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CAR-T Cell Therapy: Advances in Kidney-Related Diseases

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Keywords
Chimeric antigen receptor T · Renal malignancies · Multiple myeloma · Systemic lupus erythematosus · Acquired immunodeficiency syndrome

Abstract
Background: Chimeric antigen receptor (CAR)-T cell therapy represents a significant advancement in the field of immunotherapy, providing targeted eradication of abnormal cells through the recognition between CAR and target antigens. This approach has garnered considerable attention due to its promising results in the clinical treatment of hematological malignancies and autoimmune diseases. As the focus shifts toward exploring novel targets and expanding the application of CAR-T cell therapy to solid tumors, including renal malignancies, researchers are pushing the boundaries of this innovative treatment. However, it is crucial to address the observed comorbidities associated with CAR-T cell therapy, particularly nephrotoxicity, due to the superseding release of cytokines and impairment of normal tissue. ***Summary:*** Our review discusses the research strategies and nephrotoxicity related to CAR-T cell therapy in various kidney-related diseases and provides insights into enhancing investigation and optimization. ***Key Messages:*** CAR-T cell therapy has captured the attention of researchers and clinicians in the treatment of renal malignancies, multiple myeloma, systemic lupus erythematosus, and acquired immunodeficiency syndrome, which may lead to potential nephrotoxicity as they involve primary or secondary kidney complications. Understanding and summarizing the current research progress of CAR-T cell therapies can provide valuable insights into novel targets and combinations to optimize research models and enhance their clinical value.

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Introduction

Chimeric antigen receptor (CAR)-T cell therapy is a novel immunotherapy method that was genetically engineered to express antigen-specific, non-major histocompatibility complex (MHC)-restricted receptors on their membranes [1]. Until now, four generations of CAR-T have been established, each of which was composed of four different domains: (1) an extracellular single-chain antibody fragment (scFv) representing the antigen-binding region; (2) a hinge domain linked to a (3) transmembrane region;

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Table 1. The main clinical trial of CAR-T cell therapy in kidney-related diseases

Diseases	Target	Clinical trial	Phase	Enrolled patients (CAR-T infused patients)	Response	Toxicities (≥ grade 3)	Median follow-up, months
RCC	CAIX	NA	I	12 (12)	No response obtained	Liver enzyme disturbances 33.3%	9.5
	CD70	NCT04696731	I	19 (18)	ORR: 17%; DCR: 89%	CRS: 100% (5%); ICNAS: 18% (0%)	8
RRMM	BCMA	NCT03651128	III	254 (225)	ORR: 71%; CRR: 39%	CRS: 88% (5%); NE: 15% (3%)	18.6
	BCMA	NCT03548207	Ib/II	113 (97)	ORR: 97.9%; CRR: 82.5%	CRS: 95% (4%); NE: 21% (9%)	27.7
SLE	CD19	Compassionate-use program	\	7 (5)	DFR: 100%	CRS: 60% (none); NE: none	8
AIDS	HIV envelope glycoprotein	NCT03240328	I	13 (13)	ORR: 71%; CRR: 42%	CRS: 95% (4%); NE: 21% (11%)	7

CAR-T, chimeric antigen receptor T; RCC, renal cell carcinoma; CAIX, carbonic anhydrase IX; ORR, objective response rate/overall response rate; DCR, disease control rate; CRR, complete response rate; DFR, drug-free remission; CRS, cytokine release syndrome; NE, neurotoxicity; CD70, cluster of differentiation 70; RRMM, refractory or relapsed multiple myeloma; BCMA, B-cell maturation antigen; SLE, systemic lupus erythematosus; CD19, cluster of differentiation 19; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; NA: not available.

and (4) an intracellular domain composed of the signal transduction part (consisting of the cluster of differentiation [CD] 3 linked with one or two costimulatory domains in second or fourth CAR generations). Not surprisingly, the astounding results in terms of responses demonstrated by this strategy against hematological malignancies, such as acute B-lymphoblastic leukemia and B-cell lymphoma, have turned the clinician's attention toward solid tumors [2–6].

