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Research Article

Chimeric Antigen Receptor (CAR)-T cell Therapy in Hematological Malignancies: Current Advances, Challenges, And Future Perspectives

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Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy represents a groundbreaking advancement in cancer immunotherapy and has significantly transformed the treatment landscape for hematological malignancies. This innovative adoptive cellular therapy involves the genetic engineering of a patient's T lymphocytes to express synthetic receptors capable of recognizing specific tumor-associated antigens on malignant cells. By enabling T cells to directly identify and eliminate cancer cells in a major histocompatibility complex-independent manner, CAR-T therapy has emerged as a highly effective therapeutic strategy for patients with relapsed or refractory hematologic cancers. In recent years, CAR-T therapies targeting antigens such as CD19 and B-cell maturation antigen (BCMA) have demonstrated remarkable clinical efficacy in diseases including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma. Several CAR-T cell products have received regulatory approval and have shown high overall response rates and durable remissions in heavily pretreated patients who previously had limited treatment options.

Despite these encouraging outcomes, CAR-T therapy is associated with several limitations and safety concerns, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, antigen escape, complex manufacturing procedures, and high treatment costs. Ongoing research efforts are focused on improving CAR design, enhancing T-cell persistence, identifying novel tumor targets, and developing universal or allogeneic CAR-T cell platforms. Additionally, emerging strategies such as dual-target CAR-T cells, gene-editing technologies, and combination therapies with immune checkpoint inhibitors are being investigated to further improve therapeutic efficacy and reduce adverse effects. This review provides a comprehensive overview of CAR-T cell therapy, including its mechanism of action, structural design, clinical applications in hematological malignancies, approved CAR-T therapies, treatment-related toxicities, current challenges, and future perspectives in the evolving field of cancer immunotherapy.

Keywords: CAR-T cell therapy; Chimeric antigen receptor; Hematological malignancies; Immunotherapy; CD19; B-cell maturation antigen (BCMA); Cytokine release syndrome; Cancer immunotherapy; Adoptive cell therapy; Gene engineering

1. INTRODUCTION

Hematological malignancies comprise a heterogeneous group of cancers that originate from cells of the hematopoietic and lymphatic systems, including leukemia, lymphoma, and multiple myeloma. These malignancies arise from abnormal proliferation and differentiation of blood-forming cells within the bone marrow or lymphatic tissues. According to global cancer statistics, hematologic cancers contribute significantly to cancer-related morbidity and mortality worldwide, accounting for a substantial proportion of newly diagnosed cancer cases each year. Leukemia and lymphoma collectively represent a major burden in both developed and developing countries, affecting individuals across all age groups (1). Despite considerable advancements in diagnostic techniques and therapeutic strategies, hematological malignancies continue to pose significant clinical challenges due to disease heterogeneity, treatment resistance, and relapse.

Traditional treatment approaches for hematological malignancies include chemotherapy, radiotherapy, targeted therapy, immunotherapy, and hematopoietic stem cell transplantation (HSCT). Chemotherapeutic agents such as alkylating agents, antimetabolites, and anthracyclines have historically formed the backbone of treatment regimens for many hematologic cancers. More recently, targeted therapies such as tyrosine kinase inhibitors and monoclonal antibodies have significantly improved treatment outcomes for specific malignancies. Hematopoietic stem cell transplantation, particularly allogeneic transplantation, remains a potentially curative option for certain patients with high-risk or relapsed disease. However, these treatment modalities are often associated with significant toxicities, treatment-related complications, and variable long-term success rates (2). Furthermore, a substantial proportion of patients eventually experience relapse or develop refractory disease, highlighting the urgent need for innovative therapeutic approaches that can overcome treatment resistance and provide durable responses.

In recent years, immunotherapy has emerged as a transformative approach in cancer treatment. Unlike conventional therapies that directly target tumor cells, immunotherapy aims to stimulate or enhance the body's immune system to recognize and destroy malignant cells. Various immunotherapeutic strategies have been developed, including immune checkpoint inhibitors, monoclonal antibodies, cancer vaccines, and adoptive cell therapies. Among these approaches, adoptive T-cell therapy has gained considerable attention due to its potential to generate potent and highly specific antitumor immune responses (3).

Chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most promising advancements in adoptive cellular immunotherapy. CAR-T therapy involves the genetic modification of a patient’s own T lymphocytes to express synthetic receptors known as chimeric antigen receptors (CARs). These engineered receptors enable T cells to recognize specific tumor-associated antigens on the surface of cancer cells and initiate targeted immune responses that result in tumor cell destruction (4). A key advantage of CAR-T therapy is that CAR molecules recognize tumor antigens independently of the major histocompatibility complex (MHC), which allows them to bypass common tumor immune evasion mechanisms that impair conventional T-cell recognition. This MHC-independent antigen recognition significantly enhances the ability of engineered T cells to identify and eliminate malignant cells.

The development of CAR-T cell therapy has rapidly progressed over the past two decades, culminating in the first regulatory approval in 2017 for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia. This milestone marked a significant breakthrough in cancer immunotherapy and paved the way for further clinical development of CAR-T therapies targeting various hematologic malignancies. Since then, several CAR-T products targeting CD19 and B-cell maturation antigen (BCMA) have been approved for clinical use in conditions such as diffuse large B-cell lymphoma, mantle cell lymphoma, and multiple myeloma (5). Clinical trials evaluating these therapies have reported impressive response rates, including complete remission in a substantial proportion of patients who previously had limited treatment options.

