Clinical Translation of CAR-T Therapy in Hematologic Ocologyr

Yuan Wang*

Heifei 168 High School, Hefei, China

*Corresponding author: linmo_o@outlook.com

Abstract. Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of hematological malignancies by reprogramming a patient's T cells to target tumor-specific antigens. Despite great success in clinical care, challenges such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), neurotoxicity, and limited efficacy in solid tumors remain. Recent advances in CAR-T engineering-including dual-targeted CARs, armored CARs with cytokine-secreting capabilities, and safety switches-have enhanced tumor specificity, reduced off-target effects and improved durability. However, the immunosuppressive tumor microenvironment (TME) in solid tumors remains a key obstacle that affects the infiltration, activation, and long-term function of CAR-T cells. This review systematically analyzes the clinical translation of CAR-T therapies, focusing on their mechanism of action, efficacy in hematological and solid tumors, and management of adverse effects. We highlight the efficacy and toxicity profiles of CAR-T and summarize relevant emerging strategies such as CAR T cell therapy in combination with other immunotherapies such as checkpoint inhibitors. Our findings emphasize that CAR-T therapies are transitioning from a salvage option to a first-line contender for hematologic cancers, but their broader application will need to address durability and safety trade-offs. Future research should prioritize multifunctional CAR designs, predictive biomarkers of toxicity, and personalized manufacturing protocols to expand its accessibility. Overcoming these challenges will make CAR-T more dominant in solid and refractory cancers and bring hope to more cancer patients.

Keywords: CAR-T Cells, Hematologic Malignancies, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Clinical Translation.

1. Introduction

Significant advances in the treatment of haematological malignancies have been made with the introduction of chimeric antigen receptor T-cell therapy. This therapy has shown promising results in a variety of haematological tumours, including ALL, DLBCL, CLL and MM. For example, in ALL, CAR-T therapies have played a very important role in revolutionising outcomes for relapsed or refractory patients, especially children and young adult patients. In DLBCL, CD19-guided CAR-T has dramatically changed salvage therapy for patients with refractory disease. However, the distinct challenges presented by the immunosuppressive tumour microenvironment (TME) and T-cell dysfunction inherent to the disease must be overcome when developing CAR-T therapy for CLL. The identification of new target antigens and the development of general-purpose CAR-T cells for off-the-shelf use are some of the most promising areas of research in the field. Nevertheless, there are numerous clinical obstacles that still need to be overcome. CRS and ICANS are toxic reactions associated with CAR-T cell therapy. Of particular importance, both CRS and ICANS occur in conjunction with a systemic inflammatory response, which may also result in fever, hypotension, hypoxia, and multi-organ dysfunction. ICANS, on the other hand, is associated with a range of neurological symptoms, including confusion, seizures, and cerebral edema. It has been established that significant quantities of cytokines are discharged by activated CAR-T cells. These cells subsequently activate other immune cells, resulting in an inflammatory response. Therefore, understanding the process involved is important to prevent and treat these adverse reactions, thereby improving the safety and efficacy of CAR-T therapies. Nowadays, CAR-T cell therapy targets are mainly haematological malignancies. In the case of solid tumours, treatment is complicated by their inherent limitations. Consequently, there is a necessity for further exploration of new CAR-Ts and the refinement of their structure to achieve more precise targeted therapy [1]. In conclusion, Bringing

hope to those suffering from previously incurable diseases, the advent of CAR-T therapy has changed the treatment paradigm for a range of malignancies. Optimising CAR design, dual-target strategies, and toxicity management will be critical to expanding its therapeutic window and ensuring safer, more durable responses.

2. Mechanisms of CAR-T Cell Therapy

CAR-T cells are designed to express CARs, which are composed of antibody-derived single-chain variable fragments (scFv) for antigen recognition, hinge and transmembrane structural domains, and intracellular signalling structural domains. Intracellular structural domains typically include CD3ζ and co-stimulatory signalling domains such as CD28 or 4-1BB, which enable cytokine secretion and the proliferative capacity of CAR-T cells to be affected upon activation by antigen-expressing target cells.

