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REVIEW

Revolutionizing Immunotherapy: Unveiling New Horizons, Confronting Challenges, and Navigating Therapeutic Frontiers in CAR-T Cell-Based Gene Therapies

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Abstract: The CAR-T cell therapy has marked the dawn of new era in the cancer therapeutics and cell engineering techniques. The review emphasizes on the challenges that obstruct the therapeutic efficiency caused by cell toxicities, immunosuppressive tumor environment, and decreased T cell infiltration. In the interest of achieving the overall survival (OS) and event-free survival (EFS) of patients, the conceptual background of potential target selection and various CAR-T cell design techniques are described which can minimize the off-target effects, reduce toxicity, and thus increase the resilience of CAR-T cell treatment in the haematological malignancies as well as in solid tumors. Furthermore, it delves into cutting-edge technologies like gene editing and synthetic biology, providing new opportunities to enhance the functionality of CAR-T cells and overcome mechanisms of immune evasion. This review provides a comprehensive understanding of the complex and diverse aspects of CAR-T cell-based gene treatments, including both scientific and clinical aspects. By effectively addressing the obstacles and utilizing the capabilities of cutting-edge technology, CAR-T cell therapy shows potential in fundamentally changing immunotherapy and reshaping the approach to cancer treatment.

Keywords: CAR-T cells, immune checkpoint inhibitors, gene therapies, gene editing, predictive biomarkers

Introduction

Chimeric Antigen Receptor (CAR)-T cell therapies have emerged as a viable strategy for the treatment of many forms of cancer. CAR-T cell therapy is categorized as an ex vivo gene therapy, wherein the patient's T cells are genetically altered outside the body prior to reinfusion into the patient's system, with the purpose of specifically targeting and eliminating cancer cells.[1] This process enhances the immune system's effectiveness in fighting against the disease.[2] The efficacy of CAR-T cell therapy has facilitated the progress of other advanced therapy medical goods, showcasing the potential of gene therapy in the treatment of diverse disorders.[3] The clinical studies of this groundbreaking therapy have demonstrated exceptional efficacy, especially in patients with hematologic malignancies.[4] In addition, CAR-T cell therapy has demonstrated potential in the treatment of hematological malignancies, specifically B cell malignancies such relapsed or refractory diffuse large B cell lymphoma (DLBCL).[5] The therapy possesses the capacity to produce enduring remission and potentially even eradicate specific forms of cancer, thereby presenting a newfound sense of optimism for patients with few treatment alternatives. The emergence of CAR-T cell treatments signifies a notable progression in the realm of cancer treatment, holding the capacity to

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fundamentally transform our approach to and control of the disease. CAR-T cell therapies utilize the immune system and genetic engineering to provide a customized and focused method for treating cancer, overcoming the constraints of conventional treatments.[2] Moreover, the effectiveness of the therapy in addressing blood cancers has opened up possibilities for investigating its use in solid tumors, which pose a more intricate difficulty due to the diverse conditions within the tumor and its surroundings.[4] This therapy seeks to augment the effectiveness of CAR-T cells by modifying the tumor microenvironment through the use of tumor-targeting nanozymes. These nanozymes have the ability to boost immune activation and improve the overall therapeutic efficacy of the treatment.[6] Nevertheless, the broad implementation of CAR-T cell treatment is hindered by notable barriers, including immunity-related side events and prognostic heterogeneity.[7] These tasks involve the management of potential negative effects like cytokine release syndrome and neurotoxicity, the improvement of manufacturing methods to guarantee consistent and high-quality cell products, and the resolution of the high cost and limited availability of these advanced medicines.[2] Despite these obstacles, CAR-T cell therapy has exhibited notable advancements in the treatment of liquid malignancies, with a complete remission rate above 57%.[8] Within the realm of gene therapy, CAR-T cell therapy signifies a notable progression in the discipline. Furthermore, current research is concentrated on improving the effectiveness of CAR-T cell therapy in solid tumors, addressing the immunosuppressive mechanisms present in the tumor microenvironment, and devising techniques to counteract antigen escape and tumor relapse.[4] CAR-T cell therapy, utilized in oncology, may treat autoimmune diseases. CAR-T cells targeting specific antigens show potential in systemic lupus erythematosus.[9] In 2021, CAR-T therapy helped SLE patients achieve sustained remission. This therapy targets and depletes autoreactive B cells, where traditional treatments fail. Successful treatment of SLE implies implications in other autoimmune disorders, a major therapeutic development.[10] Figure 1 represents the significant discoveries in the field of CAR-T cell therapies.

Emerging Targets for CAR-T Cell Therapy and Next-Generation CAR-T Engineering

The immunotherapies centered on the application of triggered and genetically persuaded T cells have transfigured the area of superior precision targeting in cancer treatment. Among the various forms of T cell transfer strategies, the CAR-T cells provoke an intention of targeting cell death with the help of single-chain variable fragment (scFv) that aim at tumors.[11] This strategy causes the abolition of supposedly indistinguishable malignant cells, thereby resulting in tremendous improvements in cancer subjects.[12] CAR-T cells possess the capability of navigating the T cell specificity towards the antigens by means of fusing the binding domains of antibodies towards T cell CD3-like signaling proteins.[13] CAR-T cell immunotherapy, notably with the use of anti-CD19 CAR-T cells, has been proven to be effective in treating

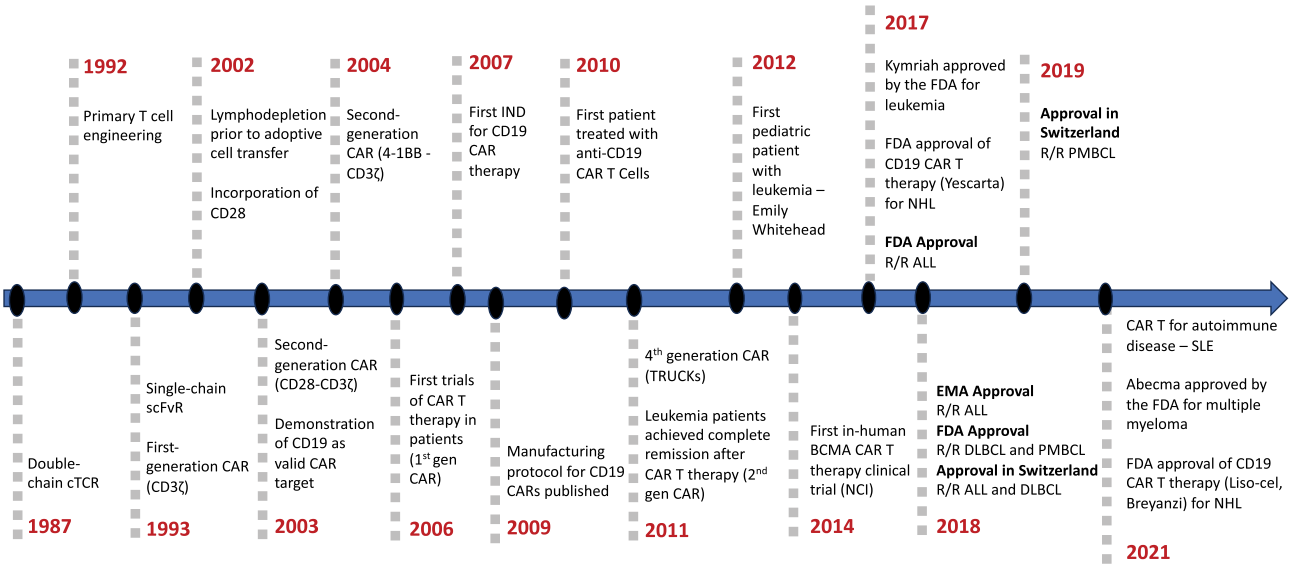

Figure 1 Timeline of the development of CAR-T cell therapies.