Kidney and renal pelvic malignancies are the sixth and ninth most common tumors in males and females globally, respectively, and renal cell carcinoma (RCC) is one of the most prevalent types [7]. The prognosis for advanced RCC remains unsatisfactory, and conventional chemotherapies rarely work [8]. Novel therapies for treating advanced or metastatic RCC, including immunotherapeutic agents (e.g., anti-programmed cell death protein 1 antibody) and immunotherapy-based combination strategies, also have low clinical complete response rates [9–13]. Excitingly, numerous studies have confirmed the efficacy of CAR-T cell therapy on several solid tumors including renal malignancies which stimulates further investigation [14–17].

Furthermore, some diseases characterized by abnormal immune cell groups or autoimmune dysfunction, such as multiple myeloma (MM), systemic lupus erythematosus (SLE), and acquired immunodeficiency syndrome (AIDS), may lead to renal function impairment through the deposition of monoclonal immunoglobulin, serum-free light chain, or immune complex in the renal unit. Interestingly, the development of numerous medications based on immunological techniques has been considerably attributed to the improvement of symptoms and prognosis in the corresponding patients, and CAR-T cell therapy is being attempted and has shown tremendous potential [18–20].

To better assess CAR-T's potential in treating kidney-related diseases, we briefly summarized the main clinical trials in Table 1 and the research progress of CAR-T cell therapy in renal malignancies and three common diseases involving the kidney (shown in Fig. 1).

CAR-T Cell Therapy in Renal Malignancies

The first CAR-T clinical study on RCC in 2003 sparked researchers' interest in CAR-T cell therapy for renal malignancies. However, owing to the lack of intracellular costimulatory domain and the murine-derived scFv in the first-generation CAR-T, it exhibited poor tumor clearance ability in patients with metastatic RCC and amplification, and CAR continued to be defective in vivo due to the auto-immunity against CAR-T cells. Moreover, all 3 patients appeared to have off-target toxicity such as liver enzyme disturbance

