the patient or a suitable donor, expanded or genetically modified under controlled laboratory conditions, and subsequently reinfused into the patient. Earlier adoptive cell therapies primarily relied on tumor-infiltrating lymphocytes or genetically engineered T-cell receptors. Although these approaches demonstrated therapeutic potential, their clinical application was limited by dependence on major histocompatibility complex (MHC)-mediated antigen presentation and restricted antigen recognition. [2,3,24]

The development of chimeric antigen receptor T-cell (CAR-T) therapy marked a major breakthrough in adoptive cellular immunotherapy. CAR-T cells are genetically engineered T lymphocytes that express synthetic receptors capable of recognizing tumor-associated surface antigens independently of MHC presentation.[2,7] Following antigen binding, intracellular signaling pathways are activated, resulting in rapid T-cell proliferation, cytokine secretion, and targeted destruction of malignant cells through multiple cytotoxic mechanisms.[2,7,15] This unique mechanism enables CAR-T cells to overcome several tumor immune-evasion strategies and produce potent antitumor responses.[2,7]

Since the first regulatory approval of a CAR-T cell product in 2017, this treatment has transformed the management of several relapsed or refractory hematological malignancies. Durable clinical responses have been demonstrated in B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, and multiple myeloma.[6,8,11,18,19,22] Nevertheless, important challenges remain, including treatment-related toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, manufacturing complexity, prolonged production times, high treatment costs, antigen escape, and limited efficacy in solid tumors.[5,9,13,21,23]

Continuous advances in genetic engineering, gene-editing technologies, manufacturing platforms, and combination immunotherapies are expected to overcome many of these limitations and broaden the therapeutic applications of CAR-T therapy. [26,27,28]

This narrative review provides a comprehensive overview of CAR-T cell therapy, covering its historical development, structural components, mechanism of action, manufacturing process, currently approved products, clinical applications, adverse effects, supportive care strategies, existing challenges, and future prospects in cancer management.

2 HISTORY AND DEVELOPMENT OF CAR-T CELLS

The development of chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most significant milestones in the evolution of cancer immunotherapy. The concept of genetically modifying T lymphocytes to recognize tumor-associated antigens originated during the 1980s, when researchers began exploring methods to enhance the specificity and cytotoxic potential of T cells against malignant cells. [1,26]

A major breakthrough occurred in 1989 when Zelig Eshhar and colleagues introduced the concept of chimeric antigen receptors by engineering T cells to express antibody-derived recognition domains linked to T-cell signaling components. This innovation enabled T cells to recognize target antigens independently of major histocompatibility complex (MHC) presentation, thereby overcoming one of the principal limitations of conventional T-cell receptor (TCR)-based immunotherapy. [1,2,28]

The first-generation CARs consisted of an extracellular antigen-recognition domain linked only to the CD3ζ intracellular signaling domain. Although these receptors were capable of recognizing tumor antigens, they demonstrated limited clinical efficacy because of poor T-cell expansion, inadequate persistence, and insufficient cytokine production following antigen stimulation. [2,7]

To overcome these limitations, second-generation CARs incorporated a single co-stimulatory domain, most commonly CD28 or 4-1BB, in addition to the CD3ζ signaling domain. The inclusion of these co-stimulatory molecules markedly enhanced T-cell activation, proliferation, persistence, cytokine secretion, and overall antitumor activity. Most currently approved CAR-T cell products are based on this second-generation design. [2,7,14]

Subsequently, third-generation CARs were developed by combining two co-stimulatory domains, such as CD28 with 4-1BB, OX40, or CD27. These constructs were designed to further enhance T-cell activation and persistence, although concerns regarding excessive immune activation and treatment-related toxicities limited their widespread clinical adoption. [2,25]

Further innovations led to the development of fourth-generation CARs, also known as T cells Redirected for Universal Cytokine-mediated Killing (TRUCKs). These engineered cells are capable of releasing immunostimulatory cytokines, such as interleukin-12 (IL-12), following antigen recognition. This strategy enhances immune activation within the tumor microenvironment and may help overcome local immunosuppression, particularly in solid tumors. [25,26]

The most recent fifth-generation CARs incorporate intracellular signaling domains derived from cytokine receptors, including the interleukin-2 receptor β (IL-2Rβ), together with STAT3/STAT5 activation motifs. These modifications aim to produce more physiological T-cell activation, improve long-term persistence, and further enhance antitumor efficacy. [27,28]

In addition to successive CAR generations, several novel strategies are currently under investigation. These include dual-target and multi-target CARs to minimize antigen escape, switchable CAR systems with built-in safety mechanisms, gene-edited CAR-T cells generated using CRISPR-Cas9 technology, and universal allogeneic "off-the-shelf" CAR-T products derived from healthy donors. These approaches seek to improve therapeutic efficacy while reducing manufacturing time, toxicity, and overall treatment costs. [13,26,27,28]