various hematological cancers.[14] At present, American and European Drug Agencies (Food and Drugs Administration and European Medicines Agency) have permitted four distinctive CD19-targeting, as well as one BCMA-targeting CAR-T product, respectively.[15,16] These treatments are implemented to cure abnormal B cell malignancies.[17–19]

In the field of leukemia, targeting CD19 was efficacious because of the effortless approachability to cancerous targets as well as the uniform expression of CD19 on the expendable population of B cells. In 2017, US FDA approved Kymriah™ (Tisagenlecleucel) and Tecartus™ (Brexucabtagene autoleucel), the first cell-based therapeutic treatment in the form of CD19-targeted CAR-T cells against B cell malignancies.[20] Despite its terrific attainments in B cell malignancies, the immune-refereed toxicities inside the TME can cause morbidity and mortality, which sublimit the prevalent use of this therapy in solid tumors. One of the barriers is linked through the loss of tumor-associated antigens (TAAs).[21] In 1993, Eshhar described the earliest CARs, which were comprised of scFv joined solitary to the CD3 complex. These "first generation" CAR-T cells proliferated poorly and were unable to facilitate complete tumor remission. Eventually, CAR-T schemes involved the merging of the scFv to a T cell receptor (TCR) domain, CD28 or CD137 Endo domains.[14] An assimilation of costimulatory domains with the CD3ξ signaling tail circumvents the requisite for outward primary and secondary commencement indicators, which begin cytotoxicity and cytokine emission upon T cell engagement.[11,14,21] The finest molecular strategies of the CARs can be accomplished by the virtue of conceivable variability of modular protein domain constituents. Over the period, the evolution in protein engineering of CARs caused significant improvements in its designs with respect to adaptation in the ectodomain, transmembrane domain, linker and hinge regions for better efficacy at treating various cancers.[22]

Despite attaining the beneficial stimulatory effects in the patients of various malignancies, the application of CAR-T therapy could not be achieved in a wider range of treatments due to its associated toxicity, safety issues and obstructed programmability.[23–26] These limitations can be relieved by means of engineering strategies to build better CAR-T cells by implanting array of antigen detection capabilities and engineering adaptor reliant approaches.[25] CAR protein expression can be regulated with the help of protease-based apparatuses. A protease merged to the CAR severs the target spot in cis position to detach a degron. This process brings stability to the structure of a CAR protein, which leads to the ON state of its expression.[27,28] Whereas the presence of the protease inhibitor foils elimination of degron, that initiates CAR degradation and switches OFF the system.[28,29] The CAR protein can be divided into two domains.[21]

To acquire the complete functionality of CAR-T activity, dimerizing remedies are required. Its activity and specificity can be coordinated with the help of diverse protein toggles. For example, the switchable CARs (sCARs) hold a bi-orthogonal tag, like peptide neoepitope (PNE), that can be steered to tumor antigens by supplementing an antigen-binding fragment exclusively for a tumor antigen.[30] The synthetic Notch receptor method involves identification of numerous TAAs to stimulate CAR-T system.[31] The attachment of an antigen causes structural modification in the synNotch receptor that triggers the delivery of transcription factor to initiate expression of another antigen of interest with respect to CAR protein.[32] The inhibitory CAR (iCAR) technique obliges detection of a TAA in the absenteeism of a healthy-tissue antigen to gain necessary CAR-T cell stimulation.[33] Fei et al evaluated a PD-1-founded anti-HLA-DR iCAR, which regulated inhibition of NK cells against HLA-DR expression for various malignancies.[34] Zhang et al reported the development of a novel BAFF-R CAR-T cell product based on single-domain antibody.[35] Bangayan et al developed a dual-inhibitory domain CAR (DiCAR) that integrates two immune cell inhibitory signaling domains to selectively control CAR-T cell cytotoxicity and enhance inhibition effectiveness in comparison to an iCAR containing only a single PD1 domain.[36] The tandem bispecific CARs involve dual extracellular antigen-binding domains.[37] The broad TAA specificity biotinylated epitopes can be targeted with the help of Universal adaptor receptors. Here, distinctive antibodies or the adaptor molecules of antigen-binding system can be dispensed to readdress specificity of CAR-T cell.[38–40]

To elevate the plasticity of CARs, a split, universal, and programmable (SUPRA) CAR method was developed.[41] It constitutes two modules that harbor a universal receptor along with leucine zipper adaptor (zipCAR) expressed on T cells. It also contains a distinct scFv associated with leucine zipper adaptor molecule (zipFv).[42] To enhance the safety aspect of CAR-T cell system, the T cell incidence as well as expression of CAR can be controlled using various methods. The dimerizing drugs elicit downstream signaling pathways to stimulate apoptosis.[43] The truncated epidermal growth factor receptor serves as the suicide tag when expressed simultaneously on the CAR-T cell.[44] Upon administration of antibodies, like cetuximab, the exclusive epitope identifier generates in-house antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) apparatuses to produce CAR-T cell apoptosis.[45] To abolish CAR-T cells, the interruption of

DNA synthesis can be achieved by means of CAR-T cells tagged with herpes simplex virus thymidine kinase (HSV-TK), which possess the capacity of transforming ganciclovir into a cytotoxic molecule.[46,47]

Combination Immunotherapies: Synergizing CAR-T with Checkpoint Inhibitors

Combining CAR-T cell therapy with immune checkpoint inhibitors is being researched in order to improve the efficacy of CAR-T cell treatments and overcome their limitations. Targeting non-solid tumors has proven to be successful for CAR-T cell therapy; however, its efficacy against solid tumors is restricted. Furthermore, questions concerning long-term impacts and safety still exist. Checkpoint inhibitors, including PD-1/PD-L1 blockade, have been approved for use in a variety of solid tumors and have revolutionized the treatment of cancer. While some combinations of checkpoint inhibitors and targeted therapy have shown synergistic effects, not all of these combinations have proven to be effective. Research has demonstrated that the use of checkpoint inhibitors in combination with targeted drugs such as PARP inhibitors, EGFR/HER2 inhibitors, and angiogenesis inhibitors can enhance clinical results. In preclinical models, combining checkpoint inhibitors with CAR-T cell therapy showed potential in improving T cell infiltration and intratumoral performance. Checkpoint inhibitors have demonstrated encouraging preclinical evidence in cancer immunotherapy.[48–50] These inhibitors, such as PD-1/PD-L1 and LAG-3, have been validated as targets in oncology and have shown efficacy in varied tumor types.[51] Small-molecule PD-L1 inhibitors have been developed with a novel mechanism of action, favorable pharmacokinetics, and in vivo efficacy in mice models. Combination therapy with checkpoint inhibitors has been showed to improve antitumor activity when compared to individual blockade of receptors. Preclinical studies show that blocking the interaction between LAG-3 and its ligands can reverse LAG-3-mediated suppression of T cell function. These findings offer a biological rationale for combining LAG-3 inhibitors with other checkpoint inhibitors as an efficient cancer immunotherapy strategy. Additionally, positive results from clinical studies have been observed in patients with advanced cancers seeing better progression-free survival when CAR-T cell therapy and immune checkpoint inhibitors are combined.[52]

