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CAR T Cell Therapy as Living Drugs in Cancer: A Comprehensive Pharmacological and Clinical Overview

Abstract

In the fight against cancer, cellular immunotherapy has emerged as a powerful tool in recent years. Chimeric antigen receptors (CARs), which are synthetic receptors comprising four components, have shown remarkable adaptability and efficacy in treating cancer. Specifically, CAR-T cell therapy involves modifying a patient's T cells to express synthetic receptors targeted towards tumor antigens. Unlike traditional drug-based cancer therapies which broadly target cancer cells, CAR-T cell therapy aims to selectively target tumors while avoiding healthy tissues. Current CAR-T cell therapies are targeted toward various antigens, with CD19 and BCMA being primarily used for hematological malignancies. Combining CAR-T cells with other drugs, such as antibodies or small molecules, has shown promising results in enhancing their efficacy.

Additionally, chemotherapy can augment CAR-T cell therapy by boosting the immune system while simultaneously reducing tumor load. The pharmacodynamics and pharmacokinetics of CAR-T cells, which function as "living drugs", are complex and require detailed consideration of the type and length of interactions between CAR-T cells and target cells. This article aims to explore the pharmacology of CAR-T cells and pinpoint significant knowledge gaps in this rapidly developing field.

Keywords: *CAR-T cell, living drugs, pharmacology, cancer*

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Introduction

In the fight against cancer, cellular immunotherapy has emerged as a potent and game-changing weapon, particularly in the form of T cells genetically modified to express chimeric antigen receptors (CAR) for patients with advanced hematological malignancies (1). The remarkable efficacy and durability of CAR-T cell therapy can be attributed to its unique mechanism of action, which operates independently of the MHC receptor, resulting in robust T cell activation and highly effective anti-tumor responses (2,3). As such, CAR-T cell therapy has revolutionized cancer treatment and is hailed as a major advancement in the pursuit of better clinical outcomes for cancer patients. CARs are complex synthetic receptors consisting of four key components, including an extracellular target antigen-binding domain, a hinge region, a transmembrane domain, and one or more intracellular signaling domains (4). Their main function is to redirect T cells to recognize and eliminate cells expressing a particular target antigen, making them an ideal tool for cancer immunotherapy (4). By genetically modifying patients' T cells to express CARs, CAR-T cell therapy harnesses the immune system to target and destroy tumor cells in a highly selective manner (5). The composition of CARs may vary between different CAR-T cell therapies but commonly include an extracellular antigen-binding domain, such as a single-chain variable fragment (scFv), and intracellular signaling domains that include a T cell receptor CD3ζ domain and a CD28 or 4-1BB costimulatory domain (5,6). These receptors have been instrumental in enabling T cells to selectively identify and bind to cancerous cells expressing a specific antigen, thereby offering a promising therapeutic approach for cancer treatment. By exploiting the power of the immune system in a targeted manner, CAR-T cell therapy represents a significant advance in the treatment of cancer, potentially offering benefits over traditional therapies that do not differentiate between healthy and cancerous tissues. As such, CARs hold great promise as a revolutionary form of cancer immunotherapy.

CAR-T cell therapy is a cutting-edge strategy that aims to combat cancer by genetically modifying a patient's T cells to recognize a specific tumor antigen. After being expanded in the lab, these CAR T cells are then infused back into the patient to target and destroy chemotherapy-resistant cancer cells with exceptional clinical outcomes and high rates of complete remission, particularly in individuals with B-cell malignancies (7). To improve the effectiveness of this therapy, researchers are exploring the use of combination therapies that pair CAR-T cell therapy with other drugs, such as antibodies or small molecules, that may enhance the treatment's potency. Furthermore, recent advancements in synthetic biology have led to the creation of next-generation CAR-T cell products. These innovative approaches have significantly decreased dysfunctionality and improved the ability to target tumor cells with low surface antigen expression levels (8–10), offering hope for the continued transformation of cancer treatment.