The clinical translation of CAR-T therapy accelerated during the early 2010s following encouraging results from early-phase clinical trials in patients with relapsed or refractory B-cell malignancies. Landmark studies demonstrated remarkable remission rates in patients with advanced leukemia and lymphoma who had exhausted conventional treatment options. [14,15,16,17]

A historic milestone was achieved in 2017 with the approval of tisagenlecleucel (Kymriah) by the U.S. Food and Drug Administration (FDA) for relapsed or refractory B-cell acute lymphoblastic leukemia, making it the first commercially available CAR-T cell therapy. Shortly thereafter, additional products—including axicabtagene ciloleucel (Yescarta), brexucabtagene autoleucel (Tecartus), lisocabtagene maraleucel (Breyanzi), idecabtagene vicleucel (Abecma), ciltacabtagene autoleucel (Carvykti), and obecabtagene autoleucel (Aucatzyl)—received regulatory approval for the treatment of various B-cell malignancies and multiple myeloma. [6,8,11,12,18,19,22]

Despite these remarkable achievements, CAR-T therapy continues to face important challenges, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), antigen escape, limited persistence of engineered T cells, manufacturing complexity, prolonged production time, and high treatment costs. Ongoing research is focused on developing safer, more effective, and more accessible next-generation CAR-T therapies capable of overcoming these limitations and expanding the role of cellular immunotherapy in both hematological and solid malignancies. [9,13,21,25,28]

3 STRUCTURE OF CAR-T CELLS

Chimeric antigen receptor (CAR)-T cells are genetically engineered T lymphocytes that express synthetic receptors capable of recognizing tumor-associated antigens independently of major histocompatibility complex (MHC)

presentation. Unlike the natural T-cell receptor, the CAR combines antibody-derived antigen recognition with intracellular T-cell signaling, enabling highly specific tumor targeting. [2,7]

A typical CAR consists of four major structural components: the extracellular antigen-recognition domain, hinge (spacer) region, transmembrane domain, and intracellular signaling domain. [2,3]

3.1 Extracellular Antigen-Recognition Domain

The extracellular domain is responsible for identifying and binding tumor-associated antigens. It usually contains a single-chain variable fragment (scFv) derived from the variable regions of a monoclonal antibody. The scFv enables CAR-T cells to recognize specific antigens expressed on the surface of tumor cells, such as CD19 in B-cell malignancies or BCMA in multiple myeloma. [2,7]

Unlike conventional T-cell receptors, antigen recognition by the scFv is independent of MHC presentation, allowing CAR-T cells to recognize tumor cells even when antigen presentation pathways are impaired. This characteristic helps overcome an important mechanism of tumor immune escape. [2,28]

3.2 Hinge (Spacer) Region

The hinge, also known as the spacer region, connects the extracellular antigen-binding domain to the transmembrane domain. It provides structural flexibility, allowing the scFv to orient correctly and bind efficiently to target antigens located at varying distances from the tumor cell surface. [2]

The length and composition of the hinge influence antigen accessibility, immune synapse formation, and overall, CAR-T cell function. Common spacer regions are derived from CD8α or the IgG1/IgG4 Fc domains. [2,25]

3.3 Transmembrane Domain

The transmembrane domain anchors the CAR within the T-cell membrane and transmits activation signals from the extracellular region to the intracellular signaling components. [2]

Commonly used transmembrane domains are derived from CD3ζ, CD8α, or CD28. The choice of transmembrane domain affects receptor stability, CAR expression, and T-cell persistence. [2,27]

3.4 Intracellular Signaling Domain

The intracellular domain is responsible for activating the engineered T cell after antigen recognition. It contains the CD3ζ signaling chain, which serves as the primary activation motif and initiates intracellular signaling pathways leading to T-cell activation, proliferation, cytokine secretion, and cytotoxic activity. [2,7]

Modern CAR constructs also incorporate one or more co-stimulatory domains, most commonly CD28 or 4-1BB (CD137). These domains provide the essential second activation signal required for optimal T-cell expansion, persistence, survival, and antitumor efficacy. CARs containing CD28 generally produce rapid T-cell activation with robust initial responses, whereas 4-1BB-containing CARs are associated with prolonged persistence and sustained antitumor activity. [2,7,14]

Recent generations of CARs have incorporated additional signaling modules, including cytokine receptor domains and STAT3/STAT5 activation motifs, to enhance T-cell proliferation, persistence, and therapeutic effectiveness while reducing functional exhaustion. [27,28]

4 MECHANISM OF ACTION

The antitumor activity of chimeric antigen receptor T-cell (CAR-T) therapy involves a coordinated sequence of cellular and molecular events that culminate in the selective elimination of malignant cells. Unlike conventional T-cell receptors, CAR-T cells recognize tumor-associated surface antigens independently of major histocompatibility complex (MHC) presentation, allowing them to bypass one of the major mechanisms of tumor immune evasion. [2,7,28]

