

Chimeric Antigen Receptor T Cell Therapy in Cancer: Mechanisms, Clinical Progress, and Persistent Challenges

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Abstract. CAR T cell therapy has become one of the most influential examples of engineered immunology in cancer treatment. Unlike conventional small molecule drugs or general cytotoxic chemotherapy, this strategy first collects the patient's T cells, genetically modifies them to express a chimeric antigen receptor, then amplified in vitro, and finally returned to the patient as an individualized cellular product. The core prospect of CAR T therapy is that immune cells can be redirected to identify tumor-associated surface antigens and produce a deep response in diseases with previous poor treatment results, especially in relapsed or refractory B cell acute lymphoblastic leukemia, large B cell lymphoma and multiple myeloma. At the same time, this field is still limited by cytokine release syndrome, neurotoxicity, prolonged cytopenias, antigen escape, poor solid tumor activity, individualized manufacturing, high cost, and long-term safety concerns. This paper summarizes the biological mechanism, clinical evidence, safety profile and future directions of CAR T therapy. It believes that CAR T therapy is not only a successful cancer treatment, but also a platform technology whose next stage of development will depend on safer engineering, more accurate tumor targeting, more scalable manufacturing, and broader patient access.

Keywords: CAR T cell therapy, Cancer immunotherapy, Cytokine release syndrome, Antigen escape, Solid tumors

1. Introduction

Cancer treatment is increasingly shifting from non-specific cytotoxic approaches to treatment based on biological specificity. Chimeric antigen receptor T cell therapy, commonly known as CAR T therapy, is one of the clearest examples of this transition, because it uses immune cells as engineered therapeutic agents. The National Cancer Institute describes CAR T therapy as a treatment in which clinicians administer a "living drug" rather than a conventional chemical compound [1]. This statement summarizes the promise and difficulty of this therapy at the same time. A living drug can amplify, persist, kill tumor cells, and interact with the patient's immune environment. However, it may also cause inflammatory toxicities, and the reactions between different patients will be different.

The clinical importance of CAR T therapy in a number of hematologic malignancies has now been fully established. The U.S. Food and Drug Administration has approved many products,

including Kymriah, Yescarta, Tecartus, Breyanzi, Abecma, Carvykti and Aucatzyl, all of which are licensed cellular and gene therapy products [2]. These approvals show that CAR T therapy has become a standard cancer treatment option for specific patients rather than merely experimental immunology. However, approval does not mean this therapy is simple, universally effective, or readily available. It still needs specialized manufacturing, rigorous clinical monitoring, and long-term follow-up. Furthermore, although significant results have been achieved in blood cancers, the treatment of solid tumors remains more challenging.

This review paper focuses on CAR T therapy in cancer. It explains the biological mechanisms and treatment design of CAR T cells and reviews their clinical applications in B cell acute lymphoblastic leukemia, large B cell lymphoma and multiple myeloma. Furthermore, this review discusses toxicity, treatment management, relapses, barriers to solid tumor treatment, drug access issues, and future engineering strategies. CAR T therapy should be considered both a major clinical breakthrough and an imperfect platform. Its future value depends not only on whether it can produce high response rates, but also on whether it can improve durability, reduce toxicity, reduce logistical barriers, and expand engineered T cells to a broader range of cancer types.

The core argument of this review is that CAR T therapy should be understood through a central tension: it is powerful because it is a living and individualized immune treatment, but this same living and individualized nature also creates challenges related to toxicity, relapse, manufacturing, access, and health economics.

2. Biological mechanism and therapeutic design

CAR T therapy is based on a basic principle that T cells can be redirected through synthetic receptors. June and Sadelain describe CAR therapy as a field of T-cell engineering and synthetic immunity [3]. In ordinary immune recognition, T cells usually rely on the antigen presentation mediated by major histocompatibility complex molecules. CARs change this logic by allowing T cells to identify surface antigens through an antibody derived binding domain. Sadelain, Brentjens and Riviere [4] define CARs as recombinant receptors that combine antigen-binding and T-cell-activating functions. This design combines recognition and activation in an engineered receptor.