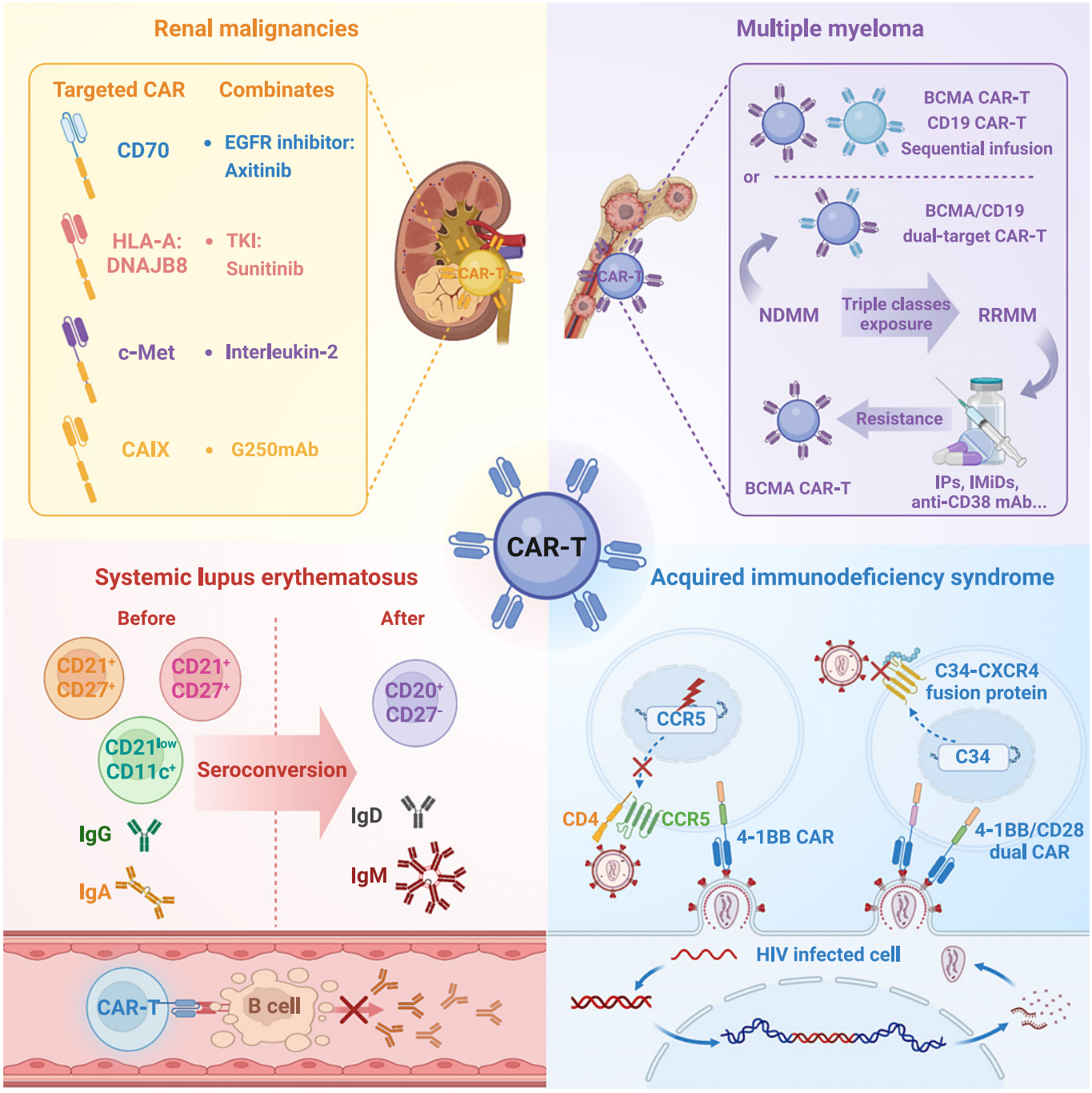

Fig. 1. Research progress of CAR-T cell therapy in renal malignancies, MM, SLE, and AIDS.

because of carboxy-anhydrase-IX (CAIX) expression in the hepatic bile duct, but there was no hepatotoxicity in patients pretreated with G250-monoclonal antibody (mAb) which recognizes CAIX epitopes [21]. Notwithstanding that, physicians did not give up on optimizing CAR-T cell therapy to eradicate renal malignancies and made great efforts and approaches to the investigation of the reliable target of renal malignancies. In 2014, Lo et al. [22] constructed a humanized second-generation CAR-T targeting CAIX that exhibited potent anti-tumor effects on CAIX-positive RCC and improved efficacy in combination with interleukin (IL)-2 in vitro

and a nude mouse model, including significant cytotoxicity, cytokine secretion, and clonal expansion capabilities, partially attributable to the up-regulation of anti-apoptotic proteins like cellular FLICE-like inhibitory protein (cFLIP), B-cell lymphoma-extra-large (BCL-xL), etc., compared to the first-generation. It suggests that modification of these genes could be used to enhance CAR-T function. In addition, the combination of CAR-T and standard therapies used in clinical treatment has been proposed and validated to improve its efficacy. Li et al. [23] established an anti-CAIX second-generation CAR-T and combinate tyrosine kinase inhibitor (TKI) (i.e., sunitinib) to eradicate the RCC cells in vitro and in vivo; the combination of sunitinib further promoted the proliferation and tumor infiltration of CAR-T cells and reduced the number of myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment (TME). Besides, the study of Mori et al. [24] indicated that anti-mesenchymal-epithelial transition factor (c-Met) CAR-T cells showed a significant killing effect and antigen specificity in a mouse model of in situ renal papillary carcinoma, and combined with Axitinib, a multi-target inhibitor such as vascular endothelial growth factor (VEGF), further enhanced the tumor clearance ability of CAR-T, especially for low reinfusion doses. However, due to the xenograft mouse models used in these studies lacking an intact immune system, a more realistic and comprehensive assessment of the impact of other immune cells in TME on CAR-T efficacy is absent.