4.1 Antigen Recognition

Following intravenous infusion, CAR-T cells circulate through the bloodstream and migrate to sites where tumor cells are present. The extracellular single-chain variable fragment (scFv) binds specifically to tumor-associated antigens expressed on the surface of malignant cells, such as CD19 on B-cell malignancies or B-cell maturation antigen (BCMA) on multiple myeloma cells. This direct antigen recognition does not require antigen processing or presentation by MHC molecules, enabling CAR-T cells to recognize tumor cells even when MHC expression is reduced or absent. [2,7]

4.2 T-Cell Activation

Binding of the scFv to its target antigen induces conformational changes that activate the intracellular CD3ζ signaling domain together with co-stimulatory molecules such as CD28 or 4-1BB. These intracellular signaling pathways trigger rapid T-cell activation, resulting in increased cellular proliferation, enhanced survival, cytokine production, and acquisition of potent cytotoxic functions. [2,3,7]

4.3 Clonal Expansion and Cytokine Secretion

Activated CAR-T cells undergo rapid clonal expansion after antigen recognition, producing large numbers of effector T cells capable of targeting malignant cells. During this process, CAR-T cells release several pro-inflammatory cytokines, including interleukin-2 (IL-2), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and other inflammatory mediators. These cytokines enhance immune activation, recruit additional immune cells, and amplify the overall antitumor response. [5,7,9]

4.4 Tumor Cell Destruction

Activated CAR-T cells eliminate tumor cells through multiple cytotoxic mechanisms. The principal pathway involves the release of perforin, which forms pores in the tumor cell membrane, allowing granzymes to enter the target cell and activate intracellular apoptotic pathways. CAR-T cells also induce apoptosis through Fas–Fas ligand (FasL) interactions and other death receptor signaling pathways. These mechanisms collectively result in selective destruction of tumor cells while sparing surrounding healthy tissues that do not express the target antigen. [7,15,16]

4.5 Memory T-Cell Formation

Following tumor elimination, a proportion of activated CAR-T cells differentiate into long-lived memory T cells. These cells persist within the patient for months or even years and provide continuous immune surveillance against tumor recurrence. Long-term persistence of CAR-T cells has been associated with durable clinical remission and sustained therapeutic responses in several hematological malignancies. [15,16,18]

5 MANUFACTURING PROCESS OF CAR-T CELLS

The manufacture of chimeric antigen receptor T-cell (CAR-T) therapy is a highly specialized, multistep process involving the collection, genetic modification, expansion, quality assessment, and reinfusion of T lymphocytes. The entire manufacturing process typically requires 2–4 weeks and must comply with stringent quality control standards to ensure product safety, potency, and consistency. [4,31,43]

5.1 Leukapheresis

The manufacturing process begins with leukapheresis, a procedure in which peripheral blood mononuclear cells (PBMCs) are collected from the patient. During this process, whole blood is withdrawn and passed through an apheresis machine that selectively isolates white blood cells while returning red blood cells, platelets, and plasma to the patient. The collected PBMCs contain T lymphocytes, which serve as the starting material for CAR-T cell production. [4,26]

5.2 T-Cell Isolation and Activation

Following leukapheresis, T lymphocytes are isolated from the collected PBMCs under sterile laboratory conditions. These cells are then activated ex vivo using anti-CD3 and anti-CD28 antibodies or antibody-coated magnetic beads, which mimic physiological T-cell receptor signaling. Activation stimulates T-cell proliferation and prepares the cells for efficient genetic modification. [2,4,26]

5.3 Genetic Modification

Activated T cells are genetically engineered to express the chimeric antigen receptor. This is most commonly achieved using viral vectors, particularly lentiviral or gamma-retroviral vectors, which integrate the CAR gene into the T-cell genome, resulting in stable receptor expression. [4,2,27]

Alternative non-viral gene delivery systems, including transposon-based platforms (such as Sleeping Beauty and PiggyBac) and CRISPR-Cas9 gene-editing technology, are also being investigated to improve manufacturing efficiency, reduce production costs, and facilitate the development of universal allogeneic CAR-T products. [26,27,28]

5.4 Cell Expansion

After successful gene transfer, genetically modified T cells are cultured in specialized bioreactors under carefully controlled conditions. Cytokines such as interleukin-2 (IL-2), interleukin-7 (IL-7), and interleukin-15 (IL-15) are

commonly used to promote cell proliferation and survival. During this stage, the engineered cells undergo substantial expansion, increasing from a relatively small starting population to millions or billions of CAR-T cells required for therapeutic infusion. [4,7,26]

5.5 Quality Control Testing

Before release for clinical use, the CAR-T cell product undergoes comprehensive quality assessment to ensure compliance with regulatory standards. Testing includes evaluation of sterility, cell viability, purity, identity, transduction efficiency, potency, endotoxin levels, and the absence of microbial contamination. Only products that satisfy predefined quality specifications are approved for patient administration. [4,12,31]