A typical CAR contains several functional parts. The extracellular antigen binding region is usually a single-chain variable fragment derived from an antibody. This region determines the target, such as CD19 on B cell malignancies, or BCMA on multiple myeloma cells. The hinge and transmembrane regions connect the binding domain with the intracellular signaling domains. Within the T cell, the CD3 zeta signaling domain provides activation, while costimulatory domains such as CD28 or 4-1BB affect expansion, persistence, cytokine production and exhaustion. Early research on chimeric immune receptors has shown that antibody type recognition could be linked to T cell activation through synthetic chains [5]. Subsequent CAR generations further enhanced the strength and durability of responses by adding costimulatory signals.

The difference between CD28 and 4-1BB is also important for clinical understanding. CD28 based CARs are often associated with faster expansion and stronger early activation, while 4-1BB based CARs are usually associated with slower expansion but longer persistence. Therefore, costimulatory domains do not only affect receptor biology. They may also influence the clinical behavior of different CAR T products.

The choice of antigen is one of the most important design decisions. An ideal antigen should be widespread on tumor cells and to be exposed to the cell surface. The expression on healthy tissues should be limited enough not to cause unacceptable injury. CD19 is a powerful target because it is expressed in many B cell malignancies, while the loss of normal B cell can be managed medically.

BCMA is also valuable in multiple myeloma because it is closely related to plasma cells and myeloma biology. In contrast, many solid tumor antigens are also expressed at low levels in normal tissues, which increases the risk of on-target and off-tumor toxicity. This means that CAR T design is not only a matter of making T cell stronger, but also of choosing a target producing a reasonable therapeutic window.

The therapeutic process itself is also very complicated, because the drug is made from cells. For most approved autologous CAR T products, T cells are first collected from the patient through leukapheresis. These cells are then activated, genetically modified through a viral or nonviral vector, expanded in culture, through quality testing, and finally returned to the clinic. Before infusion, patients usually receive lymphodepleting chemotherapy. This step reduces competing immune cells and creates a cytokine environment that supports CAR T cell expansion. Following Infusion, these engineered cells can proliferate in the body, kill antigen positive tumor cells, and sometimes persist in the form of memory like populations. Therefore, the patient receives not only a one-time infusion, but a group of dynamic immune populations.

Manufacturing is also part of CAR T therapy biology. Cell fitness, starting T cell quality, expansion conditions, vector design, transduction efficiency and release testing will all affect the final product. Patients who have received multiple rounds of therapy may have exhausted or damaged T cells, which will affect product potency. Manufacturing failures or delays are also clinically important, because patients with aggressive disease may continue to progress while waiting for the cell production. Therefore, the distinction between autologous products and allogeneic products is not just logistical. Autologous products are individualized, which can reduce the risk of graft-versus-host disease, but they are also slower and more unstable. Allogeneic products may be faster and more standardized, but they must overcome immune rejection and safety risks.

Therefore, the design of CAR T therapy involves both molecular engineering and clinical logistics. The receptor may be biologically sophisticated, and it must also be highly producible, reliable, and safe for use in advanced cancer patients. These factors make the CAR T therapy different to many traditional drugs and its efficacy depends on receptor structure, cell phenotype, production quality, disease burden, patient immune status, and the tumor microenvironment. This field has become the intersection of immunology, genetic engineering, oncology, transfusion medicine and health system organization.

3. Clinical applications and evidence

The most convincing evidence supporting CAR T therapy comes from hematologic malignancies. B cell acute lymphoblastic leukemia is a landmark setting, because CD19 is expressed on many malignant B cells and can be targeted without relying on intracellular antigen presentation. In the pivotal tisagenlecleucel study of children and young adults with relapsed or refractory B cell acute lymphoblastic leukemia, Maude et al. [6] state that the overall remission rate within 3 months was 81%. For this group of patients who have received intensive therapy and have few other options, this result makes CAR T therapy a real breakthrough, rather than a minor repair of existing treatment.

The experience with Leukemia also explains why CAR T therapy is so unique in biology. The reason that the response can be so in-depth is that a small number of infused cells can be amplified after encountering antigen. The dose measured during infusion does not fully represent the dose actually experienced within the body. Clinical response depends on in vivo proliferation, tumor burden, immune activation and persistence. B cell aplasia after CD19 directed therapy can be regarded as a biological sign that CAR T cells remain active, although it will also bring the need for

immune support. In this setting, efficacy and toxicity are associated with the same core mechanism, i.e., strong immune activation for antigen positive cells.