Unfortunately, the most current antigens reported in solid tumors are also expressed at a low level in normal tissues which can cause severe on-target/off-tumor toxicities when applying CAR-T cell therapy [25]. In particular, using human leukocyte antigen (HLA)-antigen peptide complexes as CAR-T targets has led to a significant increase in the potential selection of cell-specific antigens for renal malignancies. DNAJB8 (i.e., heat shock protein Hsp40 chaperone family, subfamily B, member 8 protein) is one of the characteristic markers of tumor stem cells, but it is not expressed on the normal cell surface. Therefore, Watanabe et al. [26] screened HLA-A which could present JB8 antigenic peptide, and proposed that CAR-T cells with targeted recognition of antigenic peptide complex could play a targeted killing role in renal tumor cells. Interestingly, the anti-HLA-A: DNAJB8 antigenic peptide complex B10-CAR T showed efficacy in eradicating RCC and osteosarcoma cells in vitro and in vivo. Moreover, CD70 is highly expressed in RCC and is considered another novel specific marker for renal carcinoma. Mak et al. [16] successfully constructed an anti-CD70 CAR-T and ulteriorly verified its ability of tumor eradication (such as cell activation and cytotoxicity) in vitro and a patient-derived xenograft mouse model [16, 27]. More recently, Allogen Therapeutics, Inc. announced the results of a phase I clinical trial of its allogeneic anti-CD70 CAR-T product, ALLO-316, at the 2023 annual meeting of the American Association of Cancer Research (AACR). The ongoing phase I TRAVERSE study enrolls 10 patients with advanced or metastatic RCC who progress despite having received standard treatment including immune checkpoint inhibitors and VEGF-targeting therapies (NCT04696731). Results showed that the objective response and disease control rates reached 30% and 100%, respectively. In terms of safety, all 10 patient cytokine release syndromes (CRSs) occurred in low grade, except for one case of grade 3, and no cases of immune effector cell-associated neurotoxic syndrome (ICANS) and graft-versus-host disease (GvHD) have been reported. These results provide a rich basis for the subsequent clinical application of CAR-T cell therapy in the treatment of renal malignancies.

CAR-T Cell Therapy in Broader Diseases with Kidney Involvement

CAR-T Cell Therapy in MM

MM is one of the most common hematological malignancies, often occurring in the elderly. It is characterized by abnormal cloned plasma cells in the bone marrow, which is often accompanied by kidney impairment by the deposition of serum-free light chain in the kidney and remains a poor prognosis [28]. Although the standardized regimen and numerous new drugs (e.g., proteasome inhibitors [IPs], immunomodulatory drugs [IMiDs], antibody-drug conjugators [ADCs], and anti-CD38 monoclonal antibodies) have been established and approved for the treatment of MM, the optimal response rate remains restricted and disease relapse is inevitable. To further improve the outcomes of patients with refractory or relapsed MM (RRMM), CAR-T cell therapy has emerged as a transformative new therapy with the potential for long-term disease control.

Until now, a piece of studies has demonstrated the excellent potential of anti-B-cell maturation antigen (BCMA) CAR-T in RRMM patient treatment, and three products have been approved for marketing worldwide (i.e., idecabtagene vicleucel [idel-cel], ciltacabtagene autoleucel [cilta-cel], equecabtagene autoleucel [equ-cel]). According to the latest results of the phase III clinical trial

of ide-cel in RRMM (NCT03651128), 254 and 132 patients were integrated into ide-cel and standard of care (SOC) groups, respectively. At a median follow-up of 18.6 months, the median progression-free survival (PFS) of the ide-cel group reached 13.3 months, compared with 4.4 months for the SOC group. Moreover, the overall response rate (ORR) and complete response rate (CRR) occurred in 71% and 39% of patients who received ide-cel infusion, while only 42% and 5% of those in the SOC group, respectively. At the same time, 88% and 15% of patients who were reinfused with anti-BCMA CAR-T observed CRS and neurotoxicity, and only 5% and 3% had an event of grade 3 or higher [29]. Moreover, at the median follow-up of 12.4 months, the phase Ib/II clinical trial data of cilta-cel (NCT03548207) achieved 97% and 67% of ORR and CRR, which exhibited manageable side effects of CRS and neurotoxicity in 95% (4% were grade 3 or higher) and 21% (9% were grade 3 or higher), respectively [5]. Recently, the updated results of the 2-year follow-up of RRMM patients who received cilta-cel also showed significant efficacy and manageability of anti-BCMA CAR-T [30]. At a median follow-up of 27.7 months, patients who were infused with cilta-cel showed 97.9% and 82.5% of ORR and CRR, respectively. Indeed, the 27-month PFS and overall survival (OS) rates reached 54.9% and 70.4%, while the PFS and OS were shorter in patients with high-risk cytogenetics, high tumor burden, and plasmacytomas. Therefore, clinicians need to further summarize these latest clinical trial data to guide the graded management of possible serious side effects and optimize prognosis after CAR-T cell therapy in MM patients.