Despite the promising results of CAR-T cell therapy, however, it also faces significant challenges that must be overcome for further progress. These include potentially life-threatening CAR-T cell-associated toxicities, limited effectiveness against solid tumors, resistance in B cell malignancies, antigen escape, limited persistence of CAR-T cells, poor tumor trafficking and infiltration, and the tumor's immunosuppressive microenvironment (11). Ongoing research and development

will be necessary to address these issues, but with the power of synthetic biology and combination strategies, CAR-T cell therapy continues to offer exciting prospects for the future of cancer treatment.

Despite its initial successes in treating hematologic malignancies, CAR-T cell therapy has proven to be less effective in treating solid tumor malignancies. One significant obstacle is the absence of unique tumor-specific antigens in solid tumors, which often express these same antigens on healthy tissues, leading to a greater risk of on-target, off-tumor toxicities. Additionally, the complex microenvironment and architecture of solid tumors present physical barriers that hinder CAR-T cells' ability to migrate and penetrate tumor tissues, ultimately reducing their anti-tumor activity (12).

To address these challenges and improve the therapeutic efficacy of CAR-T cell therapy, it is necessary to identify major gaps in our current understanding of the field and explore novel approaches for optimizing treatment. This review aims to highlight the pharmacology of CAR-T cells and propose new strategies for pharmacologically enhancing their therapeutic potential by combining them with other drugs.

By leveraging the power of combination therapies, CAR-T cell therapy may be optimized to overcome the barriers encountered when treating solid tumor malignancies. These drug combinations could include agents that address the immunosuppressive microenvironment of the tumor, improve CAR-T cell trafficking, and modify target antigens to improve the specificity of CAR-T cells and reduce the risk of toxicities. Overall, improving the effectiveness of CAR-T cell therapy is a challenging but promising area of research that holds great potential for advancing the treatment of solid tumor malignancies.

Living Drugs - Overcoming Challenges in CAR-T Cell Therapy

CAR-T cell therapy is a groundbreaking approach that has revolutionized the treatment of patients suffering from aggressive malignancies. Despite its remarkable clinical success, the limitations of CAR-T cell therapy have become more apparent with accumulating clinical experience (13,14). Unlike traditional drugs, CAR-T cells are a complex mixture of heterogeneous cells derived from the patient and undergo significant changes during manufacturing (5). As a result, evaluating the purity and predicting potency of these cells can be challenging.

Unlike traditional cancer therapies that target cancer cells broadly, CAR-T cell therapy aims to distinguish malignant tissue from healthy tissue, selectively targeting tumors. This targeted approach, while effective, presents a complex challenge in the form of off-target effects and related toxicity. Precise tumor-targeting can cause CAR-T cells to become excessively active, resulting in severe systemic toxicity through excessive cytokine secretion (5,15).

Targeting tumor-specific antigens is necessary for optimal CAR-T cell therapy, but also poses the risk of on-target, off-tumor toxicity. CAR-T cell therapy faces the challenge of developing strategies to increase the specificity of these therapies, minimize toxicities, and optimize efficacy. For this reason, researchers are exploring new ways to manipulate CAR-T cell activity and partnering CAR-T cell therapies with combination drug strategies.

Further advancements in CAR-T cell therapies conform to allow for tighter regulation and control of these cells. The application of these technologies may provide better specificity and minimize the off-target toxicities associated with CAR-T cell therapy.

Overall, the success of CAR-T cell therapy underscores the immense potential of living drugs to treat cancer and other diseases. While challenges remain, the ongoing efforts to refine this approach will undoubtedly lead to continued progress in this exciting field of medicine.

Overcoming Obstacles in the Development of CAR T Cell Therapies

The development of novel and improved therapies is often impeded by several challenges, such as low persistence of CAR T cells, antigen escape, and inadequate tumor-killing efficacy – particularly for solid tumors. High toxicity profiles, such as severe CRS and neurotoxicity, also limit the feasibility of some therapies, and the prolonged manufacturing period and high costs of current products have become additional issues (13,14).