5.6 Lymphodepleting Chemotherapy

Prior to CAR-T cell infusion, patients generally receive lymphodepleting chemotherapy, most commonly consisting of fludarabine and cyclophosphamide. This regimen reduces endogenous lymphocyte populations, creating a favorable immunological environment that enhances CAR-T cell expansion, persistence, and therapeutic activity following infusion. [7,9,10]

5.7 CAR-T Cell Infusion

After completion of lymphodepletion, the manufactured CAR-T cells are administered as a single intravenous infusion. Once infused, the engineered T cells circulate throughout the body, recognize tumor-associated antigens through their chimeric antigen receptors, undergo rapid expansion, release inflammatory cytokines, and selectively destroy malignant cells. Depending on the specific CAR-T product and disease being treated, these cells may persist for months or even years, providing ongoing immune surveillance against disease recurrence. [7,15,18]

6 FDA-APPROVED CAR-T CELL PRODUCTS

Since the approval of the first chimeric antigen receptor T-cell (CAR-T) therapy in 2017, the number of commercially available CAR-T products has steadily increased, significantly expanding treatment options for patients with relapsed or refractory hematological malignancies. [12,28]

Currently approved CAR-T therapies primarily target CD19, which is highly expressed on malignant B lymphocytes, or B-cell maturation antigen (BCMA), a cell-surface protein predominantly expressed on malignant plasma cells in multiple myeloma. [2,7]

Most approved CAR-T products utilize second-generation CAR constructs incorporating either the CD28 or 4-1BB (CD137) co-stimulatory domain. These co-stimulatory molecules play a critical role in determining CAR-T cell activation, proliferation, persistence, and long-term therapeutic efficacy. [2,7,28]

The continued approval of newer CAR-T products reflects the rapid progress of cellular immunotherapy and demonstrates its growing role in modern oncology. Ongoing clinical trials are expected to further expand the range of approved indications and target antigens in the coming years. [12,26,27]

Table 1: FDA-Approved CAR-T Cell Products

Brand Name	Generic Name	FDA Approval Year	Target Antigen	Major FDA-Approved Indications
Kymriah	Tisagenlecleucel	2017	CD19	Pediatric and young adult B-cell acute lymphoblastic leukemia (B-ALL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL)
Yescarta	Axicabtagene ciloleucel	2017	CD19	Large B-cell lymphoma (LBCL); follicular lymphoma (FL)
Tecartus	Brexucabtagene autoleucel	2020	CD19	Mantle cell lymphoma (MCL); adult B-cell acute lymphoblastic leukemia (B-ALL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
Abecma	Idecabtagene vicleucel	2021	BCMA	Relapsed/refractory multiple myeloma

Breyanzi	Lisocabtagene maraleucel	2021	CD19	Large B-cell lymphoma; chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); follicular lymphoma; mantle cell lymphoma
Carvykti	Ciltacabtagene autoleucel	2022	BCMA	Relapsed/refractory multiple myeloma
Aucatzyl	Obecabtagene autoleucel	2024	CD19	Adult relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL)

6.1 Clinical indications of CAR-T cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of several relapsed or refractory hematological malignancies by providing durable clinical responses in patients with limited therapeutic options. At present, most approved indications involve B-cell malignancies expressing CD19 or plasma cell malignancies expressing B-cell maturation antigen (BCMA). [7,12,28]

6.2 B-Cell Acute Lymphoblastic Leukemia (B-ALL)

B-cell acute lymphoblastic leukemia (B-ALL) was the first malignancy in which CAR-T therapy demonstrated remarkable clinical success. CD19-directed CAR-T therapy has produced high complete remission rates in pediatric, adolescent, and young adult patients with relapsed or refractory disease who had failed conventional chemotherapy or hematopoietic stem cell transplantation. Long-term follow-up studies have shown durable remissions in a substantial proportion of treated patients. [8,16,12]

6.3 Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) represents one of the most common indications for CAR-T therapy in adults. CD19-directed CAR-T products such as axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel have demonstrated high overall response rates and durable complete remissions in patients with relapsed or refractory disease who are unsuitable for, or have relapsed after, autologous stem cell transplantation. [6,18,19]

6.4 Mantle Cell Lymphoma (MCL)

Patients with relapsed or refractory mantle cell lymphoma have shown excellent responses to brexucabtagene autoleucel, leading to its regulatory approval. Clinical studies have demonstrated high complete response rates and prolonged progression-free survival in heavily pre-treated patients. [22,12]

6.5 Follicular Lymphoma (FL)

CAR-T therapy has become an effective treatment option for relapsed or refractory follicular lymphoma after multiple prior lines of systemic therapy. Clinical trials have reported durable responses and prolonged remission with both axicabtagene ciloleucel and tisagenlecleucel. [12,18,19]