However, remission is not equal to a cure. Some patients will still relapse after CAR T therapy, and the reason for relapse is also very enlightening in biology. In CD19 directed therapy, malignant cells may lose CD19 expression, change antigen density, or survive through other resistance mechanisms. In addition, CAR T cells themselves may not be sustainable or become exhausted. These observations show that CAR T therapy exerts evolutionary pressure on cancer. A successful initial response may clear sensitive cells, but it will also make resistant clones dominate later.

Large B cell lymphoma is another important clinical application. In the ZUMA-1 trial regarding axicabtagene ciloleucel, Neelapu et al. [7] report that "The objective response rate was 82%, and the complete response rate was 54%". These findings are very important because aggressive lymphoma after multi-line treatment has always been difficult to control. CAR T therapy creates a new option for patients who relapse after chemotherapy or relapse after transplantation. The lymphoma setting also shows that CAR T therapy can be used for bulky and biologically aggressive disease in adults, although the results will vary depending on tumor burden, inflammation, performance status and prior treatment.

Evidence from lymphoma also helps clarify the meaning of response rate. Objective response includes partial responses and complete responses, but complete responses are more meaningful clinically because it reflects a deeper level of tumor clearance. Even so, a complete response does not mean that follow-up is no longer needed. Some patients will relapse, while others may experience severe toxicity. Therefore, CAR T therapy must be integrated into a treatment pathway rather than regarded as a stand-alone miracle. Clinicians need to decide when to refer patients, whether bridging therapy is needed, how to manage high-risk disease during product manufacturing, and how to monitor relapses after infusion. These questions will change the value of the treatment in practice.

Multiple myeloma will expand the CAR T field from CD19 to BCMA, BCMA is a plasma cell marker and it has become an effective target in heavily pretreated patients. Idecabtagene vicleucel shows clinically meaningful activity in relapsed and refractory multiple myeloma [8]. Ciltacabtagene autoleucel can also produce deep responses in CARTITUDE-1 study [9]. These trials are important as the standard therapies rarely cure multiple myeloma, and patients may also develop resistance to proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies. BCMA directed CAR T therapy provides a new mechanism for patients who have exhausted conventional options.

Across these applications, the most obvious pattern is very clear. CAR T therapy performs best when tumor target is close, relatively specific, and widely expressed in malignant cells. Blood cancers often meet these requirements better than solid tumors. Leukemia, lymphoma and myeloma cells are found in blood, marrow or lymphoid tissues, and T cells have easier access to them. Solid tumors are completely different because they are composed of stromal barriers, abnormal vessels, hypoxia, oppressive immune cells and heterogeneous antigen expression. Therefore, clinical evidence supports both optimism and caution.

4. Safety, toxicity and clinical management

The therapeutic power of CAR T cells comes from immune activation, but the same activation can also produce severe toxicity. The two most closely related acute toxicities with CAR T therapy are cytokine release syndrome and immune effector cell associated neurotoxicity syndrome. Cytokine release syndrome occurs when activated immune cells release inflammatory cytokines, which may

cause fever, hypotension, hypoxia, organ dysfunction, and even the need for intensive care in severe cases. Neurotoxicity may manifest as confusion, aphasia, tremor, seizures, cerebral edema, or other neurologic changes. These toxicities are not accidental side effects unrelated to treatment. They are directly related to the immune activation that makes therapy effective.

Standardized grading is essential for clinical practice and research. Lee et al. [10] report that to improve the consistency among the different trials and treatment centers, ASTCT proposed a consensus grading system for CRS and neurologic toxicity. It will make it difficult to compare safety outcomes if there is no unified grading system because different hospitals or studies may classify the same symptoms differently. Tocilizumab, an IL-6 receptor blocker is usually used to treat CRS. The corticosteroids are often used to treat severe CRS or neurotoxicity. Brudno and Kochenderfer [11] stress that recognizing and managing toxicity is the core part of CAR T therapy. The goal of treatment is not to eliminate immune activity as immune activation is necessary to kill cancer cells, but rather to control immune activity before dangerous inflammation causes irreversible damage.