Immune escape is one of the key obstacles faced in many CAR T cell therapies, particularly those targeting CD19. This phenomenon may occur due to several mechanisms. For example, the loss of CD19 on the tumor cell surface can occur due to mutations resulting in alternate splice variants in exon 2 of the CD19 gene, which decreases CD19 expression levels. Another mechanism is linked to splice variants in exons 5 and 6 of the CD19 gene, resulting in a truncated form of CD19 that prevents binding to target antigens (16–18).

To address these challenges, researchers are exploring novel strategies to increase the persistence of CAR T cells, decrease the incidence of antigen escape, and improve tumor-killing efficacy. For instance, combinatorial approaches may be used that enhance the function of CAR T cells and reduce the immunosuppressive environment within the tumor. Additionally, innovative technologies are being developed to improve the design of CAR T cells, such as the use of dual CAR T cells or synthetic receptor systems. These approaches may increase specificity, reduce the risk of off-target toxicities, and improve CAR T cell persistence.

Overall, researchers are continuously working to advance CAR T cell therapy to overcome the challenges that limit its effectiveness. Despite the obstacles, the unique potential of CAR T cells to treat cancer and other diseases makes this an exciting field of research with much promise for the future.

Advancing CAR T Cell Specificity to Improve Targeted Therapy

Despite the promising results of CAR T cell immunotherapy, one of the main challenges is the risk of 'on-target, off-tumor' complications. This can occur when target antigens are expressed on healthy tissue cells at varying levels as well as on tumor cells. In such cases, CAR T cells can end up targeting non-cancerous cells, causing adverse effects on vital organs in addition to the intended tumor targeting (19,20).

This underscores the need for improving CAR T cell specificity to minimize off-target toxicities. Advances are being made to increase the selectivity of CAR T cells, such as the use of safer targets, strategies for fine-tuning the affinity of CARs and developing combinatorial approaches that use multiple CARs or bispecific T cells. These approaches aim to enhance specificity, reduce the risk of off-target toxicity, and improve the therapeutic window for CAR T cell therapies.

Furthermore, the treatment of solid tumors poses major challenges for CAR T cell therapy. This is due to several factors, such as a lack of suitable tumor-specific antigens, the immune suppressive properties of the tumor microenvironment, tumor heterogeneity, and challenges related to the migration and homing of CAR T cells. Overcoming these hurdles through modifications in CAR T cell design could enhance the usefulness of this therapy in treating solid tumors (5,21).

In conclusion, improving CAR T cell specificity and addressing challenges in treating solid tumors holds great promise for expanding the applications of CAR T cells and improving outcomes for patients with cancer and other diseases. Ongoing research and innovative strategies may help overcome these challenges and unlock the full potential of CAR T cell immunotherapy.

Expanding the Applications of CAR T Cell Therapies: Indications and Approved Products

CAR T cell therapies have emerged as a powerful tool for treating cancer, with different CAR T cells targeting various antigens. For hematological malignancies, CD19 and BCMA are the primary targets, while mesothelin, CEA, HER2, and GPC3 are targeted for the treatment of solid tumors. However, targeting all B cells in the body with anti-CD19 CAR T cells can cause B cell aplasia and subsequent hypogammaglobulinemia (22).

There are currently six FDA-approved CAR T cell products, four of which target anti-cluster of Differentiation (CD)19 CARs, while the latest two target B-cell maturation antigen (BCMA) (23). These include tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), lisocabtagene maraleucel (Breyanzi®), idecabtagene vicleucel (Abecma®), and ciltacabtagene autoleucel (Carvykti®) (24–27). Kymriah was the first FDA-approved CAR T product and consists of autologous T cells carrying a CAR with an anti-CD19 scFv, a CD8α hinge and transmembrane domain, CD28 costimulatory, and CD3ζ signaling domains (28).

CAR T-Cell Therapies: Revolutionizing Cancer Treatment

CAR T-cell therapies, including Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), have revolutionized cancer treatment for patients with hematological malignancies and solid tumors.