Despite the remarkable clinical success of CAR-T therapy, several challenges remain that limit its widespread application. Treatment-related toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) represent significant complications

that require careful clinical management. In addition, issues related to antigen escape, manufacturing complexity, limited accessibility, and high treatment costs pose substantial barriers to broader implementation of CAR-T therapy in clinical practice. Ongoing research efforts are focused on improving CAR design, identifying novel tumor targets, enhancing the persistence and efficacy of CAR-T cells, and developing universal or "off-the-shelf" CAR-T cell products.

Given the rapid expansion of CAR-T cell therapy and its transformative potential in oncology, a comprehensive understanding of its mechanisms, clinical applications, and challenges is essential for clinicians and researchers. Therefore, this review aims to provide an in-depth overview of CAR-T cell therapy in hematological malignancies, including its mechanism of action, structural components and generations of CAR constructs, currently approved CAR-T therapies, clinical applications in various hematologic cancers, associated toxicities, and emerging strategies that may shape the future of this innovative treatment modality.

2. MECHANISM OF CAR-T CELL THERAPY

CAR-T cell therapy is a highly specialized form of adoptive cellular immunotherapy that involves the genetic modification of a patient's own T lymphocytes to recognize and eliminate cancer cells. This therapeutic strategy harnesses the cytotoxic potential of the immune system by redirecting T cells to target specific tumor-associated antigens. Unlike conventional immunotherapies, CAR-T cells are engineered to recognize cancer cells independently of major histocompatibility complex (MHC) molecules, allowing them to overcome several mechanisms of tumor immune evasion. The therapeutic process involves a multistep procedure that includes immune cell collection, genetic modification, ex vivo expansion, conditioning chemotherapy, reinfusion of engineered cells, and tumor cell eradication (6).

The overall success of CAR-T therapy depends on efficient T-cell engineering, robust expansion, and sustained persistence of CAR-T cells in the patient's body. These processes collectively enable the immune system to recognize and destroy malignant cells with high specificity.

2.1. Leukapheresis

The first step in CAR-T cell therapy is the collection of immune cells from the patient through a procedure called leukapheresis. Leukapheresis is a specialized blood-separation technique used to isolate peripheral blood mononuclear cells (PBMCs), which include T lymphocytes, B lymphocytes, natural killer cells, and monocytes. During this procedure, blood is withdrawn from the patient and passed through an apheresis machine that separates white blood cells from other blood components. The remaining components such as red blood cells and plasma are returned to the patient through intravenous access (7).

The collected PBMCs serve as the starting material for CAR-T cell manufacturing. Among these cells, T lymphocytes are particularly important because of their ability to recognize and destroy infected or malignant cells. These T cells are isolated and prepared for genetic modification in specialized manufacturing facilities that follow strict quality control and sterility standards. The leukapheresis procedure is generally well tolerated by patients and usually takes several hours to complete.

2.2. Genetic Engineering of T Cells

After collection, the isolated T cells are genetically engineered to express chimeric antigen receptors on their surface. This genetic modification is typically achieved using viral vectors such as lentiviruses or retroviruses, which are capable of delivering the CAR gene into the T-cell genome. Once the gene is integrated, the T cells begin producing CAR molecules that enable them to recognize specific tumor antigens (8).

A chimeric antigen receptor is an artificial receptor composed of multiple functional domains, including an extracellular antigen-binding domain, a hinge region, a transmembrane domain, and intracellular signaling domains. The antigen-binding region is usually derived from a monoclonal antibody fragment known as a single-chain variable fragment (scFv). This component enables the engineered T cells to recognize tumor-associated antigens expressed on the surface of malignant cells.

Following gene transfer, the engineered T cells undergo activation and proliferation in controlled laboratory conditions. During this phase, the cells are stimulated using antibodies or other agents that mimic immune activation signals. This process ensures that the modified T cells acquire strong cytotoxic capabilities before being infused back into the patient. Recent advancements in gene-editing technologies such as CRISPR-Cas9 have further improved the efficiency and precision of CAR-T cell engineering. These technologies allow scientists to modify specific genes within T cells, thereby enhancing their persistence, reducing exhaustion, and improving antitumor activity.

2.3. Ex Vivo Expansion

After successful genetic modification, the CAR-T cells are cultured and expanded ex vivo to generate sufficient numbers of cells required for therapeutic infusion. During this stage, the engineered cells are placed in specialized culture systems that provide optimal conditions for growth and proliferation. Cytokines such as interleukin-2 (IL-2), interleukin-7 (IL-7), and interleukin-15 (IL-15) are commonly used to stimulate T-cell expansion and survival (9).

The expansion process typically lasts for several days to weeks, depending on the manufacturing protocol and the type of CAR-T product being developed. During this period, the number of CAR-T cells increases dramatically, often reaching hundreds of millions of cells. These cells undergo extensive quality control testing to ensure safety, sterility, and functionality before they are approved for patient infusion.

Quality control testing includes assessment of CAR expression levels, cell viability, absence of microbial contamination, and verification of genetic stability. Only after passing these rigorous tests are the CAR-T cells prepared for clinical administration.

2.4. Lymphodepleting Chemotherapy

Before CAR-T cell infusion, patients usually receive lymphodepleting chemotherapy as a preparatory step. This conditioning regimen typically consists of chemotherapeutic agents such as fludarabine and cyclophosphamide. The primary purpose of lymphodepleting chemotherapy is to reduce the number of existing immune cells within the patient's body, thereby creating a favorable environment for CAR-T cell expansion and persistence (10).