The timing of toxicity is also clinically important. CRS usually occurs early during the timing of CAR T cell expansion, and it may be related to tumor burden and inflammatory status. Patients with a higher disease burden during infusion may experience stronger immune activation, because there are more antigens for CAR T cells. Neurotoxicity may occur at the same time as CRS, or emerge after CRS begins to improve, so even when other symptoms seem to be under control, neurologic monitoring is still necessary. This is also why CAR T programs depend on trained teams, emergency protocols and close patient observation. Unless a treatment center has experience and can quickly obtain supportive care, this treatment cannot be safely implemented in the same outpatient setting as routine infusion.

Safety concerns are not just acute. Patients may also experience prolonged cytopenias, infections, B cell aplasia, hypogammaglobulinemia, and delayed immune recovery following CD19 directed therapy. These problems may require antimicrobial prophylaxis, immunoglobulin replacement, transfusion support and long-term monitoring. In addition, the FDA also requires updates to the boxed warning because of T cell malignancies after BCMA directed or CD19 directed autologous CAR T therapy. The agency concluded that changes to the Boxed Warning are warranted to highlight the serious risk of T cell malignancies [12]. This update does not erase the benefit of CAR T therapy, but it shows that long-term safety itself is part of the evidence base. A therapy that can persist in the body must be evaluated over time, not just the first month after infusion.

This regulatory warning also shows why post marketing surveillance is so important for living therapies. Clinical trials may involve only a few hundred patients, but approved products may eventually be used for thousands of patients in different hospitals, age groups, disease states and treatment histories. Rare risks may only appear after broader use. For CAR T therapy, clinicians and researchers must determine whether delayed malignancies are caused by insertional mutagenesis, prior chemotherapy, immune dysregulation, genetic predisposition, or other mechanisms. These problems require careful case investigation and transparent reporting. Therefore, the safety profile of CAR T therapy is not fixed at the time of approval but will continue to develop with the accumulation of more long-term data.

Therefore, the clinical management of CAR T therapy is a balance between efficacy and safety. Greater expansion and stronger immune activity may increase tumor killing, but they will also increase toxicity. Lower intensity designs may reduce toxicity while may lead to weaker antitumor activity. Patients differ from each other in tumor burden, inflammatory status, prior treatment, organ function and immune fitness. These differences help explain why the same CAR T product produces

different outcomes in different patients. Therefore, a balanced review should avoid describing CAR T therapy as a simple miracle treatment.

Access and health economics should also be discussed as part of clinical management, not only as a general statement that CAR T therapy is expensive. The overall burden includes leukapheresis, individualized manufacturing, bridging therapy, toxicity monitoring, possible hospitalization, long term follow-up, and travel to specialized centers. These costs and logistical requirements may delay infusion, limit which patients can receive treatment, and increase the financial burden on both patients and health systems.

5. Challenges and future directions

In this section, future directions relate to the current challenges they try to address. Accordingly, relapses, solid tumor barriers, manufacturing delays, and access are treated as problem-solution pairs. CAR T therapy still faces various of challenge, which can be divided into the fields of biological and clinical. In the field of biology, the main problems are still relapses and antigen escape. Sterner and Sterner [13] point out that these barriers include severe toxicity, limited activity under certain conditions, antigen escape, restricted transport and insufficient tumor invasiveness. Antigen escape suggests that cancer is not a passive target. When CAR T cells clear antigen positive cells, antigen negative or antigen low clones may survive and amplify. This issue is especially important for single target therapies. To address this problem, researchers are developing dual target CARs, tandem CARs, logic gated CARs, and sequential treatment strategies to reduce therapy's dependence on a single antigen. Therefore, dual target and logic gated designs are discussed here as direct responses to relapse and antigen escape.