The treatment process begins with the collection of the patient's T cells, which are then genetically modified to express CARs, expanded in vitro and infused back into the patient. Once infused, the CAR-T cells enter the tumour site, recognise and bind to the target antigen and are then activated. This activation proliferates CAR-T cells, cytokine production and kills tumour cells.

3. CAR-T Cell Therapy in Haematological Oncology

CAR-T cell therapy has achieved significant clinical success in the treatment of CD19-expressing malignant B-cell diseases such as ALL, DLBCL, CLL and Multi-myeloma (MM). In early clinical trials, this therapy has been shown to be very effective, with high rates of complete remission in refractory or relapsed patients.

3.1. ALL

The therapy targeting CD19 has demonstrated breakthrough efficacy in relapsed/refractory ALL (r/r ALL). A plethora of phase II clinical trials have yielded data demonstrating complete remission (CR) rates ranging from 67% to 93% among adult and paediatric patients, with the preponderance of remissions being characterised as minor residual disease (MRD)-negative. The CHOP/University of Pennsylvania team (4-1BB co-stimulation domain) achieved 90% CR in 30 patients. In the PENN/CHOP programme, after a prior allogeneic SCT there are 60% of patients had relapsed, with T cells successfully collected and manufactured from the recipient with no post-infusion GVHD. The MSKCC team (CD28 co-stimulation domain) treated 53 adult patients, achieving a CR rate of 83%. However, 42% of these patients developed grade 3-4 neurotoxicity, suggesting that CAR constructs may influence the toxicity profile. The Novartis multicentre study (tisagenlecleucel) achieved a CR rate of 81% in 75 children and young adults, a result that led to its approval as the first CAR-T product (FDA approval in 2017) [2].

Long-term follow-up data reveal heterogeneity in efficacy. Relapse was significantly more common in subjects who did not have an HSCT after CARTs (6/7; 85.7%) compared to those who did (2/21; 9.5%) ($P = 0.0001$) [2]. The CHOP team (4-1BB co-stimulation domain) reported a 12-month relapse-free survival rate of 55% in 34 patients who did not receive transplantation, with remission lasting more than 40 months in some patients, correlating with CAR-T cell persistence. These findings underscore the interplay between CAR-T durability, consolidation therapies, and long-term outcomes.

3.2. DLBCL

The efficacy of this method has been demonstrated in cases of DLBCL. After receiving rituximab-containing chemotherapy, patients with DLBCL typically have an ORR of 60% and a long-term survival rate of 50%. Nevertheless, 30% to 40% of patients will relapse and 10% will have primary refractory disease [3]. Key trial comparisons suggest that 101 patients treated with ZUMA-1

(axicabtagene ciloleucel, CD28 co-stimulatory domain) had an overall remission rate (ORR) of 82% and a complete remission rate (CR) of 54%; the JULIET trial (tisagenlecleucel, 4-1BB co-stimulatory domain) had an ORR in 111 patients of 52% and CR of 40%; TRANSCEND001 (lisocabtagene maraleucel) had an ORR of 80% and CR of 59% in the CORE cohort [3].In ZUMA-1, CRS occurred in 93% of patients (13% of which exhibited grade ≥3 toxicity), and neurological toxicity affected 64% (with 28% of these cases exhibiting grade ≥3 toxicity) [3]. New research shows that the 4-1BB structure can prolong the survival of CAR-T cells and reduce the likelihood of relapse. Studies have revealed the impact of CAR-T architecture (CD28 vs. 4-1BB) on the efficacy/toxicity balance: the CD28 domain may drive higher remissions but is accompanied by significant neurotoxicity (e.g., ZUMA-1), whereas the 4-1BB domain may potentially enhance long-term benefit by prolonging cell survival, suggesting the need to optimize design to balance risk-benefit.