Although crucial clinical trials have stringent eligibility criteria for RRMM patients, real-world patients often have more complicated illnesses and comorbidities. In real-life practice, a retrospective multicenter observational study assessed the effectiveness and safety of ide-cel in patients with RRMM (n = 196). Among 159 patients whose efficacy could be assessed, 28% of patients had organ dysfunction, including renal insufficiency (i.e., creatinine clearance <45 mL/min). The best ORR and CRR were 84% and 42% in all cohorts, respectively. Only 3% and 6% of patients developed severe CRS and ICANS. Also, at a median follow-up of 6.1 months, the median PFS and OS were 8.5 months and 12.5 months, respectively [31]. Thus, CAR-T treatment of RRMM patients in the real world also has effective clinical outcomes.

Due to the surprising efficacy of anti-BCMA CAR-T in RRMM patients, some clinical studies have tried CAR-T cells as part of first-line therapy for patients with newly diagnosed multiple myeloma (NDMM). Yan et al. [32] pioneered a prospective study using sequential anti-CD19 and anti-BCMA CAR-T cells as first-line consolidation therapy followed by lenalidomide maintenance after allogeneic hematopoietic stem cell transplantation (ASCT) in high-risk NDMM patients (n = 10). Results showed that ORR was 100% and stringent complete response (sCR) was achieved in 90% of NDMM patients. Severe CRS (grade 3 and above) and neurotoxicity were not observed. In addition, at a median follow-up of 42 months, 70% of patients remained minimal residual disease (MRD)-negative. Interestingly, an impressive study of anti-BCMA and anti-CD19 dual-target CAR-T product GC012F as first-line therapy in transplant-eligible NDMM patients (n = 13) showed significant efficacy that reaches 100% ORR and 69% sCR, respectively, with a median follow-up time of 5.3 months. In addition, comorbidity such as CRS only occurred in 23% of patients with no one above grade 3, and ICANS did not occur at any grade [19]. However, disease relapse after achieving remission according to previous therapy in MM patients was still difficult to avoid; therefore, the next step of treatment options after achieving remission in NDMM patients treated with CAR-T cells still needs further consideration. These approaches encourage us to further investigate CAR-T cells as a first-line therapy for patients with NDMM to demonstrate their feasibility.

CAR-T Cell Therapy in SLE

SLE is a complex and heterogeneous autoimmune disease characterized by highly diverse clinical manifestations, and the immune complexes may be deposited in small vessels or distal sites, eventually leading to the destruction or dysfunction of multiple organs; lupus nephritis is the most common target-organ manifestation [33]. Current treatment of SLE mainly relies on nonsteroidal drugs, glucocorticoids, antimalarial drugs, and other immunosuppressants to treat severe symptoms of organ dysfunction, while the side effects also raise concerns [34]. Due to B cells playing a central role in the pathogenesis of SLE, many B-cell-directed immunotherapies have recently been developed. Anti-B-cell activating factor (e.g., belimumab) and anti-CD20 mAb (e.g., rituximab) have been approved to deplete B cells and mitigate nephritis, but response rates of SLE patients have varied widely among studies, and disease flare and relapse after treatment remains a problem [35, 36]. Therefore, achieving more effective B-cell depletion and durable treatments in SLE patients was considered a potential target.

Jin et al. [37] constructed murine anti-CD19 CARs with CD28 or 4-1BB as the intracellular costimulatory domain and evaluated the therapeutic function in mouse models. Then, anti-CD19 CAR-T cells were transferred to MRL-lpr mice before disease onset to determine their role in SLE prevention. The results showed that the adoptive transfer of anti-CD19 CAR-T cells exhibits a more persistent B-cell depletion effect compared with antibody therapy. Allogenic anti-CD19 CAR-T-cell metastasis not only prevents the pathogenesis of the disease before symptoms develop but also shows benefits later in disease progression. They also found that CAR-T cells with a 4-1BB costimulatory domain showed better therapeutic efficiency than those with CD28. This preclinical study can serve as a proof-of-principle study and suggests that CAR-T cell therapy is a novel option for treating clinical autoimmune diseases.