The complimentary mechanisms of action of these therapies provide a rationale for this approach. Immune checkpoint inhibitors strengthen the immune system's defense against cancer, while CAR-T cell therapy directly targets cancer cells. Preclinical research has shown the advantages of this combination, such as decreased tumor burden, increased objective response rate, and enhanced long-term protection.[53] NK cells created with CARs have benefits over CAR-T cells in terms of specific killing, cell source, and efficiency against solid tumors.[54] Immune checkpoint inhibitors, which are used in cancer treatment, may influence the function of CAR-NK cell therapy.[55] Furthermore, combining CAR-T cell therapy with immune checkpoint inhibitors has demonstrated promise for boosting CAR-T cell function, antitumor effects, and minimizing toxicity in patients with lymphoid B cell malignancies.[56] Additionally, in metastatic clear cell renal cell carcinoma, the combination of cabozantinib, an inhibitor of the VEGF-VEGFR and Gas6-AXL/TYRO3/MER (TAM) axes, with PD1 inhibitors showed synergistic antitumor activity.[57] Preclinical evidence of their synergistic interaction is driving research into the integrating of immune checkpoint inhibitors and radiotherapy for the treatment of advanced or metastatic solid cancers.

The T cell infiltrates developed during various cancerous stages are capable of determining the diagnosis, the disease progression and the anticipation of clinical response to respective immunotherapies. In this regard, various subsets of T cells such as NKT cells, γδT cells and mucosa-associated invariant T cells (MAITs) have exhibited encouraging results.[58–60] The NKT cell subsets consist of a Type I: Vα14Jα18 invariant TCR α-chain, which identifies the glycosphingolipid α-galactosylceramide (α-GalCer) and correlates via CD1d molecules, and type II: non-α-GalCer molecules. The Type I-NKT cells secret IFN-γ and TNF-α enhance the antitumor effect and modulate the tumor niche.[61] Heczey et al produced anti-GD2 CAR-NK T cells that showcased higher tumor infiltration capacity that regulated better tumor regression response minus dose-limiting toxicities.[62] MAIT, another contender for CAR-T cells, has shown excellent expression of the Vα7.2–Jα33 invariant TCR α-chain that can perfoliate solid tumours.[63] Mikail et al developed anti-Her2 CAR-MAIT that showed higher efficiency against breast tumors and also B cell lymphoma.[64,65] The γδT cell subset is characterized by γδT cell receptors that are not MHC restricted. It holds the potential to cure solid tumor with less graft-

versus-host disease (GvHD) risk. In addition, their capability to direct antigen-independent cytotoxicity restricts the getaway of heterogeneous tumour cells.[66,67]

Checkpoint inhibitors have demonstrated efficacy in many clinical trials when used with standard of care chemotherapy for diverse types of malignancies. Possible synergistic mechanisms include immunogenic tumor cell death, anti-angiogenesis, selective depletion of myeloid immunosuppressive cells, and lymphopenia. Lymphopenia reduces regulatory T cells and generates room for effector T cell growth.[68] However, the complicated tumor microenvironment (TME) and the dearth of preclinical models that can replicate this complexity have made the use of CAR-T cell therapy in solid tumors difficult. Combining CAR-T therapy with checkpoint inhibitors, such γδT cells treatment, may enhance infiltration and efficacy in solid tumors, according to recent preclinical findings.[69] Clinical trials have demonstrated the promise of combining immune checkpoint inhibitors (ICIs) with CAR-T cell treatment. By overcoming immunosuppression and modulating immune responses in the tumor microenvironment, the synergy of CAR-T cells with ICIs can improve the therapeutic outcomes of CAR-T cell therapy.[70] These findings emphasize the combinatorial approach's potential to improve cancer treatment efficacy and serve as a basis for future research and development in this field. Nevertheless, additional investigation is required to maximize the efficacious combination of checkpoint inhibitors and CAR-T cells for cancer therapy.

CAR-T in Solid Tumor Therapy: Progress and Hurdles

CAR-T cell therapy has proven exceptional success in hematological malignancies, but solid tumors present unique obstacles. The immunosuppressive tumor microenvironment (TME), insufficient tumor infiltration, and unreliable tumor-specific antigens are the main barriers.[71–73] Hypoxic cores, aberrant vascularization, and increased reactive oxygen species in solid tumors prevent CAR-T cell trafficking and infiltration.[74,75] Tumor antigens are heterogeneously expressed and present in healthy tissues, making target antigen selection difficult.[76] Additionally, antigen escape, which refers to tumor cells that fail to express the antigen, and heterogeneity resulting from the expression of different tumor-associated antigens (TAAs) in solid cancers serve as challenge. On-target/off-tumor toxicity occurs when antigens are strongly expressed in both healthy cells and tumor cells.[77,78] To address this, researchers are looking into bystander effects, such as antigen spreading, when CAR-T cells activate other CD8 T cells against non-targeted antigens.[79] Innovative models, such as solid tumor-on-chip, have been developing to predict the safety and efficacy of CAR-T cell therapy in clinical settings.[72] In addition to lack of reliable tumor-associated antigens, solid tumors also present challenges such as an immunosuppressive tumor environment and decreased T cell infiltration.[75] The efficacy of CAR-T therapy in solid tumors is restricted by immunosuppressive tumor environments and a deficiency of reliable tumor-associated antigens.[72] The intricate microenvironments of solid tumors prevent CAR-T cells from infiltrating and functioning.[73] In order to address these issues, scientists are investigating into methods like using chemokine receptors to increase the functioning and specificity of CAR-T cells, combining immune checkpoint inhibitors, and developing cost-effective, tumor microenvironment-specific CAR-T cells.[75] Additional immune cells, including macrophages and NK cells, are also being researched as potential alternatives for solid tumor immunotherapy.[74] CAR-T therapy with radiation can also improve the TME and expand CAR-T cells.[80] Moreover, CAR-NK and CAR-M cells may have clinical benefits, including decreased toxicity and better infiltration.[81] Moreover, efforts are being explored to promote tumor infiltration and boost anticancer efficaciousness through the regional administration of CAR-T cells via hydrogel platforms.[71] Despite these efforts, CAR-T cells typically exhibit exhaustion and need combo therapies like PD-1 blocking to persist and anti-tumor activity. CAR-T cell therapy for solid tumors is difficult, but new approaches may make it more effective. Figure 2 depicts a typical image illustrating the obstacles faced by CAR-T cell therapy when targeting solid tumors.