6.6 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Although targeted therapies have improved the management of chronic lymphocytic leukemia and small lymphocytic lymphoma, some patients develop refractory disease. CD19-directed CAR-T therapy has demonstrated promising efficacy in selected patients, particularly when combined with Bruton tyrosine kinase (BTK) inhibitors. Ongoing clinical trials continue to refine its role in these diseases. [12,14,28]

6.7 Multiple Myeloma

The introduction of BCMA-targeted CAR-T therapies has significantly improved outcomes in relapsed or refractory multiple myeloma. Products such as idecabtagene vicleucel and ciltacabtagene autoleucel have produced deep and durable responses in patients who have received multiple previous lines of therapy. These therapies represent a major advance in the management of advanced multiple myeloma. [11,12]

6.8 Other Hematological Malignancies

Beyond currently approved indications, CAR-T therapy is being investigated for additional hematological malignancies, including acute myeloid leukemia (AML), Hodgkin lymphoma, T-cell malignancies, and other non-Hodgkin lymphomas. Although early clinical studies have shown encouraging results, these applications remain largely investigational because of challenges related to target antigen selection and treatment-associated toxicity. [25,26,28]

7 ADVERSE EFFECTS OF CAR-T CELL THERAPY

Although chimeric antigen receptor T-cell (CAR-T) therapy has demonstrated remarkable efficacy in the treatment of hematological malignancies, it is associated with unique and potentially life-threatening toxicities resulting from excessive immune activation and cytokine release. The most clinically significant adverse effects include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), B-cell aplasia, prolonged cytopenias, infections, and tumor lysis syndrome (TLS). Early recognition, prompt intervention, and multidisciplinary supportive care are essential to optimize patient outcomes. [5,9,21,28]

7.1 Cytokine Release Syndrome (CRS)

Cytokine release syndrome is the most common acute toxicity following CAR-T cell therapy. It results from rapid activation and proliferation of CAR-T cells after antigen recognition, leading to the release of large quantities of inflammatory cytokines, particularly interleukin-6 (IL-6), interferon-gamma (IFN-γ), interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF). [5,9]

Clinical manifestations range from mild fever, fatigue, myalgia, nausea, and anorexia to severe hypotension, hypoxia, capillary leak syndrome, coagulopathy, multiple organ dysfunction, and shock. Symptoms generally develop within the first few days after CAR-T cell infusion and vary according to tumor burden, CAR-T cell expansion, and the specific CAR construct used. [5,9,21]

Management is guided by toxicity grading and includes supportive care, intravenous fluids, antipyretics, supplemental oxygen, vasopressor support when indicated, and intensive care monitoring in severe cases. Tocilizumab, an interleukin-6 receptor antagonist, is the first-line treatment for moderate to severe CRS, while corticosteroids are reserved for patients with severe or refractory disease. [5,9,21]

7.2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is the second most common serious toxicity associated with CAR-T therapy. Although its exact pathophysiology remains incompletely understood, endothelial activation, disruption of the blood-brain barrier, and cytokine-mediated neuroinflammation are believed to play central roles. [9,21,28]

Clinical manifestations include headache, confusion, impaired attention, aphasia, tremor, dysgraphia, encephalopathy, seizures, reduced consciousness, and, rarely, cerebral oedema. ICANS frequently occurs after or concurrently with CRS but may also develop independently. Neurological assessment using validated scoring systems, such as the Immune Effector Cell-Associated Encephalopathy (ICE) score, is recommended for early detection. [9,21]

Management primarily consists of supportive neurological care, frequent neurological monitoring, seizure prophylaxis in selected patients, and corticosteroids for moderate to severe ICANS. Unlike CRS, tocilizumab has limited efficacy in isolated neurotoxicity because of its poor penetration across the blood-brain barrier. [9,21]

7.3 B-Cell Aplasia and Hypogammaglobulinemia

CD19-targeted CAR-T therapy eliminates both malignant and normal B lymphocytes, resulting in prolonged B-cell aplasia and hypogammaglobulinemia. Although B-cell aplasia serves as a marker of persistent CAR-T cell activity, it also increases susceptibility to recurrent bacterial and viral infections due to impaired humoral immunity. [7,9,28]

Management includes regular monitoring of serum immunoglobulin concentrations, administration of intravenous immunoglobulin (IVIG) replacement therapy in patients with symptomatic or severe hypogammaglobulinemia, appropriate vaccination strategies, and infection prophylaxis when indicated. [9,21]

7.4 Prolonged Cytopenias

Persistent neutropenia, anemia, and thrombocytopenia are commonly observed following CAR-T therapy. These cytopenias may result from lymphodepleting chemotherapy, bone marrow suppression, inflammatory cytokine release, previous intensive anticancer treatments, or underlying bone marrow dysfunction. [9,13]