Lymphodepletion also helps eliminate regulatory T cells and other immunosuppressive components that could inhibit CAR-T cell activity. Additionally, this step increases the availability of homeostatic cytokines such as IL-7 and IL-15, which promote the survival and proliferation of infused CAR-T cells. As a result, lymphodepleting chemotherapy significantly enhances the therapeutic effectiveness of CAR-T therapy.

2.5. CAR-T Cell Infusion

Following the completion of lymphodepleting chemotherapy, the engineered CAR-T cells are infused into the patient through intravenous administration. The infusion process is generally similar to a blood transfusion and typically takes place in specialized clinical settings where patients can be closely monitored for potential adverse reactions (11).

After infusion, CAR-T cells begin to proliferate rapidly within the patient's body. These cells circulate through the bloodstream and migrate to tumor sites where cancer cells expressing the target antigen are present. Once they encounter these malignant cells, CAR-T cells bind to the tumor antigen and initiate immune activation.

The expansion and persistence of CAR-T cells in vivo are critical factors that influence therapeutic success. In some cases, CAR-T cells can persist in the patient's body for months or even years, providing long-term immune surveillance against cancer recurrence.

2.6. Tumor Cell Killing

CAR-T cells eliminate cancer cells through several cytotoxic mechanisms that collectively result in tumor destruction. When CAR-T cells recognize tumor-associated antigens on cancer cells, they

become activated and release cytotoxic molecules such as perforin and granzymes. Perforin forms pores in the target cell membrane, allowing granzymes to enter and trigger apoptosis in the cancer cell (12).

In addition to direct cytotoxicity, CAR-T cells also produce inflammatory cytokines such as interferon-gamma, tumor necrosis factor-alpha, and interleukin-6. These cytokines recruit additional immune cells to the tumor microenvironment and amplify the antitumor immune response. CAR-T cells can also stimulate other components of the immune system, including macrophages and natural killer cells, further enhancing tumor cell elimination.

Another important feature of CAR-T therapy is the ability of engineered T cells to proliferate after recognizing tumor antigens. This expansion allows a relatively small number of infused CAR-T cells to generate a large population of active immune cells capable of sustained tumor surveillance.Collectively, these mechanisms enable CAR-T cells to produce potent and durable antitumor responses in patients with hematological malignancies. However, the same immune activation that contributes to tumor eradication can also lead to adverse effects such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which require careful clinical management.

3. Structure And Generations Of CAR-T Cells

Chimeric antigen receptors (CARs) are synthetic receptors that are genetically engineered into T lymphocytes to enable them to recognize and eliminate tumor cells. These receptors are designed to combine the antigen-binding specificity of antibodies with the cytotoxic and proliferative capabilities of T cells. CAR molecules consist of multiple functional domains that work together to facilitate antigen recognition, T-cell activation, signal transduction, and tumor cell killing. The modular structure of CARs allows scientists to modify individual components to enhance therapeutic efficacy, improve persistence, and reduce treatment-related toxicities (13).

A typical CAR structure consists of four major domains: the antigen recognition domain, hinge region, transmembrane domain, and intracellular signaling domain. Each of these domains plays a critical role in determining the overall functionality and therapeutic performance of CAR-T cells.

3.1. Antigen Recognition Domain

The antigen recognition domain is the extracellular component of the CAR molecule responsible for binding to tumor-associated antigens expressed on the surface of cancer cells. This domain is usually composed of a single-chain variable fragment (scFv) derived from monoclonal antibodies. The scFv contains variable regions from both the heavy and light chains of an antibody, which are linked together by a flexible peptide linker. This design allows the CAR to specifically recognize and bind to target antigens with high affinity and specificity (13).

One of the major advantages of the antigen recognition domain is that it enables CAR-T cells to recognize tumor antigens independently of major histocompatibility complex (MHC) molecules. Conventional T-cell receptors require antigen presentation through MHC molecules to recognize cancer cells. However, many tumors evade immune detection by downregulating MHC expression. CAR-T cells overcome this limitation because the scFv domain directly binds to antigens present on the tumor cell surface, thereby bypassing MHC-dependent antigen presentation.

Several tumor-associated antigens have been identified as potential targets for CAR-T therapy. Among these, CD19 is the most widely studied and clinically successful target for B-cell malignancies such as acute lymphoblastic leukemia and non-Hodgkin lymphoma. Other targets under investigation include CD20, CD22, CD30, CD33, and B-cell maturation antigen (BCMA), particularly in the treatment of multiple myeloma.

3.2. Hinge Region

The hinge region, also known as the spacer domain, connects the antigen recognition domain to the transmembrane domain. This region provides structural flexibility and spatial orientation that allows the CAR molecule to effectively interact with target antigens on tumor cells. The hinge region plays

an important role in determining the distance between the T-cell membrane and the tumor cell surface, which can significantly influence antigen binding and T-cell activation.

Different hinge regions have been used in CAR design, including those derived from immunoglobulin G (IgG), CD8α, or CD28 molecules. The length and composition of the hinge region can affect CAR stability, receptor signaling, and antigen accessibility. For example, longer hinge regions may improve antigen binding in cases where the target antigen is located closer to the tumor cell membrane. Conversely, shorter hinge regions may reduce nonspecific interactions and improve receptor stability.

The choice of hinge region is therefore an important factor in optimizing CAR-T cell functionality and minimizing potential off-target effects.

3.3. Transmembrane Domain

The transmembrane domain is responsible for anchoring the CAR molecule within the T-cell membrane and connecting the extracellular components of the receptor with the intracellular signaling domains. This domain is typically derived from proteins such as CD3ζ, CD28, or CD8α.