Overcoming the above-mentioned limitations requires discovering reliable tumor-associated antigens as well as developing tumor microenvironment-specific CAR-T cells.[73] Molecular imaging and cell tracking can provide light on the therapeutic hurdles associated with solid tumors while also aiding in the effective delivery of CAR-T cells. Overall, more investigation and development are required to maximize the success of CAR-T cell therapy in treating solid tumors, even though it has demonstrated promise in treating hematological cancers. Furthermore, axicabtagene ciloleucel and tisagenlecleucel, two CAR T-cell therapies for relapsed or refractory B-cell lymphomas, have significantly boosted cure rates.[82] However, real-world application differ greatly from randomized controlled trials (RCTs). RCTs, the gold standard for therapy efficacy evaluation, generally use highly selected patient populations that do not fully represent routine

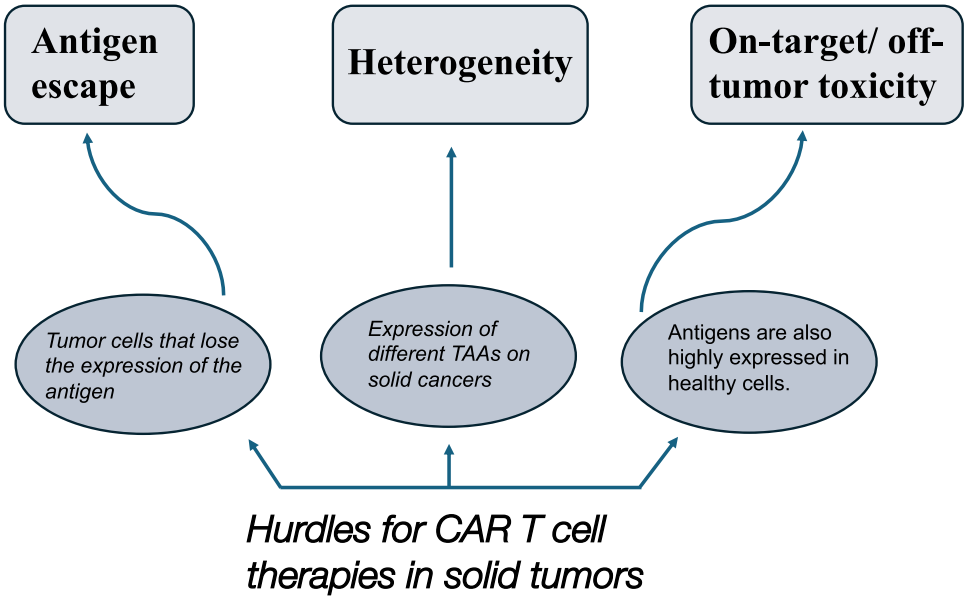

Figure 2 Image illustrating the obstacles faced by CAR-T cell therapy when targeting solid tumors.

clinical practice's more diverse patient demographics.[83,84] For instance, real-world patients are older, have more comorbidities, and have worse functional status than trial participants, which can affect clinical outcomes.[85,86] Real-world evidence (RWE) from electronic health records and disease registries serves to fill this gap by revealing CAR T-cell therapies' safety, effectiveness, and wider application in more heterogeneous populations of patients.[87] Real-world data can validate RCT efficacy, as proven by German claims data resembling CHAARTED trial outcomes in metastatic hormone-sensitive prostate cancer.[88] Moreover, real-world studies have shown the viability and limitations of CAR T-cell therapy in trial-ineligible patients, emphasizing the necessity to address side effects like cytokine release syndrome and neurotoxicity.[89,90] RWE must evolve to evaluate and optimize CAR T-cell therapies to fulfill the demands of a broader population of patients and handle regulatory and economic constraints.[91] Thus, RWE and RCT data must be integrated to improve CAR T-cell therapy and patient outcomes in real-world. Table 1 summarizes the aggregation of clinical trials progress on CAR-T Cell Immunotherapy.

Gene Editing Technologies in CAR-T: CRISPR and Beyond

Gene editing technologies, such as CRISPR-Cas9, have shown potential in improving CAR-T cell therapy by providing targeted modifications to genes for enhanced efficacy and durability.[92–94] Conventional gene editing tools based on nuclease activity, such as CRISPR-Cas9, can cause undesired genomic alterations and genotoxicity. The Pin-point™ base editing technology uses modular RNA aptamers to achieve high editing efficiency and purity at target sites, resulting in reduced chromosomal translocations.[95] CRISPR-based gene editing and screening have enabled the direct genomic manipulation of immune cells, contributing to the discovery of novel factors that reprogram and regulate immune responses.[96] Non-viral CRISPR/Cas9 nano-formulations were developed as well to improve the safety, efficiency, and specificity of cancer gene editing. Furthermore, precision genome engineering techniques like Cas9 RNP-mediated gene editing have been employed to produce PD-1-deficient CAR-T cells, resulting in greater tumor cell killing and improved CAR-T cell immunotherapy efficacy.

However, recent gene editing tools like Base and Prime Editing minimize the risk of harmful events, but their ability to make edits is limited.[97] High-frequency gene editing in primary immune cells, including T cells, has been demonstrated by novel gene-editing systems based on metagenomic data, with insignificant impact on cell viability.[95] CRISPR-Cas9 technology can be applied to engineer allogeneic CAR-T cells, target inhibitors of T lymphocyte function, and maximize the efficacy and safety of CAR-T therapy.[98] These developments in gene editing technology could enhance CAR-T immunotherapy's effectiveness, safety, and accessibility for the treatment of different cancers.

Table 1 Compilation of Clinical Trial Status on CAR-T Cell Immunotherapy (Information Based on Study Records Available on "Clinicaltrials.gov")

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases
NCT02905188	Glypican 3-specific Chimeric Antigen Receptor Expressing T Cells for Hepatocellular Carcinoma (GLYCAR)	COMPLETED	Hepatocellular Carcinoma	• GENETIC: GLYCAR T cells • DRUG: Cytoxan • DRUG: Fludarabine	PHASE1
NCT01865617	Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphoma, or Acute Lymphoblastic Leukemia	COMPLETED	• CD19-Positive Neoplastic Cells Present • Recurrent Adult Acute Lymphoblastic Leukemia • Recurrent Chronic Lymphocytic Leukemia • Recurrent Diffuse Large B-Cell Lymphoma • Recurrent Mantle Cell Lymphoma • Recurrent Non-Hodgkin Lymphoma • Recurrent Small Lymphocytic Lymphoma • Refractory Acute Lymphoblastic Leukemia • Refractory Chronic Lymphocytic Leukemia • Refractory Diffuse Large B-Cell Lymphoma • Refractory Mantle Cell Lymphoma • Refractory Non-Hodgkin Lymphoma • Refractory Small Lymphocytic Lymphoma	BIOLOGICAL: Autologous Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing T Lymphocytes	PHASE1 PHASE2
NCT02107963	A Phase I Trial of T Cells Expressing an Anti-GD2 Chimeric Antigen Receptor in Children and Young Adults With GD2+ Solid Tumors	COMPLETED	• Sarcoma • Osteosarcoma • Neuroblastoma • Melanoma	• BIOLOGICAL: Anti-GD2-CAR engineered T cells • DRUG: AP1903 • DRUG: Cyclophosphamide	PHASE1
NCT03049449	T Cells Expressing a Fully-Human Anti-CD30 Chimeric Antigen Receptor for Treating CD30-Expressing Lymphomas	COMPLETED	• Lymphoma, Large-Cell, Anaplastic • Enteropathy-Associated T-Cell Lymphoma • Lymphoma, Large B-Cell, Diffuse • Lymphoma, Extranodal NK-T-Cell • Lymphoma, T-Cell, Peripheral	• BIOLOGICAL: Anti-Tumor Necrosis Factor (TNF) Receptor Superfamily Member 8 (CD30) Chimeric Antigen Receptor (CAR) T cells • DRUG: Cyclophosphamide • DRUG: Fludarabine	PHASE1

(*Continued*)

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Table 1 (Continued).