Both CAR T-cell therapies target different antigens and have shown remarkable efficacy in treating various cancers. Here are the indications for Kymriah and Yescarta:

Indications for Kymriah (26,29):

- B-cell acute lymphoblastic leukemia (ALL) in patients up to 25 years of age
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Indications for Yescarta (30-31):

- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including DLBCL NOS, PMBCL, and high-grade B-cell lymphoma, after two or more lines of systemic therapy
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

CAR T-cell therapy is a promising treatment option for patients with relapsed or refractory cancers. However, it is essential to note that the therapy carries risks of adverse effects, such as cytokine release syndrome (CRS) and neurotoxicity. Close monitoring and management of these adverse effects are necessary for the safe and effective use of CAR T-cell therapy.

In conclusion, CAR T-cell therapy is a revolutionary treatment option that has shown remarkable results for patients with relapsed or refractory hematological malignancies and solid tumors. Ongoing research and development of new CAR T-cell therapies could provide new hope for patients with cancer.

Adverse Effects Associated with Kymriah and Yescarta: Importance of Patient Selection, Monitoring, and Management

While Kymriah and Yescarta have shown remarkable efficacy in treating hematological malignancies and solid tumors, they can also cause adverse effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

CRS is the most common adverse effect associated with CAR T-cell therapy, characterized by fever, chills, hypotension, and elevated levels of inflammatory cytokines. ICANS is a potentially life-threatening condition that affects the central nervous system, causing confusion, seizures, and cerebral edema.

Therefore, careful patient selection, monitoring, and management are necessary for successful CAR T-cell therapy. Patients should be screened for preexisting medical conditions, autoimmune disorders, and infections before receiving CAR T-cell therapy. Clinicians should also closely monitor patients for signs of adverse effects and manage them promptly to minimize their impact on the patient's health and treatment outcomes.

In conclusion, while CAR T-cell therapy is a revolutionary treatment option for cancer patients, the potential adverse effects associated with it highlight the importance of careful patient selection, monitoring, and management. Clinicians must balance the efficacy of the therapy with its potential risks and manage adverse effects quickly and efficiently to ensure the best outcomes for patients.

Tecartus: A Revolutionary Treatment for Relapsed or Refractory MCL or ALL

Brexucabtagene autoleucel, marketed as Tecartus, is a CAR T-cell therapy specifically developed for patients experiencing relapse or refractoriness to traditional therapies. Tecartus works by targeting CD19 in B-cell malignancies, making it a game-changer for patients with limited treatment options.

Tecartus is approved for two indications, as per (32,33):

1. Adult patients with relapsed or refractory mantle cell lymphoma (MCL)
2. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

MCL is one of the most challenging malignancies to treat, with limited therapeutic options once standard treatments fail. With Tecartus, patients with relapsed or refractory MCL now have access to a promising new treatment that can potentially improve their outcomes.

Like MCL, B-cell precursor ALL is characterized by limited therapeutic alternatives once patients experience relapse or refractoriness to standard therapy. Tecartus offers a hopeful alternative for adults with relapsed ALL, improving their chances of remission and a good quality of life.

However, Tecartus therapy has its potential side effects, such as CRS and ICANS. Doctors need to closely monitor patients and provide immediate medical attention to manage the adverse effects effectively.

In conclusion, Tecartus CAR T-cell therapy is an effective, yet crucial alternative for adults with relapsed or refractory MCL and B-cell precursor ALL. This revolutionary treatment provides new hope to those who have no treatment options left and can ultimately help patients achieve remission and a better quality of life.

Breyanzi: A Newly FDA-Approved Treatment for Relapsed or Refractory Large B-cell Lymphoma

Breyanzi (lisocabtagene maraleucel) is a CAR T-cell therapy approved by the FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Here are the indications for Breyanzi (34,35):

1. Patients with refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
2. Patients with refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy, and they are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
3. Patients with relapsed or refractory disease after two or more lines of systemic therapy.

LBCLs are a heterogeneous group of B-cell lymphomas that cause significant morbidity and mortality. Breyanzi provides a new treatment option for patients with relapsed or refractory disease who have exhausted other available therapies.

Although Breyanzi therapy has been shown to provide significant clinical benefits, it can result in severe side effects such as cytokine release syndrome (CRS) and neurotoxicity. Therefore, close monitoring of patients and management of adverse effects are essential to ensure the safe and effective use of Breyanzi.