The transmembrane domain plays a crucial role in maintaining receptor stability and facilitating signal transmission from the extracellular antigen recognition domain to the intracellular signaling pathways. It also contributes to the proper assembly and expression of the CAR molecule on the surface of engineered T cells.

Different transmembrane domains may influence the strength and duration of CAR signaling. For example, CD28-derived transmembrane domains have been associated with enhanced receptor stability and stronger activation signals, while CD8α-derived domains may contribute to improved CAR expression and reduced tonic signaling.

3.4. Intracellular Signaling Domain

The intracellular signaling domain is the most critical component of the CAR structure because it is responsible for initiating T-cell activation following antigen recognition. This domain typically contains the CD3ζ signaling motif, which is derived from the T-cell receptor complex and plays a key role in transmitting activation signals within the T cell.

When the CAR binds to its target antigen, the CD3ζ domain becomes phosphorylated, triggering intracellular signaling pathways that lead to T-cell activation, proliferation, cytokine production, and cytotoxic activity against tumor cells (14).

In addition to CD3ζ, modern CAR constructs often include one or more costimulatory signaling domains such as CD28 or 4-1BB (CD137). These costimulatory domains enhance T-cell activation, improve cell survival, and increase the persistence of CAR-T cells in vivo. The inclusion of costimulatory domains has been a major advancement in CAR-T technology, significantly improving the clinical efficacy of these therapies.

3.5. Generations of CAR-T Cells

Since the development of the first CAR constructs in the late 1980s, CAR-T technology has undergone significant evolution. Several generations of CAR-T cells have been developed to enhance therapeutic effectiveness and overcome limitations associated with earlier designs.

Generation	Characteristics
First	CD3ζ signaling domain only
Second	CD3ζ plus one costimulatory domain (CD28 or 4-1BB)
Third	Multiple costimulatory domains
Fourth	Cytokine-secreting CAR-T cells (TRUCKs)

3.6. First-Generation CAR-T Cells

First-generation CAR-T cells contained only the CD3ζ intracellular signaling domain without additional costimulatory molecules. Although these CAR-T cells were capable of recognizing tumor antigens, their clinical efficacy was limited due to poor persistence, insufficient activation, and limited

proliferation. As a result, first-generation CAR-T therapies produced weak and short-lived antitumor responses.

3.7. Second-Generation CAR-T Cells

Second-generation CAR-T cells were developed to overcome the limitations of first-generation constructs. These CARs incorporate an additional costimulatory signaling domain, most commonly CD28 or 4-1BB, along with the CD3ζ activation domain. The addition of these costimulatory signals significantly enhances T-cell activation, proliferation, cytokine production, and persistence in vivo.

Most currently approved CAR-T therapies use second-generation CAR constructs. For example, therapies targeting CD19 for B-cell malignancies commonly utilize either CD28 or 4-1BB costimulatory domains. These CAR-T cells have demonstrated remarkable clinical efficacy and durable responses in patients with relapsed or refractory hematological cancers (15).

3.8. Third-Generation CAR-T Cells

Third-generation CAR-T cells incorporate two costimulatory signaling domains, such as CD28 combined with 4-1BB or OX40. The aim of this design is to further enhance T-cell activation, survival, and antitumor activity. Preclinical studies have shown improved cytokine production and enhanced cytotoxic effects with third-generation CAR constructs. However, clinical studies have produced mixed results, and these constructs are still under investigation.

3.9. Fourth-Generation CAR-T Cells (TRUCKs)

Fourth-generation CAR-T cells, also known as **TRUCKs (T cells Redirected for Universal Cytokine Killing)**, represent an advanced modification of second-generation CAR-T cells. These cells are engineered to release pro-inflammatory cytokines such as interleukin-12 upon activation. The released cytokines help recruit additional immune cells to the tumor microenvironment and enhance antitumor immune responses.

Fourth-generation CAR-T cells are designed to overcome immunosuppressive tumor microenvironments and improve therapeutic outcomes, particularly in solid tumors.Second-generation CAR-T cells remain the most widely used constructs in clinical practice due to their optimal balance of efficacy, safety, and persistence. However, ongoing research continues to explore newer CAR designs that may further improve therapeutic outcomes and expand the applications of CAR-T therapy in oncology.

4. TARGET ANTIGENS IN CAR-T THERAPY

The effectiveness of CAR-T cell therapy largely depends on the identification and selection of appropriate tumor-associated antigens. Ideal target antigens should be highly expressed on malignant cells while having minimal or no expression on normal tissues to reduce the risk of off-target toxicity. Additionally, these antigens should be consistently expressed on cancer cells and play an essential role in tumor survival or proliferation, thereby minimizing the likelihood of antigen loss and disease relapse. The discovery and validation of suitable target antigens have been critical to the success of CAR-T therapy in hematological malignancies.

In hematologic cancers, several cell surface antigens have been identified as potential targets for CAR-T therapy. Among these, CD19 and B-cell maturation antigen (BCMA) have demonstrated the most significant clinical success and are currently used in several approved CAR-T therapies. In addition to these well-established targets, other antigens such as CD20, CD22, CD30, and CD33 are being actively investigated to broaden the therapeutic applications of CAR-T therapy.

4.1. CD19

CD19 is one of the most extensively studied and clinically validated targets for CAR-T cell therapy. It is a transmembrane glycoprotein that is expressed throughout most stages of B-cell development, beginning from early B-cell precursors and continuing through mature B cells. Importantly, CD19 is highly expressed in many B-cell malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and various types of non-Hodgkin lymphoma (16).