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases
NCT00924326	CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma	COMPLETED	• Primary Mediastinal B-cell Lymphoma • Diffuse, Large B-cell Lymphoma • Diffuse Large B-Cell Lymphoma Transformed From Follicular Lymphoma • Mantle Cell	• DRUG: Fludarabine • DRUG: Cyclophosphamide • BIOLOGICAL: Anti-cluster of differentiation 19 (CD19)-CAR PBL • DRUG: Aldesleukin • DRUG: Fludarabine • DRUG: Cyclophosphamide	PHASE1 PHASE2
NCT03483103	Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006)	COMPLETED	• Lymphoma, Non-Hodgkin • Lymphoma, Nonhodgkin • Lymphoma, B-Cell • Lymphoma, Large B-Cell, Diffuse	BIOLOGICAL: lisocabtagene maraleucel	PHASE2
NCT02215967	Study of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma	COMPLETED	• Myeloma, Plasma-Cell • Myeloma-Multiple	• DRUG: Cyclophosphamide • DRUG: Fludarabine • BIOLOGICAL: Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T cells	PHASE1
NCT03958656	T-cells Expressing an Anti-SLAMF7 CAR for Treating Multiple Myeloma	COMPLETED	• Myeloma-Multiple • Myeloma, Plasma-Cell	• DRUG: Cyclophosphamide • DRUG: Fludarabine • DRUG: Rimiducid • BIOLOGICAL: Anti-Signaling lymphocytic activation molecule F7 (SLAMF7) chimeric antigen receptor (CAR) T cells	PHASE1
NCT01475058	CD19 CAR T Cells for B Cell Malignancies After Allogeneic Transplant	COMPLETED	• Philadelphia Chromosome Negative Adult Precursor Acute Lymphoblastic Leukemia • Philadelphia Chromosome Positive Adult Precursor Acute Lymphoblastic Leukemia • Recurrent Adult Acute Lymphoblastic Leukemia • Recurrent Adult Diffuse Large Cell Lymphoma • Recurrent Adult Immunoblastic Large Cell Lymphoma • Recurrent Mantle Cell Lymphoma| Refractory Chronic Lymphocytic Leukemia	BIOLOGICAL: allogeneic cytomegalovirus-specific cytotoxic T lymphocytes	PHASE1 PHASE2

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NCT01593696	Anti-CD19 White Blood Cells for Children and Young Adults With B Cell Leukemia or Lymphoma	COMPLETED	• ALL • B Cell Lymphoma • Leukemia • Large Cell Lymphoma • Non-Hodgkin Lymphoma	BIOLOGICAL: Anti-Cluster of Differentiation (CD)19-Chimeric antigen receptor (CAR)	PHASE1
NCT04026737	Cardiovascular Effects of CART Cell Therapy	COMPLETED	• Leukemia • Lymphoma • Cardiotoxicity • Risk Factor, Cardiovascular • Immunotherapy		
NCT03338972	Immunotherapy With BCMA CAR-T Cells in Treating Patients With BCMA Positive Relapsed or Refractory Multiple Myeloma	COMPLETED	• Recurrent Plasma Cell Myeloma • Refractory Plasma Cell Myeloma	• BIOLOGICAL: Autologous Anti-BCMA-CAR-expressing CD4+/CD8 + T-lymphocytes FCARH143 • DRUG: Cyclophosphamide • DRUG: Fludarabine • PROCEDURE: Leukapheresis	PHASE1
NCT03744676	A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting (TRANSCEND-OUTREACH -007)	COMPLETED	• Lymphoma, Non-Hodgkin • Lymphoma • Lymphoma, B-Cell • Lymphoma, Large B-Cell, Diffuse • Neoplasms • Neoplasms by Histologic Type • Lymphoproliferative Disorders • Lymphatic Diseases • Immunoproliferative Disorders • Immune System Disorder	BIOLOGICAL: lisocabtagene maraleucel	PHASE2
NCT03430011	Study Evaluating the Safety and Efficacy of JCARH125 in Subjects With Relapsed and/or Refractory Multiple Myeloma	COMPLETED	Multiple Myeloma	• BIOLOGICAL: JCARH125 • BIOLOGICAL: JCARH125 + anakinra	PHASE1 PHASE2
NCT01454596	CAR T Cell Receptor Immunotherapy Targeting EGFRvIII for Patients With Malignant Gliomas Expressing EGFRvIII	COMPLETED	• Malignant Glioma • Glioblastoma • Brain Cancer • Gliosarcoma	• BIOLOGICAL: Epidermal growth factor receptor (EGFRv)III Chimeric antigen receptor (CAR) transduced PBL • DRUG: Aldesleukin • DRUG: Fludarabine • DRUG: Cyclophosphamide	PHASE1 PHASE2

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For CAR-T cell therapy, CRISPR-Cas9 technology has several advantages. Effective and controllable genetic modification has become possible, enabling the knockout of genes that inhibit T cell function and the regulation of CAR-T cell activity within the tumor microenvironment.[99,100] Multiple T cell exhaustion pathways can be targeted simultaneously using CRISPR-Cas9, resulting in CAR-T cells with increased effector activity and enhanced tumor cell killing.[101] Furthermore, CRISPR-Cas9 can be applied to effective gene silencing and non-viral gene transfer, minimizing the possibility of genomic rearrangements, and facilitating the development of safer and more potent CAR-T cell therapies.[102,103] However, using CRISPR-Cas9 for CAR-T cell therapy has several drawbacks as well. During the genome editing process, off-target effects, such as unexpected genetic modifications, might happen. The safety and potential long-term repercussions of CRISPR-edited CAR-T cells are called questionable by this. It is imperative to cautiously analyze and tackle these possible limitations to ensure the efficaciousness, safety, and accessibility of CRISPR-edited CAR-T cell therapies.