In conclusion, Breyanzi is a promising treatment option for patients with relapsed or refractory large B-cell lymphoma. Its approval offers new hope to those with limited treatment options, however, close observation is still crucial to prevent fatal complications.

Abecma is a medication indicated for adult patients who have relapsed or refractory multiple myeloma. In order to qualify for this treatment, patients must have undergone four or more prior lines of therapy, which must include an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody as a standard part of their treatment regimen. This medication serves as an important and effective option for

those with this type of cancer who have already undergone multiple rounds of treatment (27).

Carvykti is a medication recommended for adult patients who have relapsed or refractory multiple myeloma. For this treatment to be an option, patients must have undergone at least four prior lines of therapy that included a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This medication provides a valuable option for those who have exhausted standard treatment options and are in need of alternative methods for managing their cancer (36).

CAR T Cell Therapy: Understanding Pharmacokinetics and Pharmacodynamics

Pharmacokinetics:

Cellular kinetics is a term used to describe how cell-based therapies interact with the body over time. CAR-T cells are unique due to their living nature and exhibit distinctive pharmacokinetic (PK) properties that differ from small and large molecules. Traditional PK concepts such as distribution, metabolism, and excretion do not apply to CAR-T cells.

Unlike other therapies, CAR-T cells do not undergo metabolism or clearance pathways. Upon infusion, they undergo rapid expansion and distribution and can persist in the body for multiple years. Their concentration levels are measured by the number of cells per unit volume or copy number and decrease gradually over time (37, 38).

The IV infusion of CAR-T cells addresses any concerns about adsorption but it is crucial to review the ways in which distribution, metabolism, and excretion work for these living cells. While they exhibit unique pharmacokinetic (PK) characteristics due to their living nature, traditional PK concepts and properties for small and large molecules like metabolism and clearance do not apply to CAR-T cells. It is believed that after they have exerted their antitumor effects, CAR-T cells, similar to natural T cells, disperse through the tissues and eventually die, yet the exact mechanisms of elimination are still not fully comprehended. Research indicates that CAR-T cells deprived of survival factors or experiencing excessive activation-induced cell death (AICD) are removed from circulation through the reticuloendothelial system of the liver and spleen (39).

CAR-T cells exhibit unique pharmacokinetic properties that differ greatly from traditional drugs due to their robust proliferative capacity when encountering antigen-expressing targets. A subset of these cells can also persist in vivo as memory cells for several years (5). The kinetics of CAR-T cells are influenced by several factors, including the CAR construct that arms the T cells. The costimulatory domain, typically derived from CD28 or 4-1BB, is crucial for initiating and sustaining clonal T-cell proliferation (40).

CAR-T cells possess unique and strong proliferative capacity upon antigen exposure, a property that sets them apart from traditional drugs. Additionally, a subset of these cells can function in vivo as memory cells for several years, requiring a distinct set of pharmacokinetics (41). Several crucial factors that impact CAR-T cells' kinetics in vivo exist, with the first being the CAR construct that arms the T cells. The costimulatory domain, usually derived from CD28 or 4-1BB, plays a critical role in initiating and maintaining clonal T cell proliferation. Another critical factor that can influence CAR-T cell kinetics and long-term engraftment is the qualitative difference in T cell subsets obtained from individual patients. Besides these intrinsic cellular factors, extrinsic factors, such as tissue distribution, could also impact CAR-T cells' kinetics. For example, Tisagenlecleucel has a prolonged persistence in patients with DLBCL, despite having a lower peak concentration in peripheral blood, than in patients with B-ALL. This feature could account for the variability in distribution between blood and tissues in these patients. (42, 43).

Pharmacodynamics:

The pharmacodynamic considerations associated with CAR-T cells are complex due to these living drugs' unique characteristics. To design an effective therapy, it is crucial to consider the type and duration of interactions between the CAR-T cells and target cells, taking into account several variables such as the CAR binding affinity, the number of CAR molecules per T cell that impacts cellular avidity, the prevalence of the targeted antigen on cancer cells and in serum, and the effector-to-target cell ratio. In addition, the type and maturation stage of effector cells, as well as related cell types such as NK cells or macrophages, must be taken into account, as they are likely to impact pharmacodynamic parameters differently. (44,45).