3.3. CLL

CAR-T cell therapy has demonstrated remarkable clinical efficacy in the treatment of CLL. In a prospective trial (NCT02348216), 19 patients with CLL received autologous anti-CD19 CAR-T cells (CTL119) alongside ibrutinib after lymphodepletion [4]. In the present study, complete morphological remission (CR) in bone marrow was achieved at the 3-month follow-up by 94% of patients (17/18 evaluable patients) with the remaining 78% (14/18 patients) achieving MRD negativity by deep sequencing. The 4-1BB structure has been demonstrated to prolong the persistence of CAR-T cells, thereby reducing the risk of relapse [4]. Notably, 43% (6/14) met iwCLL CR criteria, a marked improvement compared to historical CAR-T monotherapy CR rates (21–29%) [4]. Despite frequent CRS (95% of patients, 18/19), most events were mild (grade 1–2: 15/19), with only 3 requiring tocilizumab [4]. Mechanistically, transcriptomic profiling of CAR-T cells revealed distinct signatures correlating with clinical response. In CR patients, CAR-T cells exhibited enriched memory-related genes (e.g., TCF7, LEF1) and IL-6/STAT3 pathway activation, whereas non-responders (NR) showed upregulated glycolysis, exhaustion (PD-1, LAG-3), and apoptosis pathways [5]. CR patients also demonstrated higher frequencies of CD27++PD-1−−CD8++ T cells in pre-infusion leukapheresis samples, a subset critical for sustained tumor control in murine models [5]. These cells displayed elevated IL-6 receptor expression and STAT3 phosphorylation upon stimulation, correlating with robust in vivo expansion. This study highlights that CAR-T efficacy in CLL depends on memory T-cell signatures (TCF7/STAT3) and pre-existing CD27++PD-1−− subsets, while treatment failure links to exhaustion/glycolytic pathways, suggesting biomarker-driven optimization of CAR-T products.

3.4. MM

Multiple myeloma (MM) is a plasma cell malignancy that remains incurable and recurs in almost all patients despite prolonged survival through novel therapeutic agents that have emerged in recent years. In patients with relapsed/refractory MM (R/R MM), BCMA-targeted CAR-T cell therapy has yielded impressive results. A total of 70 patients underwent CAR T-cell therapy at a dose of 300 × 10^6 cells, while 54 patients received a dose of 450 × 10^6 CAR T cells, and 4 patients were administered a dose of 150 × 10^6 CAR T cells. The overall occurrence rate of CRS (cytokine release syndrome) across all grades was 83.6%. Among these, severe CRS (grade ≥3) occurred in 5.5% of the patients (7 individuals), which included one fatality. Severe neurotoxicity (grade ≥3) was noted in 3.1% of the cases (4 patients). For the entire cohort, the overall response rate (ORR) reached 73.4%, with the most significant ORR of 81.5% observed in patients receiving the highest CAR T-cell dosage [6]. In a further study, 25 patients were treated with LCAR-B38M, which demonstrated objective remission in 88% of patients, with a median progression-free survival of 12 months. In a further clinical trial, 16 patients with R/R MM were treated with BCMA/CD38 bispecific CAR-T cells, and after a median follow-up of 11.5 months, clinical responses were observed in 14 of them, with 13 achieving CR [7]. Furthermore, this therapies for MM patients have attempted a variety of antigenic targets, such as CD19 and CD138, to improve treatment efficacy and reduce relapse.

A 62-year-old female patient with MM relapsed after multiple treatments. The patient received anti-BCMA CAR-T cell therapy and developed grade 2 CRS after treatment, which resolved after symptomatic treatment. Three months after treatment, the patient's bone marrow examination showed complete remission with negative MRD. Twelve months after treatment, the patient was still in complete remission with a significantly improved quality of life. This case demonstrates that CAR-T cell therapy has significant clinical efficacy in patients with multiple myeloma (MM), with the potential to induce long-term disease remission and improve quality of life.

4. Toxicities Associated with CAR-T Cell Therapy

Despite its clinical success, the therapy is associated with significant toxicities, primarily CRS and ICANS. These toxicities result from the powerful immune effector responses induced by CAR-T cells.