Patients with prolonged cytopenias are at increased risk of infection and bleeding complications. Management includes regular complete blood count monitoring, blood product transfusion when required, administration of granulocyte colony-stimulating factor (G-CSF) in selected patients, and supportive care until hematological recovery occurs. [13,21]

7.5 Infections

Patients receiving CAR-T therapy are highly susceptible to bacterial, viral, and fungal infections because of prolonged neutropenia, B-cell aplasia, hypogammaglobulinemia, and previous exposure to immunosuppressive therapies. Opportunistic infections may occur during both the early and late post-treatment periods. [9,13,28]

Preventive measures include antimicrobial prophylaxis according to institutional protocols, vaccination after immune recovery, regular surveillance for infectious complications, patient education, and prompt initiation of appropriate antimicrobial therapy whenever infection is suspected. [9,21]

7.6 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome is a potentially life-threatening metabolic emergency that may develop following rapid destruction of malignant cells by CAR-T therapy, particularly in patients with a high tumor burden. Massive cellular breakdown leads to the release of intracellular contents into the circulation, resulting in hyperuricemia, hyperkaliemia, hyperphosphatasemia, hypocalcemia, metabolic disturbances, and acute kidney injury. [21,25]

Patients at high risk should receive aggressive intravenous hydration, close monitoring of electrolytes and renal function, and prophylactic urate-lowering therapy with allopurinol or Ras uricase when appropriate. Early identification and prompt management substantially reduce morbidity and mortality associated with tumor lysis syndrome. [21,25]

8 SUPPORTIVE CARE AND MONITORING OF PATIENTS RECEIVING CAR-T CELL THERAPY

The successful administration of chimeric antigen receptor T-cell (CAR-T) therapy requires comprehensive supportive care and close clinical monitoring before, during, and after treatment. Although CAR-T therapy has demonstrated remarkable efficacy in several hematological malignancies, its unique toxicity profile necessitates a multidisciplinary approach involving hematologists, oncologists, intensivists, neurologists, pharmacists, nurses, and other healthcare professionals. Early recognition and prompt management of treatment-related complications are essential for improving patient outcomes. [5,9,21,28]

8.1 Pre-treatment Assessment

Before initiating CAR-T therapy, patients undergo a comprehensive clinical evaluation to determine their suitability for treatment. This assessment includes disease staging, evaluation of tumor burden, performance status, organ function, baseline neurological examination, infection screening, and laboratory investigations such as complete blood count, liver and renal function tests, coagulation profile, inflammatory markers, and serum immunoglobulin levels. Appropriate patient selection helps minimize treatment-related complications and improves therapeutic outcomes. [9,28]

8.2 Monitoring During CAR-T Therapy

Following CAR-T cell infusion, patients require close monitoring, particularly during the first two weeks, when the risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) is highest. Vital signs, oxygen saturation, hemodynamic status, fluid balance, and neurological function should be assessed frequently. Laboratory monitoring should include complete blood count, serum electrolytes, renal and hepatic function tests, C-reactive protein (CRP), ferritin, coagulation parameters, and inflammatory biomarkers to facilitate early detection of treatment-related toxicities. [5,9,21]

8.3 Neurological Assessment

Regular neurological evaluation is essential for the early identification of ICANS. Patients should be monitored for alterations in mental status, speech disturbances, tremors, seizures, impaired attention, and changes in the level of consciousness. The Immune Effector Cell-Associated Encephalopathy (ICE) score is commonly used to assess neurological function and to grade the severity of neurotoxicity. Early recognition enables timely intervention and may prevent progression to severe neurological complications. [9,21,28]

8.4 Infection Prevention and Supportive Therapy

Patients receiving CAR-T therapy are at increased risk of bacterial, viral, and fungal infections because of prolonged neutropenia, lymphodepleting chemotherapy, B-cell aplasia, and hypogammaglobulinemia. Preventive measures include appropriate antimicrobial prophylaxis, regular infection surveillance, vaccination after immune recovery according to current guidelines, and intravenous immunoglobulin (IVIG) replacement therapy in selected patients with persistent hypogammaglobulinemia. Patients should also receive education regarding infection prevention and the importance of seeking immediate medical attention if fever or other symptoms of infection develop. [9,13,21]

8.5 Supportive Management of Toxicities

The management of CAR-T-related toxicities relies on early recognition and prompt intervention. Patients with mild CRS may require only supportive measures such as antipyretics, intravenous fluids, and oxygen supplementation. Moderate to severe CRS should be managed with tocilizumab and, when indicated, corticosteroids. Patients with severe ICANS require intensive neurological monitoring, corticosteroid therapy, seizure management when appropriate, and admission to an intensive care unit if neurological deterioration occurs. Early multidisciplinary management has significantly reduced treatment-related mortality associated with CAR-T therapy. [5,9,21]