Among all current challenges, solid tumors represent the greatest biological challenge. NCI pointed out that compared with blood cancers, the progress in solid tumors "has lagged" [1]. There are several reasons. Solid tumors may not have an antigen that can be expressed evenly on cancer cells without appearing at all on essential normal tissues. In addition, CAR T cells must traffic to tumor sites, penetrate physical barriers, resist hypoxia and nutrient deprivation, and maintain function in an immunosuppressive microenvironment. Majzner and Mackall [14] state that the clinical experience of CAR T cells has revealed the key factors related to efficacy, resistance and barriers to success. Similialy, Rafiq, Hackett and Brentjens [15] also emphasize engineering strategies aimed at overcoming trafficking, activation and safety obstacles, especially in solid tumors. Future solid tumor CAR T therapy will likely require armored CARs, which can secrete cytokines or checkpoint blocking molecules, regional delivery, resistance to suppressive signals, and target designs to avoid harming normal tissues. Here, regional delivery is intend to overcome the transport barriers, while armored CARs are meant to answer the suppressive tumor microenvironment.

Access is another core limitation. CAR T therapy is expensive, labor-intensive, and highly concentrated in limited geographic areas. Autologous manufacturing requires individualized collection and production, leading to waiting times and quality variations. Patients usually need to travel to specialist centers and remain nearby during periods of highest toxicity risk. These practical problems transform what was initially a biological innovation into a challenge for society and the healthcare system. It will be impossible to truly transform the treatment landscape for all eligible cancer patients if there is only a very small number of eligible patients who have access to this therapy.

Because autologous manufacturing creates delay, quality variation, and access barriers, allogeneic and gene edited products are discussed here as a response to this specific challenge. One of the most

important future directions is the development of allogeneic and gene edited CAR T products. NCI explains that allogeneic CAR T therapies may be available immediately as 'off-the-shelf' treatments for any patient [1]. This method could address some of the delays in autologous cell production, but it will also introduce new biological risks. Donor T cells may be rejected by the patient's immune system or may lead to graft-versus-host disease. Gene editing offers possible solutions. Depil et al. [16] review the promise and difficulty of off the shelf allogeneic CAR T cells. Eyquem et al. proved that using CRISPR/Cas9 to insert CAR directionally into TRAC locus can enhance antitumor activity in experimental models, which suggests that precise gene editing may not only improve product uniformity, but also function [17]. However, gene editing also raises new safety questions, such as off target effects, chromosomal rearrangements, persistence, and regulatory oversight.

Another future challenge is to decide how CAR T therapy should be combined with other cancer treatments. If CAR T cells are used earlier in the disease course, they may be more effective when the tumor burden is lower and the patient's immune system is less damaged. They may also be combined with checkpoint inhibitors, targeted therapy, radiation, vaccines, oncolytic viruses, or agents that can change the tumor microenvironment. However, combinations will also increase toxicity and make it more difficult to determine which component brings benefit or harm. Therefore, the next stage of clinical research should focus on rational combinations, careful biomarkers, and trial designs that can measure durability, quality of life, cost and long-term safety, rather than response rate alone.

Finally, the evaluation of future CAR T products should include patient centered outcomes. A response that only lasts for a short time, requires repeated hospitalization, or leads to severe long term immune suppression may have different meanings for patients than suggested by the same response rates alone. Therefore, future studies should not only report remission and survival, but also time away from hospital, infection burden, neurologic recovery, financial burden and quality of life. This broader evaluation method is highly consistent with the essence of CAR T therapy, because this treatment affects the patient at biological, clinical and social levels simultaneously.

6. Conclusion

In summary, CAR T therapy is one of the most important developments in modern cancer immunotherapy, because it proves that engineered immune cells can become effective anticancer drugs. Its most prominent clinical achievements have been achieved in hematologic malignancies, especially B cell acute lymphoblastic leukemia, large B cell lymphoma and multiple myeloma. At the same time, the limitations of this therapy are equally important, including CRS, ICANS, delayed toxicities, relapses, antigen escape, poor solid tumor activity, manufacturing delays, cost and access barriers. Thus, the next stage of this field should not be judged only by whether CAR T cells can produce impressive response rates in selected trials. It should be judged according to whether CAR T therapy can become safer, more durable, more scalable and more equitable. If the future engineering technologies can reduce toxicity, target heterogeneous tumors, prevent recurrence, and simplify production, CAR T therapy may develop from a specific breakthrough targeting only certain blood cancers into a broader platform for cancer treatment.

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