4.1. CRS

CRS is a potentially life-threatening systemic inflammatory response triggered by immune activation therapies, most commonly observed following CAR-T cell infusion. CRS is characterized by fever (≥38°C), low blood pressure, insufficient oxygen levels, and dysfunction of multiple organs. These symptoms typically manifest within 2 to 7 days following infusion. However, in 8-15% of cases, delays of up to 14 days have also been observed [8]. The severity spectrum ranges from grade 1 (mild febrile reactions) to grade 4 (life-threatening organ failure), with neurological toxicity occurring in 20-40% of severe cases [9].

The pathophysiology involves a three-phase cytokine cascade initiated by CAR-T cell activation upon antigen recognition. Pro-inflammatory cytokines, including IL-6, IFN-γ, and GM-CSF are released by activatedCAR-T cells [10]. The process of secondary activation of macrophages and monocytes is induced by these mediators through Fcγ receptor signalling. This in turn leads to a high production of interleukins. This cytokine storm induces endothelial activation with increased vascular permeability (mediated by angiopoietin-2 upregulation), coagulopathy, and tissue hypoxia through multiple mechanisms including inducible nitric oxide synthase overexpression.

4.2. ICANS

ICANS, also known as neurotoxicity, usually presents as an encephalopathy characterised by disorientation, aphasia and lethargy. Severe patients may experience seizures, motor weakness and brain swelling. ICANS usually occurs after remission of CRS and is thought to be the result of central nervous system (CNS) infiltration by CAR T cells and cytokines. The pathophysiology of ICANS is characterised by disruption of the BBB and accumulation of inflammatory cytokines within the CSF. Elevated CSF levels of IL-6, IL-1 and IFNγ are frequently observed among patients with ICANS. Treatment of ICANS includes supportive care and corticosteroids to reduce inflammation. Tocilizumab is generally ineffective in the treatment of ICANS, probably due to its poor penetration of the BBB.

5. Future Directions

The clinical application of this therapy in haematological malignancies is revolutionary, but challenges remain as well. The present research endeavours to enhance the security and efficacy of the method by means of optimising CAR design, increasing T-cell persistence and reducing toxicity. New strategies include designing CARs with modified co-stimulatory structural domains to fine-tune T-cell activation and cytokine production. In addition, combining CAR T-cell therapy with other immunotherapeutic agents, such as checkpoint inhibitors, may improve anti-tumour efficacy and overcome drug resistance.

The therapeutic intervention is currently being expanded in order to encompass other haematological malignancies and solid tumours. One of the most promising research areas in this

field is the identification of new target antigens and the development of off-the-shelf generic CAR-T cells.

6. Conclusion

CAR-T cell therapy has revolutionised the management of haematological malignancies, achieving remarkably high rates of remission in many malignancies. This review assesses the clinical efficacy, mechanisms, and challenges of CAR-T therapy, emphasizing that it could evolve into a first-line option for the treatment of cancer. The review emphasises the dual role of CAR-T. Innovations in CAR-T structure, such as dual-targeted CARs and armoured cytokine-secreting constructs, enhance tumour specificity and durability. The selection of the co-stimulation domain exerts a direct influence on clinical outcomes. In addition, personalized therapies offer more options for mitigating adverse events such as CRS and ICANS. However, this analysis reveals key gaps in current knowledge. First, the mechanisms underlying differences in neurotoxicity between CAR-T constructs remain unclear. Second, while HSCT consolidation therapy improves durability in ALL and DLBCL, its role in MM and CLL requires further validation.

Limitations of this review include a focus on hematologic malignancies, with limited discussion of applications in emerging solid tumors, and a lack of cost-effectiveness analysis, which is critical for global access. In addition, long-term follow-up data on the durability of CAR-T beyond 5 years remain scarce and do not allow for definitive conclusions about therapeutic potential.

Future studies must prioritize multifunctional CAR designs that integrate safety switches, TME regulatory elements, and resistance to failure. For solid tumors, it is important to overcome immunosuppressive barriers by combining therapies (e.g., checkpoint inhibitors) or targeting novel antigens. Finally, standardized toxicity management protocols and manufacturing processes need to be developed to achieve universal access. By addressing these challenges, CAR-T therapies can transcend current limitations and provide lasting help for a broader range of cancer types and patient populations.

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