Biomarkers and Predictive Indicators Associated with Response to CAR-T Cell Therapies

Genetically manipulated allogeneic and autologous CAR-T cell therapy has been one of the most promising immunotherapies for cancer treatment, particularly in hematological malignancies of the current decade. Seven CAR-T cell immunotherapies have been approved by the FDA for treating lymphocytic leukemia, including B cell malignancies and multiple myeloma. Tisagenlecleucel (Kymriah®), an anti-CD19 CAR-T cell therapy, was the first FDA-approved treatment for B cell precursor acute lymphoblastic leukemia patients with evidence of non-response to conventional therapy or who had relapsed more than twice.[104–106] Subsequently, four more axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), lisocabtagene maraleucel (Breyanzi®), and relmacabtagene autoleucel (Relmacel; brand name Carteyva® in China only) CD19-specific CAR-T cell therapies for the treatment of various B cell malignancies were approved. Later, idecabtagene vicleucel (Abecma™) and ciltacabtagene autoleucel (Carvykti®), BCMA-specific CAR-T cell therapies for multiple myeloma, were also approved in February 2022.[105,107–110]

The recent advancements and ongoing improvement of CAR-T therapies arose as a potent method for treating hematological malignancies.[111] The treatment of B-cell acute lymphoblastic leukemia (B-ALL) with CD19 CAR-T cells showed tremendous efficacy, with a complete remission of 70–90%.[18,112] However, several obstacles are still present to hinder the treatment outcomes and utility of CAR-T cell therapy, including life-threatening CAR-T cell-associated toxicities, inhibition and resistance in B cell malignancies, limited efficacy against solid tumors, antigen escape, poor trafficking, limited persistence, infiltration, and the immunosuppressive microenvironment. Biomarkers could play a prime role in personalized cancer care regarding the prediction of CAR-T-related toxicity, efficacy, and relapse of CAR-T therapy. It is crucial to prioritize the development of new biomarkers and the validation of current ones in order to incorporate them into cancer care practice. In order to make CAR-T cell treatment more widely available to a larger number of patients, it is crucial to speed up the clinical implementation of modified CAR-T products and personalized management strategies.

Predictive Biomarkers for Therapeutic Response in CAR-T Cell Therapy

The principal goal of cancer treatment is the overall survival (OS) and event-free survival (EFS) of patients. There is an urgent need for feasible predictive biomarkers for long-term and short-term CAR-T therapy outcomes. Several studies reported that patients' baseline characteristics, T cell functionality of constructed CAR-T cells, and minimal residual diseases post-CAR-T therapy could be strongly associated with therapeutic response. Prior to CAR-T therapy, various patient-related factors, including gender, age, treatment history, p53 status, tumor burden, immunoglobulin heavy chain variable region gene IGH variable (IGHV) mutation status, and chromosome 17p deletions, were found to have no significant correlation with the response to CAR-T cell therapy.[17,113–115] Some studies have found no direct effect of these factors on therapeutic outcomes, whereas others imply potential indirect effects or within specific subgroups. TP53 mutations are linked to poor prognosis and therapy resistance in lymphomas such as DLBCL and B-ALL.[116,117] In DLBCL, TP53 mutations were associated with inferior complete response (CR) and overall survival (OS) rates, suggesting that TP53 status could be a useful biomarker for CAR-T risk stratification.[118] In another study, TP53 mutation status did not significantly affect outcomes in DLBCL patients treated with CAR-T cells, emphasizing the need for bigger

cohort validation.[119] Age and gender also have conflicting results. Some studies reported no significant impact on leukemia-free survival (LFS) and OS in B-ALL patients treated with CAR-T cells, while others suggested that older age could be associated with less favorable outcomes due to higher toxicity and lesser efficacy.[120,121] For high tumor burden patients, dose fractionation of CAR-T cells is recommended to reduce toxicity, indirectly suggesting that patient-specific factors like tumor burden may affect therapeutic outcomes.[122] CAR-T cell kinetics, which vary by patient and tumor type, may also affect therapeutic efficacy and toxicity.[123] Thus, a more nuanced discussion that takes into account these contradicting evidences would provide a balanced view, noting that some patient-related factors may not have a direct correlation but may still affect CAR-T therapy outcomes in specific contexts or subgroups.

Elevated levels of serum LDH (lactate dehydrogenase) have been observed in cancer patients; this could be associated with high tumor burden, proliferation in B cell malignancies, and disease progression. The increased serum LDH levels were correlated with a poor prognosis and a negative therapeutic outcome in most cancer patients.[124] Serum LDH levels in CAR-T therapy could be a potentially negative prognostic biomarker in cancer. An investigation conducted on adult patients with B-ALL indicated that a decreased pre-lymphodepletion LDH level and an elevated platelet count were distinct factors linked to improved EFS. Furthermore, it has been proposed that patients exhibiting elevated pre-lymphodepletion LDH levels and a decreased platelet count may necessitate systemic treatment prior to CAR-T cell infusion. However, LDH levels are not directly linked to the immune system, making them less promising for predictive biomarkers for CAR-T therapy responses.[125] In non-small cell lung cancer (NSCLC) and large B cell lymphoma, serum LDH levels have been associated with treatment response and overall survival.[126,127] In CAR T cell therapy, LDH levels are critical to assessing treatment response, although they have limited effect on the immune system.[128] Combining LDH levels with additional biomarkers like carcinoembryonic antigen (CEA) can help predict clinical outcomes and guide treatment decisions in CAR T cell therapy patients.[129] Routine monitoring of LDH levels can improve early therapy response assessment and patient outcomes in immune-related therapies like CAR T cell therapy. It was observed that elevated CRP at baseline was associated with poor treatment outcomes of CAR-T therapy, and the presence of circulating tumor DNA (ctDNA) in peripheral blood samples at the first week of CAR-T infusion was also correlated with poor response to CAR-T therapy. Both baseline CRP and the presence of ctDNA during the initial stage of CAR-T cell therapy could be reliable predictive biomarkers for CAR-T therapy response.[130,131] A study conducted in B-ALL and B cell non-Hodgkin lymphoma (NHL) patients with CAR19/22-T cell therapy reported that macrophage inflammatory protein (MIP)-3α is a highly sensitive and specific prognostic predictor for non-response (NR) and early relapse (ER) to therapies. Extensive clinical validation of biomarkers like CD19 has led to their successful use in CAR T-cell therapies for B-cell malignancies.[132] GPC3 and TGF-b have been quantified using advanced image analysis in preclinical models and demonstrate high correlation with pathologist assessment, suggesting a robust preclinical validation stage.[133] CAR T-cell detection and quantification technologies including flow cytometry and quantitative PCR are well-established, but study application varies, affecting comparability and reproducibility.[134] Despite advances like droplet digital PCR, NanoString, and single-cell RNA sequencing, detection timepoint and frequency remain a challenge.[134,135] Reproducibility across studies and clinical trials requires standardized reporting and validation protocols.[136,137] In addition, molecular assays and imaging technologies for in vivo CAR T-cell tracking and visualization are improving, but they need thorough validation to prove their clinical utility.[138] Some biomarkers and detection technologies are well-validated, but others are still in preclinical or early clinical trials, requiring more research to demonstrate their reliability and reproducibility.