8.6 Long-Term Follow-up

Long-term follow-up is necessary to monitor treatment response, persistence of CAR-T cells, disease relapse, late toxicities, prolonged cytopenias, secondary malignancies, and recovery of immune function. Regular clinical assessment, laboratory investigations, imaging studies when indicated, and disease-specific monitoring should be continued for months to years after treatment. Survivorship care should also include psychosocial support, rehabilitation services, and patient education to optimize quality of life following CAR-T therapy. [12,28]

9 LIMITATIONS AND CHALLENGES OF CAR-T CELL THERAPY

Despite the remarkable clinical success of chimeric antigen receptor T-cell (CAR-T) therapy, several limitations continue to restrict its broader clinical application. One of the major challenges is the complex and individualized manufacturing process. Most currently approved CAR-T products are autologous, requiring T lymphocytes to be collected from each patient through leukapheresis, followed by ex vivo genetic modification, expansion, quality testing, and transportation before reinfusion. This multistep process is technically demanding, resource-intensive, and usually takes two to four weeks to complete. During this manufacturing period, patients with aggressive or rapidly progressing malignancies may experience disease progression, which can delay or even prevent treatment. [4,26,28]

The high cost of CAR-T therapy represents another important barrier to its widespread use. In addition to the expense of manufacturing the cellular product, treatment costs include lymphodepleting chemotherapy, prolonged hospitalization, intensive monitoring, management of treatment-related toxicities, and specialized supportive care. Consequently, access to CAR-T therapy remains limited in many low- and middle-income countries where healthcare resources and specialized treatment centers are scarce. [13,25]

Treatment-related toxicities also remain a significant concern. Although advances in supportive care have improved patient safety, serious complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) continue to occur in a proportion of patients. Severe cases may require intensive care unit admission, hemodynamic support, mechanical ventilation, or prolonged hospitalization. In addition, persistent cytopenias, infections, and B-cell aplasia may contribute to long-term morbidity and require ongoing clinical monitoring and supportive management. [9,13,21]

Another important limitation is disease relapse after an initial therapeutic response. Relapse may result from inadequate persistence of infused CAR-T cells, progressive T-cell exhaustion, or tumor cells losing expression of the target antigen. This phenomenon, known as antigen escape, enables malignant cells to evade immune recognition and remains one of the leading causes of treatment failure. To address this challenge, researchers are developing dual-target and multi-target CAR-T cell strategies designed to recognize more than one tumor antigen simultaneously, thereby reducing the likelihood of immune escape. [13,25,27]

Although CAR-T therapy has achieved remarkable outcomes in hematological malignancies, its efficacy in solid tumors has been considerably more limited. Several biological factors contribute to this reduced effectiveness, including tumor antigen heterogeneity, poor trafficking and infiltration of CAR-T cells into tumor tissue, the presence of a highly immunosuppressive tumor microenvironment, and the lack of tumor-specific antigens that can be safely targeted. Overcoming these barriers remains one of the greatest challenges in the future development of cellular immunotherapy. [23,25,26]

Long-term clinical benefit also depends on the persistence and functional integrity of CAR-T cells after infusion. Continuous antigen stimulation may eventually lead to T-cell exhaustion, characterized by reduced proliferative capacity, impaired cytokine secretion, and diminished cytotoxic activity. Current research is focused on optimizing CAR design, modifying co-stimulatory domains, incorporating cytokine signaling pathways, and applying gene-editing technologies to enhance CAR-T cell persistence and maintain durable antitumor responses. [2,27,28]

In addition to biological challenges, the delivery of CAR-T therapy requires specialized infrastructure, highly trained multidisciplinary teams, advanced laboratory facilities, and strict manufacturing standards. These logistical

requirements limit the availability of CAR-T therapy to selected tertiary care centers. Ongoing efforts to develop automated manufacturing platforms and universal allogeneic "off-the-shelf" CAR-T products may reduce production time, lower treatment costs, and improve global accessibility in the future. [4,26,27]

Overall, although CAR-T therapy has transformed the treatment of several relapsed and refractory hematological malignancies, challenges related to manufacturing complexity, treatment cost, toxicity, disease relapse, antigen escape, limited efficacy in solid tumors, and healthcare accessibility continue to hinder its widespread implementation. Continued advances in genetic engineering, manufacturing technologies, and supportive care are expected to address many of these limitations, thereby expanding the therapeutic potential of CAR-T therapy in the years ahead. [13,25,27,28]

10 FUTURE DIRECTIONS OF CAR-T CELL THERAPY

Chimeric antigen receptor T-cell (CAR-T) therapy continues to evolve rapidly, with ongoing research focused on improving its efficacy, safety, accessibility, and applicability to a broader range of diseases. Although current CAR-T therapies have achieved remarkable success in relapsed or refractory hematological malignancies, several technological advances are expected to overcome existing limitations and further transform the field of cellular immunotherapy. [13,25,27,28]