Although CAR-T cells have shown promising clinical outcomes in CD19-targeted CAR-T cell products, there is increasing data supporting BCMA-targeted CAR-T cells (46,47). However, the clinical response of CAR-T cells is heavily influenced by the histology of the disease (34). For instance, patients with B-ALL may have a higher response rate to CD19-targeted CAR-T cell products, while patients with DLBCL or CLL may have a lower response rate (5,36,40-42). Various factors may contribute to this difference, including differences in tumor location, tumor cell attributes, tumor microenvironments, or the quality of a patient's T cells, which may be affected by the disease type (26,48,49).

Combination Therapy: Boosting of CAR T Cells

Combination therapy has become a highly promising approach to enhancing CAR-T cell performance by combining these cells with other drugs, including antibodies or small molecules.

As advances in synthetic biology continue, next-generation CAR-T-cell products have been developed that are more efficient and can target cancer cells with lower surface antigen numbers (9,50). This novel approach has opened up new possibilities for treating solid tumors, particularly through the combination of CAR-T cells with other therapeutic approaches. Through various studies, it has been observed that combination therapy has considerably improved the effectiveness of CAR-T cell therapy while also significantly mitigating its side effects (51-53). CAR-T cell combination therapy exhibits great potential in improving the effectiveness of cancer treatment. To optimize the performance of CAR-T cells, combination therapies involving antibodies or small molecules have gained popularity. The progress in synthetic biology has facilitated the development of novel CAR-T cell products that are more durable and proficient in targeting tumor cells with low surface antigen levels. These advancements have revolutionized cancer treatment and offer a viable solution to overcome CAR-T cell dysfunctionality (9,50). Combinatorial therapies involving various treatment modalities have exhibited significant potential in cancer treatment, particularly for solid tumors. These treatments include chemotherapy, radiotherapy, oncolytic viruses, cancer vaccines, cytokines, checkpoint inhibitors, Bi-specific T-cell engagers (BiTEs), immunomodulatory agents, Hematopoietic stem cell transplantation (HSCT), and metabolic inhibitors (1,53). These therapies have shown the ability to modify the tumor microenvironment and optimize the structure of CAR-T cells. Furthermore, they aid in bridging CAR-T cells to tumor cells, targeting multiple antigens, and circumventing tumor-immune escape mechanisms, which ultimately enhances the safety and efficacy of CAR-T cell therapy while limiting toxicity (54).

Studies have shown that chemotherapy can significantly enhance the effectiveness of CAR-T cell therapy when used in combination with it. The use of chemotherapy is beneficial as it enhances the immune function and reduces the tumor load. Research has shown that the combination of chemotherapy with CAR-T cell therapy is more effective than monotherapy alone (54,55).

Radiation therapy has also proved to be a beneficial adjunctive treatment in conjunction with checkpoint inhibitors and tumor vaccines. This treatment modality enables the creation of a tumor microenvironment that encourages CAR T-cell infiltration and trafficking into tumor sites. By utilizing combination therapies, specifically those with radiotherapy, we have been able to manipulate the tumor microenvironment to surmount numerous obstacles to effective treatment (56,57).

Oncolytic virotherapy (OVT) is an optimistic cancer immunotherapy that employs virus-mediated targeting of tumor cells for destruction while leaving healthy cells unaffected. By incorporating OVT in the treatment plan, we can heighten the effectiveness of CAR T cells in solid tumors. OVT achieves this by inducing the release of the tumor-associated antigen upon tumor cell lysis, thus impeding antigen loss. In addition, OVT can help reverse tumor-mediated immunosuppression, which ultimately translates to an intensification of CAR-T cell persistence in the tumor microenvironment. Furthermore, OVT can also arm CAR-T cells with therapeutic molecules, including powerful chemokines, that can boost their therapeutic potential (58–61).