Patients with higher MIP3α levels after sequential CAR19/22 T cell infusion had much better progression-free survival (PFS) outcomes than patients with lower MIP3α levels. This study suggested that MIP3α could be a promising prognostic biomarker for the post-CAR-T therapy treatment response in terms of a prognostic predictor for NR/ER to therapies.[139] Researchers had reported that the epigenetic characteristics of leukemia cells, such as hypermethylation of DNA, a stem cell-like phenotype and inherent plasticity, and decreased antigen presentation, were independent of CD19 status, and the leukemia subtype could be playing a crucial role in developing resistance to CAR-T therapy in AL patients. Moreover, the epigenetic status of leukemia cells may be used as a potential early predictive biomarker for resistance to CAR-T cell therapy.[140,141] It was observed that significantly higher numbers of "exhausted" T cells (differentiated CD3+CD27-CD28-T cells) in lymphoma patients were associated with a low response to CAR-T cell therapy. Therefore, the low frequency of "exhausted" T at leukapheresis could be a potential pre-infusion predictive

biomarker for the responsiveness of CAR-T cell therapy.[142] In solid tumors, exhausted T cells with inhibitory receptors such as PD-1, LAG-3, and TIM-3 prevent CAR-T cell therapy. These markers are associated with reduced proliferative capacity, impaired anti-tumor activity, and attenuated persistence of CAR-T cells.[143] Chronic antigen stimulation and the immunosuppressive tumor microenvironment (TME) cause substantial transcriptional, epigenetic, and metabolic reprogramming, exhausting T cells.[144,145] For instance, PD-1, LAG-3, and TIM-3 are highly expressed in tumor-infiltrating lymphocytes (TILs) and are linked to T-cell activation, but also with a proapoptosis, suggesting a complicated interplay between exhaustion and activation.[146] To alleviate T-cell exhaustion, numerous therapies have been explored. Immune checkpoint blockade (ICB) targeting these inhibitory receptors has showed promise in reinvigorating exhausted T cells, however not all patients respond durably.[147] Cytokine therapy and metabolic pathway modifications targeting the TME are also being investigated to improve CAR-T cell efficacy.[148] Regulatory T cells (Tregs) also show exhaustion-like phenotypes under persistent stimulation, which may restrict their therapeutic potential in autoimmunity and transplantation. This suggests that comparable mechanisms may be at play across different T cell subsets.[149] A unified exhaustion definition incorporating metabolic, epigenetic, transcriptional, and activation-based markers (M.E.T.A.) could improve understanding and improve targeted interventions. T-cell exhaustion can be addressed by ICB, metabolic reprogramming, and TME regulation to improve cancer CAR-T cell therapy outcomes.[146]

CAR-T cell therapies' efficacy and safety depend on epigenetic modifications that affect T-cell differentiation, exhaustion, and tumor infiltration. Cancer stem cells (CSCs) promote their initiation and maintenance by aberrant epigenetic reprogramming, allowing them to evade immune defenses and resist therapies. Targeting these epigenetic modifications can improve CAR-T therapy outcomes.[150] Integrating omics technologies like epigenomics has helped discover tumor-specific antigens and molecular characteristics linked with CAR-T cell therapy's anti-tumor effects and toxicity.[151] CAR-T cells' in vivo performance is affected by epigenetic regulation, which may improve memory phenotype, trafficking, and fitness, leading to more effective immunotherapies.[152] Modulating epigenetic factors such as DNA methylation, histone modification, and chromatin remodeling may improve CAR-T therapy's safety and efficacy.[35] Epigenetic modifications could improve targeting mechanisms for CAR-T therapies in hematologic malignancies, reducing side effects and off-target effects.[153] Understanding epigenomic events within the tumor immune microenvironment (TIME) is essential for exploiting epigenetic modification reversibility for cancer diagnosis, progression tracking, and treatment.[154] CAR-T therapy combined with other treatments, such as radiation, may benefit from epigenetic insights to overcome solid tumor therapeutic limits.[155] Overall, epigenetic biomarkers have the potential to improve CAR-T therapy's predictive and therapeutic efficiency, making them a promising research and clinical application.

Biomarkers for CAR-T Cell Functionality

The study found that the specific characteristics of T cells, including the presence of immune checkpoints like TIM-3, PD-1, and LAG-3, as well as the immune microenvironment, can affect the effectiveness and behavior of CAR-T cells in fighting tumors. However, the proper functions of CAR-T cells are essential for their effective therapeutic response and durable remission.[129,156] Numerous previous studies have reflected that the less differentiated T cells were strongly correlated with the expansion, persistence, and tumor-killing ability of CAR-T cells.[114,157] A mouse model study on B-ALL revealed that the functionally modified CAR-T product with CD8+ Tscm cells is more effective in terms of prolonged antitumor activity and survival.[158] It was also suggested that the number of CD8+CD45RA+CCR7+ Tscm cells in CAR-T cell products was linked to the speed at which CAR-T cells grew.[159] Furthermore, in vivo investigations indicated that the presence of Tscm cells in the final CAR-T cell product was a favorable indicator for the expansion of CAR-T cells. Conversely, the presence of Tem cells and CD57+ cells in the final product had a detrimental effect on CAR-T cell proliferation and the effectiveness of anti-tumor activity.[160]

Biomarkers for Immune Checkpoints

It was also observed that the high-level expression of immune checkpoint proteins such as LAG-3, PD-1, and T cell immunoglobulin-3 (TIM-3) was associated with T cell exhaustion and could be associated with a lower response to anti-CD19 and CAR-T cell therapies.[19] PD-1 expression on activated T cells, NK cells, and B cells can inhibit the growth of

T cells, the production of cytokines, and the cytotoxicity that could result in tumor cells evading the immune system.[161] Similarly, TIM-3 and LAG-3 have a role in exerting negative regulation on T cell activation.[162] A study indicated that the dysfunctional response group had a considerably larger number of LAG-3+ T cells and TIM-3+ T cells compared to the functional response group. However, both groups had equal frequencies of PD-1+ CD4+ CAR-T cells and PD-1+ CD8+ CAR-T cells. Higher numbers of PD-1+ CD4+ T cells and PD-1+LAG-3+ CD8+T cells were seen in the group with trouble responding. Moreover, the findings also revealed that more expression of LAG-3 together with low secretion of TNF-α was correlated with early therapeutic failure, and the low frequency of TNF-α+/TIM-3-CD8+ T cells in CD19 CAR-T cell products may be a risk factor for low persistence of CAR-T cells and early relapse.[140] So, having too much PD-1, LAG-3, and TIM-3 on immune cells could be a way to tell early on how well a CAR-T treatment will work.

Biomarkers for the Immune Microenvironment

The suppressive immune microenvironment status could be unfavourable for T cell function and associated with inferior survival. The activated myeloid and lymphoid lineages of immune cells can indicate a lower immune-suppressed environment, which could be suitable for the expansion and persistence of CAR-T cells. A study observed that the B cell lymphoma patients treated with CD19 CAR-T cells had low monocytic myeloid-derived suppressor cell counts (CD14+ CD33+ HLA-DR cells) and showed a better response. Also, patients who had more expression of myeloid activation markers (IL-12, DC-Lamp) and lymphocyte effector markers (Fas ligand, TRAIL) had a longer overall survival.[163] Furthermore, polyfunctional T cells produce cytokines and chemokines such as IFN-γ, MIP-1, IL-8, granzyme-B, IL-17A, and IL-5, which can reduce immunosuppression caused by the tumor microenvironment and could enhance clinical outcomes in CD19 CAR-T cell therapy. The increased serum levels of IL-15, MCP-1, and IL-7, which are associated with CAR-T cell expansion, could also impact the positive outcome of CD19 CAR-T cells.[164,165] IL-12 is produced by immune cells (T cells, NK cells, dendritic cells, and macrophages), which induces the secretion of several inflammatory cytokines, including IL-6, IL-8, IL-15, IL-18, IFN-ϒ, TNF-α, and GM-CSF. It also increases the cytotoxic functions of T cells and NK cells.[166] Similarly, IL-18, which activates monocytes and lymphocytes, could enhance the antitumor activity of CAR-T cells as well as decrease the number of immunosuppressive cells.[167–169]