The consistent expression of CD19 on malignant B cells makes it an ideal target for CAR-T therapy. When CAR-T cells engineered to recognize CD19 encounter cancer cells expressing this antigen, they bind to the tumor cells and initiate cytotoxic immune responses that lead to tumor destruction. CD19-targeted CAR-T therapy has demonstrated remarkable clinical outcomes, particularly in patients with relapsed or refractory B-cell acute lymphoblastic leukemia.

Several CAR-T products targeting CD19 have been approved for clinical use, including tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel. Clinical trials evaluating these therapies have reported high overall response rates and durable remission in patients who previously failed multiple lines of treatment. In many cases, patients with advanced disease have achieved complete remission following CAR-T therapy.

However, CD19-targeted therapy is also associated with certain limitations. Because CD19 is expressed on both malignant and normal B cells, CAR-T therapy often results in B-cell aplasia, which can lead to hypogammaglobulinemia and increased susceptibility to infections. Despite this complication, B-cell aplasia is considered a manageable side effect that can be treated with immunoglobulin replacement therapy.

Another challenge associated with CD19-targeted therapy is antigen escape, where cancer cells lose or downregulate CD19 expression, resulting in disease relapse. This phenomenon has prompted researchers to investigate alternative targets and dual-target CAR-T strategies to overcome resistance.

4.2. BCMA

B-cell maturation antigen (BCMA), also known as TNFRSF17, is another important target antigen in CAR-T therapy, particularly in the treatment of multiple myeloma. BCMA is a member of the tumor necrosis factor receptor superfamily and is predominantly expressed on plasma cells and late-stage B cells. Importantly, BCMA is highly expressed on malignant plasma cells in multiple myeloma, making it an attractive therapeutic target (17).

BCMA plays an important role in the survival and proliferation of plasma cells by interacting with ligands such as APRIL and BAFF. These interactions promote cell growth and inhibit apoptosis, thereby contributing to the progression of multiple myeloma. Targeting BCMA with CAR-T cells allows selective elimination of malignant plasma cells while sparing most other immune cells.

Several BCMA-targeted CAR-T therapies have demonstrated promising clinical results in patients with relapsed or refractory multiple myeloma. Approved therapies such as idecabtagene vicleucel and ciltacabtagene autoleucel have shown high response rates in clinical trials, including significant rates of complete remission. These therapies have provided new treatment options for patients with advanced multiple myeloma who have limited therapeutic alternatives.

Despite their effectiveness, BCMA-targeted therapies also face certain challenges. One of the major limitations is antigen downregulation or loss, which can lead to disease relapse after treatment. Additionally, soluble BCMA present in the bloodstream may interfere with CAR-T cell binding to tumor cells. Ongoing research aims to address these limitations through improved CAR design and combination therapies.

4.3. Emerging Targets

Although CD19 and BCMA have been the most successful CAR-T targets to date, researchers are actively investigating additional tumor antigens that may expand the applicability of CAR-T therapy in hematologic malignancies. Emerging targets such as CD20, CD22, CD30, and CD33 are currently being explored in preclinical studies and clinical trials (18).

CD20 is another B-cell surface antigen commonly expressed in B-cell lymphomas. It is already widely targeted by monoclonal antibody therapies such as rituximab. CAR-T cells targeting CD20 are currently under investigation as potential treatments for patients with B-cell malignancies who relapse after CD19-directed therapies.

CD22 is another B-cell antigen that is often expressed in patients with acute lymphoblastic leukemia. CAR-T therapies targeting CD22 have been developed as an alternative treatment for patients who experience relapse due to CD19 antigen loss.

CD30 is primarily expressed in certain lymphomas, including Hodgkin lymphoma and anaplastic large cell lymphoma. CAR-T cells targeting CD30 are being investigated in clinical trials and have shown promising results in early studies.

CD33 is a myeloid differentiation antigen expressed in acute myeloid leukemia (AML). CAR-T therapies targeting CD33 are currently being studied as potential treatments for AML, although challenges related to toxicity and off-target effects remain significant concerns.

In addition to these targets, several novel antigens such as CD123, FLT3, and SLAMF7 are also being explored as potential CAR-T targets in hematologic cancers. The identification of new tumor antigens and the development of multi-target CAR-T therapies may help overcome antigen escape and improve treatment outcomes.

5. FDA-APPROVED CAR-T THERAPIES

Several CAR-T therapies have been approved for clinical use in hematological malignancies.

Therapy	Target	Indication
Tisagenlecleucel	CD19	B-cell acute lymphoblastic leukemia
Axicabtagene ciloleucel	CD19	Diffuse large B-cell lymphoma
Brexucabtagene autoleucel	CD19	Mantle cell lymphoma
Lisocabtagene maraleucel	CD19	Large B-cell lymphoma
Idecabtagene vicleucel	BCMA	Multiple myeloma
Ciltacabtagene autoleucel	BCMA	Multiple myeloma

These therapies have significantly improved treatment outcomes for patients with relapsed or refractory hematologic cancers (19, 20).

6. CLINICAL APPLICATIONS IN HEMATOLOGICAL MALIGNANCIES

CAR-T cell therapy has demonstrated significant therapeutic potential in the treatment of several hematological malignancies, particularly in patients with relapsed or refractory disease who have limited treatment options. The success of CAR-T therapy in hematologic cancers is largely attributed to the accessibility of tumor cells in the bloodstream and lymphatic system, as well as the presence of well-defined surface antigens that can be targeted by engineered T cells. Over the past decade, CAR-T therapies targeting antigens such as CD19 and B-cell maturation antigen (BCMA) have produced remarkable clinical responses in diseases including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma. Numerous clinical trials have reported high response rates and durable remissions in patients who previously failed conventional therapies.