Cancer vaccines represent immunotherapeutic approaches that selectively target tumor-associated epitopes, thereby inciting an adaptive immune response. One promising strategy to overcome existing limitations of CAR-T cell therapy, including target antigen down-regulation and exhaustion, involves combining CAR-T cells with cancer vaccines (62). By utilizing vaccine strategies, we can fortify CAR-T cells via two primary mechanisms: antigen-presenting cells or HLA-dependent signaling to stimulate CAR-T cells, and direct stimulation of dual or bi-specific CAR-T cells within the tumor site (62,63).

Cytokines play a vital role in modulating immune responses and are pivotal in various immunological processes. Cytokine administration, particularly in combination with CAR-T cells, shows promise in enhancing the therapeutic potential of such cells. While cytokines assume many diverse biological roles, modulation of immune function is their most critical application. However, certain tumors can subvert the immune system by secreting immunosuppressive cytokines such as IL-4. Hence, developing CAR-T cells that are resistant to IL-4 immunosuppressive effects can improve their efficacy in controlling tumors. Inverted cytokine receptors (ICRs) have displayed the ability to neutralize IL-4 immunosuppressive activity in tumors that produce IL-4, thus enhancing the therapeutic response of CAR-T cells (64, 65).

Checkpoint blockade (CPB) is a rapidly expanding field of interest within cancer immunotherapy that leverages immune checkpoint inhibitors (CPIs) to enhance immune system function, increase immune cell infiltration and persistence, and ultimately control tumor growth. The combination of CAR-T cells with PD-1 CPB represents an auspicious avenue for CAR-T cell combination therapy and has garnered significant attention in recent research (53).

Bispecific T cell engagers (BiTEs) are dual-specific antibodies that contain two ScFvs from different antibodies, facilitating a connection between CAR-T cells and various tumor cells, resulting in efficient tumor-cell killing (66). By controlling the function of CAR-T cells while enhancing their efficacy and reducing toxicity, BiTEs have emerged as a promising therapeutic tool. When used together, BiTEs and CAR-T cells produce synergistic anti-tumor responses that represent a

promising combination treatment strategy. The use of this novel combinational therapy with CAR-T cells holds the potential to overcome the limitations of tumor antigens' loss, antigen heterogeneity, limited efficacy, and persistence of CAR-T cells (67,68).

Conclusion

Side effects of CAR T cells

When considering the use of CAR-T cells, it is crucial to acknowledge the potential side effects that come with this therapy. Both Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) are the most significant adverse events observed in the administration of CD19- and BCMA-targeting CAR-T cells (69,70). Understanding these side effects and monitoring patients closely is crucial for mitigating potential risks and ensuring the success of the treatment.

CRS

Cytokine Release Syndrome (CRS) is a systemic reaction that typically occurs between the first day and second week following the infusion of chimeric antigen receptor (CAR) T-cells. The severity of CRS is often related to the tumor burden (71). Previous experimental studies have identified several mechanisms contributing to the pathogenesis of CRS:

(a) Following activation, CAR-T cells release various cytokines, including IL-6, IL-10, TNF-α, GM-CSF, and IFN-γ. Amongst these cytokines, IL-6 levels are the highest, contributing significantly to CRS induction.

(b) Lysed tumor cells release vast amounts of cytokines, including TNF-α.

(c) IFN-γ triggers the activation of immune cells, primarily macrophages, which produce several cytokines such as IL-6, IL-1, IL-10, TNF-α, and NO.

(d) IL-6 causes a robust immune response and plays a significant role in the production of CRS (70,72,73). Understanding these mechanisms is critical in preventing and addressing the potential side effects of CAR-T cell therapies.

The incidence of CRS varies significantly among different clinical studies, such as tisagenlecleucel in pediatric and young patients with refractory B-cell acute lymphoblastic leukemia and tisacel and axicabtagene-ciloleucel in adult patients with refractory B-cell non-Hodgkin's lymphoma (31,74).

The treatment approach for CRS differs depending on the severity of the CRS grade. Patients with grade 1 CRS receive symptomatic treatment, while those with grade 2 CRS undergo supportive and symptomatic treatment. Patients with grade 3 and 4 CRS, particularly the elderly or those with severe complications, require supportive treatment and immunosuppressive therapy (75). It is critical to carefully monitor and manage the severity of CRS during CAR-T cell therapy to prevent and alleviate potential complications and ensure the success of the treatment.