Future Prospects and Challenges

The potential of CAR-T cell-based gene therapies to transform cancer treatment is highly promising. Although CAR-T cell therapy has achieved significant success in treating hematological malignancies, there are still difficulties and opportunities that need to be addressed. Comprehending the immunological characteristics and surroundings of solid tumors is essential for enhancing the effectiveness of immunotherapies. Furthermore, improvements in the accuracy and selectivity of CAR-T cell identification by flow cytometry and PCR are crucial for boosting the accuracy and surveillance of CAR-T cell treatment. CAR-T therapy has revolutionized cancer treatment, especially for hematologic malignancies, although it presents technological and logistical obstacles. Antigen escape, when tumor cells evade the target antigen, and the immunosuppressive tumor microenvironment, which reduces CAR-T cell efficacy in solid tumors, are technical hurdles.[170–172] Technical challenges include improving CAR-T cell persistence and overcoming drug-resistant relapse.[173,174] The necessity for specialist institutes with excellent processes and the high expense and complexity of producing patient-specific CAR-T cells limit accessibility.[175–177] Different national and supranational interpretations of CAR-T products, as shown in the Russian Federation, exacerbate regulatory issues.[178] Technical solutions like engineering CAR-T cells to better infiltrate tumors and resist immunosuppressive environments and logistical solutions like decentralized manufacturing models and regulatory harmonization to reduce costs and improve access are needed to address these issues.[179] As required by the European Medicines Agency, CAR-T cell efficacy and safety must be monitored over time. By systematically addressing these obstacles, CAR-T therapy can be made more effective and accessible to more patients.

Ensuring broader accessibility and affordability of novel cellular and immunotherapy treatments requires careful consideration of quality, cost, and access during their delivery. Optimizing the safety and tolerability of CAR-T cell therapy requires the careful management of adverse effects, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. The relapse mechanism and treatment method following CAR-T cell therapy in B cell hematological malignancies are currently being actively researched. The goal is to tackle the obstacles of disease recurrence and improve

therapeutic techniques. In addition, the investigation of several categories of T cells, such as memory cells and effector cells, along with the development of advanced CAR-T immunotherapy, presents potential avenues for improving the effectiveness and long-lasting effects of CAR-T cell treatment. The advancement of immunotherapy, specifically the production of CD8+ T cells from hematopoietic stem cells, is a notable achievement in cellular immunotherapy. This has the potential to broaden the scope of these treatments, making them more applicable. The critical focus lies in surmounting challenges and applying coping mechanisms for CAR-T cell immunotherapy in solid tumors. This endeavor holds substantial potential for expanding the advantages of CAR-T cell therapy to a wider array of cancer types. Ensuring the long-term effectiveness of CAR-T cell therapy relies on the persistence and development of memory cells. CAR-T cell therapy has been successful in treating hematological malignancies such B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma, earning FDA approval.[72,180,181] Its efficacy in solid tumors is restricted by the lack of reliable tumor-specific antigens, poor T-cell infiltration, and immunosuppressive tumor microenvironments.[73,182,183] Antigen escape, T-cell exhaustion, and severe toxicities such cytokine release syndrome and neurotoxicity hamper CAR-T cell therapy's use.[184–186] Using bi-specific chimeric antigen receptors, immune checkpoint inhibitors, and immuno-PET/-SPECT for better monitoring and optimization are among the innovative ways to improve CAR-T cell efficacy.[187] CAR-Treg therapies for autoimmune disorders and CAR-T cell applications beyond oncology suggest a promising future for this technology. However, the high cost and complexity of CAR-T cell manufacture require cost-effective production methods and improved clinical application approaches. The future for CAR-T cell therapy is optimistic, but these complex issues must be addressed to maximize its potential across cancer types and other diseases. Thus, CAR-T cell therapy has considerable potential, but its efficacy and future applications should be examined in light of its existing limits and ongoing advances. Ongoing research endeavors to tackle these obstacles and enhance the durability of CAR-T cell therapy. Moreover, comprehending the role of tumor cell dedifferentiation in promoting immune evasion and immunotherapy resistance offers valuable knowledge for developing strategies to overcome resistance mechanisms and improve treatment results. The engineering of CAR-T cells for the treatment of solid tumors and the advancement of immunotherapies that activate T cells demonstrate the ongoing progress of CAR-T cell technology and its ability to fulfill medical demands that have not been met in cancer treatment. Utilizing combinatorial methods to enhance the effectiveness of CAR-T cell therapy in hematological malignancies, along with investigating single-cell imaging of T cell immunotherapy responses in living organisms, are novel strategies aimed at further improving the efficacy of CAR-T cell therapy. CAR-T cell therapy has revolutionized the course of therapy of hematological malignancies by targeting CD-19 and B-cell maturation antigens in B-cell acute lymphoblastic leukemia and large B-cell lymphoma.[72,73] Extending this achievement to solid tumors is difficult. The TME of solid tumors is complicated and immunosuppressive, with dense extracellular matrices, hypoxic cores, and inhibitory cytokines that impede CAR-T cell infiltration and function.[74,75,188] CAR-T cells' efficacy in solid tumors is further complicated by tumor antigen heterogeneity and antigen escape.[189–191] To overcome these obstacles, researchers are augmenting CAR-T cells with chemokine receptors, combining CAR-T therapy with immune checkpoint inhibitors, and establishing dual-target CARs to enhance specificity and limit off-target effects.[192,193] Alternative immune cells such CAR-NK and CAR-M cells are being studied for tumor infiltration and decreased toxicity. Advanced methods like single-cell RNA sequencing and artificial intelligence are identifying solid tumor biomarkers to refine CAR-T cell design and predict therapy responses. Despite these advances, multicenter clinical trials are needed to confirm the efficacy and safety of combinatorial and novel solid tumor treatments. In solid tumors, CAR-T cell therapy poses considerable challenges, although ongoing research and technical improvements may improve patient outcomes.

Overall, the future outlook for CAR-T cell-based gene therapies is marked by continuous progress in comprehending the tumor microenvironment, enhancing methods for detection and monitoring, mitigating side effects, optimizing treatment approaches, and broadening the scope of cellular immunotherapy. These combined efforts contribute to the ongoing development and improvement of CAR-T cell therapy, leading to its wider and more efficient use in treating different types of cancer.

Conclusions

To summarize, CAR-T cell therapy has emerged as a viable treatment method for hematological malignancies, specifically B cell malignancies. In addition, CAR-T cell-based gene therapies are an innovative method in the field of cancer treatment, providing new opportunities for patients with resistant or recurring malignancies. Despite the presence

of obstacles such as adverse events and prognostic heterogeneity, the distinctiveness and strength of CAR-T cells have demonstrated notable therapeutic efficacy. Continuous research and clinical trials are crucial in advancing the field of CAR-T cell therapies. These efforts aim to enhance the effectiveness and widen the range of cancer treatments, ultimately leading to improved outcomes. CAR-T cell therapy is a sort of gene therapy that is a major breakthrough in the industry. It provides new optimism for patients with hematological malignancies that are resistant to treatment or have relapsed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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