6.1. Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia is an aggressive hematological malignancy characterized by the uncontrolled proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Despite advancements in chemotherapy and hematopoietic stem cell transplantation, patients with relapsed or refractory ALL often have poor prognoses and limited therapeutic options.

CAR-T cell therapy targeting the CD19 antigen has revolutionized the treatment landscape for B-cell acute lymphoblastic leukemia. CD19 is widely expressed on B-cell lineage cells, making it an ideal target for immunotherapy. Clinical trials evaluating CD19-directed CAR-T therapies have demonstrated remarkable efficacy in patients with relapsed or refractory disease.

One of the most significant studies evaluating CAR-T therapy in ALL is the **ELIANA trial**, which investigated the efficacy of tisagenlecleucel in pediatric and young adult patients with relapsed or refractory B-cell ALL. The trial reported complete remission rates exceeding 80%, with many patients achieving durable responses after a single infusion of CAR-T cells (21). These results led to the approval of tisagenlecleucel as the first CAR-T therapy for the treatment of B-cell acute lymphoblastic leukemia.

CAR-T therapy has shown particular promise in patients who have relapsed after stem cell transplantation or who are resistant to conventional chemotherapy. In many cases, CAR-T therapy has enabled patients to achieve complete remission and proceed to potentially curative stem cell transplantation. However, relapse due to antigen loss or CD19 downregulation remains a challenge, prompting the development of CAR-T therapies targeting alternative antigens such as CD22.

6.2. Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma and is characterized by rapidly growing malignant B cells within lymph nodes or extranodal tissues. Standard treatment typically involves combination chemotherapy regimens such as R-CHOP, which includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. While many patients respond well to initial therapy, approximately 30–40% of patients experience relapse or develop refractory disease.

CAR-T cell therapy has emerged as an effective treatment option for patients with relapsed or refractory diffuse large B-cell lymphoma who have failed conventional therapies. Several CAR-T products targeting CD19 have been approved for this indication, including axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel.

Clinical trials such as the **ZUMA-1 trial** demonstrated the efficacy of axicabtagene ciloleucel in patients with refractory large B-cell lymphoma. The study reported high overall response rates and durable remissions, with a substantial proportion of patients achieving complete responses. These outcomes were significantly better than those observed with conventional salvage chemotherapy (22).

CAR-T therapy has therefore become a standard treatment option for patients with relapsed or refractory DLBCL who are not eligible for stem cell transplantation or who have failed previous treatments. Long-term follow-up studies have shown that some patients treated with CAR-T therapy remain disease-free for several years, suggesting the potential for long-lasting remission.

6.3. Multiple Myeloma

Multiple myeloma is a malignant plasma cell disorder characterized by the accumulation of abnormal plasma cells in the bone marrow and the production of monoclonal immunoglobulins. Although several novel therapies including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies have improved patient outcomes, multiple myeloma remains an incurable disease for many patients.

CAR-T cell therapy targeting B-cell maturation antigen (BCMA) has emerged as a promising treatment for patients with relapsed or refractory multiple myeloma. BCMA is a cell surface protein that is highly expressed on malignant plasma cells and plays an important role in plasma cell survival and proliferation.

Several BCMA-targeted CAR-T therapies have demonstrated remarkable clinical efficacy in patients with advanced multiple myeloma. Clinical trials evaluating therapies such as **idecabtagene vicleucel** and **ciltacabtagene autoleucel** have reported high overall response rates in patients who had previously received multiple lines of therapy. In some studies, response rates have exceeded 70–90%, with many patients achieving deep and durable responses (23).

For example, the **CARTITUDE-1 trial** evaluating ciltacabtagene autoleucel demonstrated impressive clinical outcomes in heavily pretreated patients with multiple myeloma. A large proportion of patients achieved complete or stringent complete responses, highlighting the transformative potential of CAR-T therapy in this disease.

Despite these promising results, challenges such as relapse due to antigen escape, limited persistence of CAR-T cells, and treatment-related toxicities remain important considerations. Ongoing research is focused on improving CAR design, developing dual-target CAR-T therapies, and combining CAR-T therapy with other immunotherapeutic approaches to enhance long-term outcomes in multiple myeloma.

7. ADVERSE EFFECTS OF CAR-T THERAPY

Although CAR-T cell therapy has demonstrated remarkable clinical efficacy in the treatment of hematological malignancies, it is also associated with unique and sometimes severe toxicities. These adverse effects are primarily related to the intense immune activation triggered by the infused CAR-T cells. Unlike conventional chemotherapy, CAR-T therapy produces immune-mediated toxicities that require specialized monitoring and management. The most commonly observed complications include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and B-cell aplasia. Early recognition and appropriate management of these adverse effects are essential to ensure patient safety and optimize treatment outcomes.

7.1. Cytokine Release Syndrome (CRS)

Cytokine release syndrome is the most common and clinically significant adverse effect associated with CAR-T therapy. CRS occurs as a result of rapid immune activation following the recognition of tumor cells by CAR-T cells. When CAR-T cells bind to their target antigen, they release large amounts of inflammatory cytokines such as interleukin-6 (IL-6), interferon-γ, tumor necrosis factor-α, and interleukin-2. These cytokines activate other immune cells including macrophages and endothelial cells, resulting in a systemic inflammatory response (24).

The onset of CRS typically occurs within a few days after CAR-T cell infusion, although the timing may vary depending on the specific CAR-T product and tumor burden. The severity of CRS ranges from mild flu-like symptoms to life-threatening systemic inflammation.