Recently, an exciting study reported by Mackensen et al. [20] showed the first convincing clinical results of anti-CD19 CAR-T cell therapy in treating refractory SLE patients. Compassionate-use CAR-T cells were administered to 4 female and 1 male SLE patient between the ages of 18 and 24 who all exhibited kidney involvement and glomerulonephritis that was histologically established. The results showed that after the infusion of CAR-T cells, they expanded well in vivo and mediated deep B-cell depletion, with significant improvement in all SLE-related clinical symptoms and normalization of anti-double-stranded DNA antibody seroconversion. Surprisingly, nephritis ceased in all 5 patients, and drug-free remission was maintained during a longer follow-up period, even after the reappearance of B cells. CAR-T cell therapy was well tolerated, with only mild CRS (3 patients occurred in grade 1) and no other severe comorbidities observed. All investigations above indicated that anti-CD19 CAR-T cell therapy is feasible, tolerable, and with great potential in SLE treatment. Of course, since anti-CD19 CAR-T also eradicates normal B cells, resulting in hypogammaglobulinemia, the potential risk of infection and long-term immunodeficiency need to be supported and optimized by more studies. As with other diseases, long-term follow-up data are still needed on PFS and risk factors for relapse after CAR-T cell therapy in SLE patients to help investigators modify better therapeutics.

CAR-T Cell Therapy in AIDS

AIDS is one of the most high-profile infectious diseases caused by human immunodeficiency virus (HIV) infection, leading to the threat of infection, malignancies, and multiple organ dysfunction due to the destruction of the patient's cellular immunity. There is no doubt that AIDS can also be characterized by kidney diseases which perform as HIV-associated nephropathy, immune-complex kidney disease, non-collapsing focal segmental glomerulosclerosis, comorbid kidney disease, etc., as well as kidney injury resulting from prolonged exposure to antiretroviral therapy or opportunistic infection [38]. Despite the development of effective combined antiretroviral therapy, there is still an increase in HIV resistance and viral residuals, which eventually lead to viral rebound. Until now, hematopoietic stem cell transplantation from C-C chemokine receptor 5 (CCR5) Δ32 donors has been the only known cure for AIDS [39–42].

In theory, HIV-infected cells can be recognized and killed by specific T cells, however, previous research indicated that autologous cytotoxic T lymphocyte (CTL) clearance of HIV-infected cells has failed due to escape mutations, downregulated MHC-I expression, and CTL depletion, whereas CAR-T cell therapy is considered a potential cure for AIDS by directly recognizing target antigens whose activation is independent of MHC [43–45]. Meanwhile, to dispel the concern of CAR-T cells infected by HIV, the transduction of C34 and C-X-C chemokine receptor type 4 (CXCR4) fusion inhibitors and engineered nucleases conferring them resistance to HIV introduce C34 conjugated to the amino terminus of CXCR4 and deletion at the CCR5 locus in T cells, respectively. The investigation of Hale et al. [46] used scFv based on high-affinity broadly neutralizing monoclonal antibodies (bNAbs), targeting the HIV envelope glycoprotein, to construct HIV-targeted CAR constructs that simultaneously introduce CARs and disrupt CCR5 by homology-directed recombination and demonstrated in an in vitro model that CCR5-targeted integration of HIV-CART cells can effectively inhibit HIV replication. Maldini et al. [47] constructed a dual-endodomain CAR-T that simultaneously expressed both 4-1BB/CD3-ζ and CD28/CD3-ζ which showed greater expansion ability and expressed C34-CXCR4 fusion inhibitor to protect CAR-T cells from HIV infection. In their humanized mouse model, the dual-endodomain CAR-T cells significantly reduced tissue viral burden and acute viremia, especially when combined with antiretroviral drugs.