Tocilizumab and glucocorticoids are the primary immunosuppressants used in the treatment of CRS. According to the latest ASTCT consensus, Tocilizumab is recommended for CRS with a grade ≥2 (75,76). The recommended dosage for Tocilizumab is 8 mg/kg for patients with a body weight ≥ 30 kg and 12 mg/kg for patients with a body weight < 30 kg. The maximum dose per infusion should not exceed 800mg (76,77).

ICANS, also known as neurotoxicity, is the second most common adverse event associated with CAR-T cell therapy, often occurring simultaneously with or after CRS (reference 82). The incidence of ICANS seems to depend on several factors, including the patient's age, disease burden, and the specific CAR-T cell product used (26,70). Proper management and monitoring of ICANS are crucial to ensuring the safety and efficacy of CAR-T cell therapy.

ICANS has a complex pathogenesis that involves various mechanisms. Elevated levels of cytokines such as IL-1, IL-6, IL-15, TNF-α, and IFN-γ in the blood play a significant role. These cytokines impact the development and progression of CRES, which is closely linked to the severity of ICANS (76, 78). Moreover, activation of endothelial cells in the central nervous system increases the permeability of the blood-brain barrier, enabling cytokine entry into the cerebrospinal fluid, thereby driving the development of ICANS. Furthermore, CAR-T cells can also penetrate the cerebrospinal fluid, resulting in CNS damage. The incidence of ICANS is directly linked to the tumor burden and the severity of CRS (76, 78). Appropriate measures must be taken to monitor and manage ICANS in patients who undergo CAR-T cell therapy, as it has significant implications for treatment outcomes.

ICANS can manifest with a range of neurological symptoms, from mild delirium, headache, and aphasia to reduced consciousness, tremors, seizures, and cerebral edema (79-81). Recommended therapeutic regimens for treating ICANS vary by grade. For grade 1 ICANS, fasting, hydration, nutritional support, and improved neurological exams are advised, with the administration of Tocilizumab (8mg/kg intravenous) or siltuximab (11mg/kg intravenous) in cases that present concurrently with CRS. For grade 2 ICANS, tocilizumab or siltuximab should be administered first, and if they prove ineffective or comorbidities are present, glucocorticoids such as dexamethasone (10mg/kg every 6 hours) or methylprednisolone (1mg/kg every 12 hours) may be necessary. Proper management and monitoring of ICANS can have a significant impact on treatment outcomes and the safety of patients who undergo CAR-T cell therapy.

In cases of grade 3 ICANS, patients should be transferred to the ICU for more advanced treatment and administered glucocorticoids until their condition improves to grade 1

ICANS. Once their condition is stable, the dose of glucocorticoids should be gradually tapered off. Those with grade 4 ICANS should be given high-dose methylprednisolone (1g/day for three days) and then have their dose tapered down over nine days. For patients experiencing seizures related to CRES, glucocorticoids combined with levetiracetam (500-1000mg every 12 hours) should be used. Those with increased intracranial pressure should receive glucocorticoids in concert with acetazolamide. Lastly, patients with cerebral edema will benefit from high-dose glucocorticoids, hyperventilation, and hypertonic therapy (75, 81-89). Effective treatment and management of ICANS are essential for patient safety and promoting successful CAR-T cell therapy outcomes.

As highlighted earlier, the development of methods that allow for the quantification of the relationship between CAR-T cell mechanism of action and clinical outcomes could offer an appealing platform for addressing many elements of MIDD (e.g., improving the likelihood of regulatory success, facilitating personalized dosing for specific patient populations, etc.). Nevertheless, building such models is currently difficult due to insufficient clinical data. More clinical data and experiences obtained from many CAR-T cell therapies may make it easier to develop quantitative approaches.

Authors' contributions

All three authors were involved in the design and formulation of the argument.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical declarations

I now declare all ethical standards have been respected in the preparation of the submitted article.

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