Common symptoms of cytokine release syndrome include:

- Fever
- Hypotension
- Hypoxia
- Tachycardia
- Fatigue
- Organ dysfunction

In severe cases, CRS may progress to multi-organ failure, requiring intensive medical care. To standardize the assessment of CRS severity, several grading systems have been developed, including the American Society for Transplantation and Cellular Therapy (ASTCT) grading system.

Management strategies for CRS depend on the severity of symptoms. Mild cases are usually treated with supportive care such as antipyretics, intravenous fluids, and oxygen therapy. Moderate to severe CRS often requires pharmacological intervention. The monoclonal antibody **tocilizumab**, an interleukin-6 receptor antagonist, is considered the first-line treatment for CRS. Tocilizumab works by blocking IL-6 signaling and reducing systemic inflammation. Corticosteroids may also be used in severe cases to suppress excessive immune activation (25).

7.2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is another important adverse effect associated with CAR-T therapy. ICANS refers to a spectrum of neurological complications that occur following CAR-T cell infusion and are believed to result from systemic inflammation and disruption of the blood-brain barrier. Elevated levels of inflammatory cytokines can lead to increased permeability of the blood-brain barrier, allowing immune cells and inflammatory mediators to enter the central nervous system (26).

The clinical manifestations of ICANS vary widely and may include mild neurological symptoms or severe life-threatening complications. Early symptoms often include headache, confusion, difficulty concentrating, and impaired speech. As the condition progresses, patients may develop seizures, delirium, motor weakness, or cerebral edema.

Neurological symptoms typically occur after or concurrently with cytokine release syndrome, although ICANS may also develop independently. To assess the severity of neurotoxicity, clinicians

commonly use the Immune Effector Cell-Associated Encephalopathy (ICE) score, which evaluates cognitive functions such as orientation, attention, and language ability.

Management of ICANS primarily involves supportive care and close neurological monitoring. Corticosteroids are often used as first-line treatment to reduce neuroinflammation. Unlike CRS, tocilizumab is generally less effective for treating ICANS because IL-6 receptor blockade does not adequately penetrate the central nervous system. In severe cases, intensive care management may be required to control seizures and prevent neurological deterioration.

7.3. B-Cell Aplasia

B-cell aplasia is another common adverse effect observed in patients receiving CAR-T therapies targeting CD19. Because CD19 is expressed on both malignant and normal B cells, CAR-T therapy eliminates not only cancerous B cells but also healthy B cells. This results in prolonged B-cell depletion and impaired humoral immunity (27).

As a consequence of B-cell aplasia, patients may develop **hypogammaglobulinemia**, which is characterized by reduced levels of immunoglobulins in the blood. This condition increases the risk of recurrent infections, particularly bacterial and viral infections.

Although B-cell aplasia represents an expected on-target effect of CD19-directed CAR-T therapy, it is generally considered manageable. Patients with persistent hypogammaglobulinemia are typically treated with **intravenous immunoglobulin (IVIG) replacement therapy** to restore immune function and prevent infections. In many cases, B-cell recovery occurs gradually over time as CAR-T cell activity declines.

8. CHALLENGES AND LIMITATIONS

Despite the remarkable clinical success of CAR-T cell therapy, several challenges and limitations continue to restrict its widespread application. These limitations involve economic, technical, biological, and clinical factors that must be addressed to improve the accessibility and effectiveness of CAR-T therapy.

One of the most significant barriers to CAR-T therapy is its **high treatment cost**. The manufacturing process involves complex genetic engineering, specialized laboratory facilities, and personalized cell production, which significantly increases the overall cost of therapy. In many cases, the cost of a single CAR-T treatment can exceed several hundred thousand dollars, making it inaccessible to many patients worldwide (28).

Another major challenge is the **complex manufacturing process**. CAR-T therapy requires individualized cell manufacturing for each patient, which involves multiple steps including leukapheresis, genetic modification, cell expansion, and quality testing. This process can take several weeks, during which patients with aggressive cancers may experience disease progression. Additionally, manufacturing failures or insufficient T-cell quality may prevent some patients from receiving the therapy.

Antigen escape and tumor relapse represent another important limitation of CAR-T therapy. In some patients, tumor cells may lose or downregulate the target antigen, such as CD19, allowing them to evade immune detection and leading to disease relapse. To address this challenge, researchers are developing dual-target CAR-T therapies that target multiple antigens simultaneously (29).

Another limitation is the **limited efficacy of CAR-T therapy in solid tumors**. Unlike hematological malignancies, solid tumors present additional barriers such as an immunosuppressive tumor microenvironment, physical barriers to T-cell infiltration, and heterogeneous antigen expression. These factors significantly reduce the effectiveness of CAR-T cells in solid cancers.

Finally, **treatment-related toxicities** remain an important concern. Although CRS and ICANS can often be managed with appropriate medical interventions, severe cases may lead to life-threatening complications. Continuous monitoring and improved toxicity management strategies are essential to ensure patient safety (30).

9. FUTURE PERSPECTIVES

CAR-T cell therapy has emerged as one of the most transformative breakthroughs in cancer immunotherapy. Despite the remarkable clinical success observed in hematological malignancies, several limitations such as treatment-related toxicities, antigen escape, manufacturing complexity, and limited accessibility continue to restrict its broader clinical application. Consequently, ongoing research efforts are focused on developing innovative strategies to improve therapeutic efficacy, enhance safety, and expand the applicability of CAR-T therapy to a wider range of malignancies. Advances in genetic engineering, cellular manufacturing, and immunotherapy combinations are expected to significantly shape the future of CAR-T therapy in oncology.