Moreover, Liu et al. [18] developed a bNAbs-derived CAR-T cell product that validated the safety and antiviral activity of CAR-T cells and enrolled 14 patients with AIDS to exert specific cell-killing effects on HIV-1-infected cells (NCT03240328). Results showed that CAR-T

delayed the rebound of HIV viremia in patients after discontinuation of antiretroviral drugs and cell-associated viral US RNA and HIV-proviruses were effectively reduced during CAR-T treatment, although CAR-T depletion and viral rebound eventually occurred in all patients tested at the median 5.3-week. Therefore, further studies are needed for the use of CAR-T for HIV treatment, including further engineering to delay the rebound of viremia and CAR-T cell depletion, and considering the feasibility of combining CAR-T with antiretroviral therapy.

CAR-T Cell Therapy-Related Kidney Injury

Although CAR-T cell therapy is a promising immunotherapy of hematological malignancies, it has also been reported to have a high incidence of treatment-related toxicities, such as CRS, ICANS, and myelosuppression [48]. In addition, previous studies have indicated that CAR-T cell therapy is associated with nephrotoxicity, especially acute kidney injury (AKI), and when complicated with CRS and profound hypotension, patients are more likely to develop AKI due to acute tubular injury which may lead to a poorer prognosis and death [49–51]. On top of that, tumor lysis syndrome and cytokine-mediated kidney injury might be involved, but the proof and precise mechanisms by which CAR-T results in the development of AKI are yet unclear [52].

In 78 patients with diffuse large B-cell lymphoma (DLBCL) undergoing anti-CD19 CAR-T treatment, a retrospective examination of toxicities revealed that CRS occurred in 85% of patients, electrolyte abnormalities in at least 75% of patients, and AKI occurred in 19% of patients: 8 patients had decreased renal perfusion, 6 patients had acute tubular necrosis, and one patient had a urinary obstruction. Moreover, patients with severe CRS exhibit 9.8-fold higher odds of developing AKI than patients with milder grades after CAR-T cell therapy [49]. Similarly, Kanduri et al. [53] performed a meta-analysis of 22 cohort studies that included 3,376 patients and confirmed that the incidence of CAR-T cell therapy-associated AKI reached 18.6% and progressed to the need for dialysis in approximately 4.4% of patients. Indeed, they found a strong correlation between CRS severity and AKI occurrence. Due to these potential impacts of CRS on decreased kidney perfusion and tubular impairment, comprehensive clinical management guided by the grade of CRS may help clinicians reduce kidney injury when considering applying CAR-T cell therapy, where intravenous rehydration, anti-IL-6 therapy (e.g., tocilizumab), and corticosteroids have important value.

Mellili et al. reported one patient with B-cell-derived lymphoproliferative disease after kidney transplantation of 17 years who received anti-CD19 CAR-T cell therapy due to intolerance to conventional therapy and discontinued all potentially nephrotoxic drugs (omeprazole and acyclovir) [54]. The data showed a gradual decrease in glomerular filtration rate 12 days after CAR-T infusion in the absence of observable CRS and ICANS. Renal biopsies showed a mild tubulointerstitial lymphocyte infiltration similar to acute immunoallergic tubulointerstitial nephritis without infiltrating CAR-T cells or lymphoma B cells, confirming that non-CRS mechanisms of kidney injury after CAR-T cell therapy remain to be investigated. Moreover, other potential factors may contribute to kidney injury in patients who received CAR-T cell therapy, such as the fact that patients with concomitant myelosuppression often suffer from severe neutropenia, and secondary infections may increase their renal burden [51].

Therefore, early identification of risk factors for kidney injury in patients who received CAR-T cell therapy can give preemptive treatment, thereby helping to reduce the incidence of AKI and its subsequent adverse outcomes. Recently, Herrmann et al. [50] have led a retrospective study to evaluate the association of demographic and clinical parameters, comorbidities, blood biomarker levels, and other factors with the development of AKI within the first month after anti-CD19 CAR-T cell therapy in patients with refractory non-Hodgkin lymphoma (NHL). These studies provide some identifiable risk factors or biomarkers that can predict AKI and are of great help to clinicians in managing CAR-T cell therapy. Also, the appliance of nephrotoxic drugs (antibiotics, non-steroidal anti-inflammatory drugs, etc.) in patients treated with CAR-T needs to be considered more fully.