10.1 Next-Generation CAR Designs

Advances in CAR engineering have led to the development of next-generation CAR constructs with enhanced antitumor activity and improved safety profiles. Fifth-generation CARs incorporate cytokine receptor signaling domains that promote more physiological T-cell activation and prolonged persistence. Other innovative approaches include dual-target and multi-target CARs, which simultaneously recognize two or more tumor-associated antigens to reduce antigen escape and improve treatment durability. [2,27,28]

10.2 Armoured CAR-T Cells

Armoured CAR-T cells, also known as fourth-generation CAR-T cells or TRUCKs (T cells Redirected for Universal Cytokine-mediated Killing), are genetically engineered to secrete immunostimulatory cytokines such as interleukin-12 (IL-12) after antigen recognition. These cytokines enhance the activity of surrounding immune cells and help overcome the immunosuppressive tumor microenvironment, particularly in solid tumors. [25,26]

10.3 Allogeneic "Off-the-Shelf" CAR-T Therapy

Current CAR-T therapies are primarily autologous, requiring individualized manufacturing for each patient. The development of allogeneic CAR-T cells derived from healthy donors has the potential to reduce manufacturing time, lower treatment costs, and improve accessibility. Gene-editing technologies are being used to minimize the risk of graft-versus-host disease and immune rejection, making universal "off-the-shelf" CAR-T products an important area of ongoing research. [26,27,28]

10.4 Gene-Editing Technologies

Modern gene-editing tools, particularly CRISPR-Cas9, are being explored to improve CAR-T cell function by enhancing persistence, reducing T-cell exhaustion, and eliminating inhibitory immune checkpoint molecules. These technologies also facilitate the production of universal CAR-T cells and may improve manufacturing efficiency and product consistency. [27,28]

10.5 Combination Therapy

Combining CAR-T therapy with other anticancer treatments may further enhance clinical outcomes. Current studies are evaluating combinations with immune checkpoint inhibitors, monoclonal antibodies, targeted therapies, oncolytic viruses, radiotherapy, and conventional chemotherapy. Such strategies aim to improve CAR-T cell expansion, overcome tumor immune evasion, and enhance antitumor responses, particularly in patients with resistant disease or solid tumors. [7,25,28]

10.6 Expanding Applications Beyond Cancer

Although CAR-T therapy has primarily been developed for cancer treatment, its potential applications are expanding into other medical fields. CAR-based cellular therapies are currently being investigated for autoimmune diseases such as systemic lupus erythematosus and myasthenia gravis, chronic viral infections including HIV, and selected fibrotic disorders. Early clinical studies suggest that engineered immune cells may provide durable disease control beyond oncology. [27,28]

11 CONCLUSION

Chimeric antigen receptor T-cell (CAR-T) therapy has emerged as one of the most significant advances in modern cancer immunotherapy, fundamentally changing the treatment landscape for several relapsed and refractory hematological malignancies. By genetically engineering T lymphocytes to recognize tumor-associated antigens independently of major histocompatibility complex (MHC) presentation, CAR-T therapy provides highly specific and potent antitumor activity, leading to durable clinical responses in patients with limited therapeutic options.

The successful clinical application of CAR-T therapy in B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, and multiple myeloma has established it as an important component of precision oncology. Continuous improvements in CAR design, manufacturing techniques, patient selection, and supportive care have further enhanced treatment efficacy and safety.

Despite these remarkable achievements, several challenges remain, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, prolonged cytopenias, infections, antigen escape, manufacturing complexity, high treatment costs, and limited efficacy in solid tumors. Addressing these limitations is essential to maximize the therapeutic potential of CAR-T therapy and to improve patient access worldwide.

Ongoing advances in next-generation CAR constructs, dual-target and Armoured CAR-T cells, gene-editing technologies, allogeneic "off-the-shelf" products, and combination immunotherapeutic strategies are expected to overcome many of these challenges. In addition, expanding research into autoimmune diseases, infectious diseases, and other immune-mediated disorders suggests that the applications of CAR-based cellular therapies may extend well beyond oncology.

In conclusion, CAR-T cell therapy represents a transformative milestone in cellular immunotherapy and precision medicine. Continued research, technological innovation, and collaborative clinical efforts are expected to improve its safety, accessibility, and long-term effectiveness, enabling CAR-T therapy to benefit a wider range of patients and play an increasingly important role in the future of personalized healthcare.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Author contribution

Kesiya V Chacko was responsible for the original draft preparation of the manuscript. Kesiya V Chacko and Anu Anna Babu contributed to the study's conceptualization and design. Anu Anna Babu, Kesiya V Chacko and Jayakumar K S were involved in reviewing and editing the manuscript for important intellectual content.

Disclosure of conflict of interest

The authors declare no conflict of interest

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