One of the most promising strategies currently under investigation is the development of **dual-target CAR-T therapies**. Traditional CAR-T cells are designed to recognize a single tumor antigen, such as CD19 or BCMA. However, tumor cells can evade immune detection by downregulating or losing the target antigen, leading to disease relapse. Dual-target CAR-T cells are engineered to recognize two different tumor antigens simultaneously. This approach reduces the likelihood of antigen escape and improves the durability of treatment responses. For example, dual-target CAR-T therapies targeting CD19 and CD22 are currently being evaluated for the treatment of B-cell malignancies. Similarly, dual-target strategies targeting BCMA and other plasma cell antigens are being explored in multiple myeloma (31).

Another important development in CAR-T therapy is the creation of **universal or allogeneic CAR-T cells**. Conventional CAR-T therapy uses autologous T cells collected from the patient, which requires individualized manufacturing for each treatment. This process is time-consuming, expensive, and may not be feasible for patients with rapidly progressing disease. Universal CAR-T cells are generated from healthy donor T cells and genetically modified to prevent immune rejection and graft-versus-host disease. These "off-the-shelf" CAR-T products could be manufactured in advance, stored, and administered to patients when needed. The development of allogeneic CAR-T therapy has the potential to significantly reduce manufacturing time, improve accessibility, and lower treatment costs.

Advancements in **gene-editing technologies**, particularly CRISPR-Cas9, have also opened new opportunities for improving CAR-T cell design and functionality. CRISPR-based gene editing allows precise modification of specific genes within T cells, enabling scientists to enhance CAR-T cell persistence, improve tumor targeting, and reduce treatment-related toxicities. For instance, gene editing can be used to remove inhibitory receptors that contribute to T-cell exhaustion or to eliminate endogenous T-cell receptors that could cause graft-versus-host disease in allogeneic CAR-T therapies. These technological advancements are expected to produce next-generation CAR-T cells with improved safety and therapeutic performance (32).

Another promising strategy involves **combination therapy with immune checkpoint inhibitors**. Tumor cells often create an immunosuppressive microenvironment that inhibits the activity of immune cells, including CAR-T cells. Immune checkpoint proteins such as PD-1 and CTLA-4 play a critical role in suppressing T-cell activation. Combining CAR-T therapy with immune checkpoint inhibitors may enhance the persistence and antitumor activity of engineered T cells by overcoming tumor-induced immune suppression. Several clinical trials are currently investigating the efficacy of combining CAR-T therapy with checkpoint blockade agents in patients with hematological malignancies (33).

In addition to these approaches, researchers are exploring **armored CAR-T cells**, which are engineered to secrete cytokines or other immune-modulating molecules that enhance antitumor responses. These modified CAR-T cells can improve immune cell recruitment and overcome immunosuppressive tumor environments. Other emerging strategies include **CAR-NK cell therapy**, which utilizes natural killer cells instead of T cells, and **next-generation CAR constructs** designed to improve specificity and reduce toxicity (34, 35).

Future research will also focus on expanding the use of CAR-T therapy beyond hematological malignancies to include solid tumors. However, solid tumors present unique challenges such as antigen heterogeneity, poor immune cell infiltration, and immunosuppressive tumor

microenvironments. Addressing these barriers will require innovative CAR designs, improved delivery strategies, and combination therapies.

10. CONCLUSION

Chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most significant breakthroughs in modern cancer immunotherapy, particularly in the treatment of hematological malignancies. By genetically engineering T lymphocytes to recognize specific tumor-associated antigens, CAR-T therapy enables the immune system to directly target and eliminate malignant cells with high specificity. Over the past decade, CAR-T therapy has demonstrated remarkable clinical success in several hematologic cancers, including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma. The approval of multiple CAR-T products targeting CD19 and B-cell maturation antigen has significantly improved treatment outcomes for patients with relapsed or refractory disease who previously had limited therapeutic options.

The development of CAR-T therapy has also highlighted the importance of precision medicine and personalized immunotherapy in oncology. The ability to engineer immune cells tailored to a patient's specific tumor characteristics represents a paradigm shift in cancer treatment. Clinical trials have consistently demonstrated high response rates and durable remissions in heavily pretreated patients, underscoring the transformative potential of CAR-T therapy in hematological malignancies.

Despite these promising outcomes, several challenges remain that limit the widespread implementation of CAR-T therapy. Treatment-related toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome require careful monitoring and specialized management. In addition, issues related to antigen escape, limited persistence of CAR-T cells, complex manufacturing processes, and high treatment costs present significant barriers to broader accessibility. Addressing these challenges will require continued advancements in CAR engineering, improved manufacturing technologies, and the development of safer therapeutic strategies.

Recent innovations such as dual-target CAR-T therapies, universal allogeneic CAR-T cells, and CRISPR-based gene editing technologies offer promising solutions to overcome current limitations. Furthermore, combination therapies involving immune checkpoint inhibitors and other immunomodulatory approaches may enhance the efficacy and durability of CAR-T responses. Advances in next-generation CAR designs, including armored CAR-T cells and multi-antigen targeting strategies, may further improve treatment outcomes and reduce the risk of relapse.

In addition to hematological malignancies, ongoing research is exploring the application of CAR-T therapy in solid tumors. Although several biological barriers currently limit the effectiveness of CAR-T therapy in solid cancers, emerging strategies aimed at improving tumor infiltration and overcoming the immunosuppressive tumor microenvironment may expand the therapeutic scope of CAR-T therapy in the future.

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