Conclusion

For decades, the treatment of renal malignancies has still been dominated by surgical resection, and there is still a lack of therapeutic regimens that precisely target tumor cells and are effective in the long term, even though immune checkpoint inhibitors and tyrosine kinase inhibitor drugs have been widely tried. As one of the most promising approaches in tumor immunotherapy, CAR-T

cell therapy has shown exciting results in the clinical treatment of hematologic malignancies. Therefore, many researchers have worked to discover more renal tumor-specific antigens, construct specific CAR, and validate the combination therapy based on CAR-T [16, 23, 26]. Interestingly, the study of Xiao et al. [55] investigated that the signaling transduction and activation of CAR-T cells were also highly influenced by the narrow intermembrane space which depends on the size of the CAR extracellular domain and neighbor molecular, which provides a new insight into the promotion of CAR-T cell therapy.

Moreover, pieces of the study indicated that the subgroup of CAR-T cells performs different biological functions, such as CD8-positive CAR-T is mainly responsible for tumor eradication yet CD4-positive. CAR-T plays a key role in exacerbating CRS but maintaining long-term responses, and the "ratio balance" of CD4-positive/CD8-positive may exhibit greater efficacy [56–58]. Wang et al. [59] confirmed that mixed CD4-positive/CD8-positive anti-CAIX CAR-T showed better renal tumor invasion and cytotoxicity, with less immune checkpoint and exhaustion gene expression, which indicated the mechanistic role of different CAR-T groups should be further investigated. The latest in vivo research on CAR-T cells has utilized cell lines and immunodeficient nude mice or NSG mice. This simple and easy-to-implement experimental setting has assisted researchers in identifying and screening regulatory elements that can enhance CAR-T cells' function and combine agents. However, a comprehensive understanding of the potential impact of other immune cells in the TME is currently lacking. Additionally, the diversity of tumor cells in clinical patients in these studies was often overlooked. Therefore, the construction and design of patient-derived xenografts (PDX) models, as well as mouse spontaneous tumor models, may offer a more thorough perspective for validating CAR-T cell therapies.

Excitingly, some other peripatetic cell therapies such as CAR-natural killer (CAR-NK) cell and tumor-infiltrating lymphocyte (TIL) have been proposed in the field of renal tumor treatment, and showing better tumor infiltration ability, fewer toxic comorbidities, and promising treatment options continue to be explored [60]. Zhang et al. [61, 62] developed two kinds of third-generation CAR-NK cells by targeting EGFR and CAIX and confirmed the cytotoxicity on human renal tumor cell lines in vitro and in vivo. Meanwhile, they found that the combination of cabozantinib could enhance the function of CAR-NK cells by decreasing PD-L1 expression on tumor cells and inhibiting some immunosuppressive cells (such as MDSCs and Treg cells) in the TME, and bortezomib pretreatment significantly improved the tumor eradication of CAR-NK cells.

As aforementioned, these findings emphasized the potentiality of adoptive cell therapy in kidney-related disease treatment. Indefinitely, the cell heterogeneity, antigen escape, and immunosuppressive TME of solid tumors and complications such as acute kidney injury occurring during CAR-T cell therapy are still important difficulties in renal tumor treatment. Additionally, xenogeneic rejection has hindered research on the comorbidities linked to CAR-T cell therapy in immune-competent mice, since the interactions between the intrinsic immune system and CAR-T cells are responsible for adverse effects like CRS and myelosuppression. Hence, it is imperative to develop murine CAR-T to analyze the pathophysiological mechanisms of CAR-T cell therapy-associated complications in immunocompetent mice.

Indeed, some researchers are trying to apply CAR technology to the treatment of broader autoimmune diseases. Jyothi et al. [63] constructed a heterodimeric chimeric receptor-T cell containing the autoantigenic peptides MHC-II and CD3ζ to recognize and eradicate autoreactive T cells for the treatment of experimental autoimmune encephalomyelitis, which provides a new idea for CAR technology.

In summary, we discussed the advances in CAR-T cell therapy in treating renal malignancies and three common diseases accompanied by kidney impairment. Moreover, the major challenges of CAR-T cell therapy in kidney-related diseases, such as disease-specific targets, tissue infiltration, immunosuppressive TME, and CAR-T viability in vivo, and the overall regimen of therapeutic strategy and the timing of CAR-T optimization, such as in combination with surgery, radiotherapy, and targeted agents, still need to be continuously explored.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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