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Current and future perspectives on CAR-T cell therapy for renal cell carcinoma: A comprehensive review

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In the clinical setting of renal cell carcinoma (RCC), immune reactions such as tumor-specific T cell responses can be spontaneous events or can be elicited by checkpoint inhibitors, cytokines, and other immunotherapy modalities. The results from immunotherapy have led to significant advances in treatment methods and patient outcomes. The approval of nivolumab primarily as a second-line monotherapy and the latest approval of novel combination therapies as first-line treatment have established the significance of immunotherapy in the treatment of RCC. In this perspective, chimeric antigen receptor (CAR)-T cell therapy represents a major advance in the developing field of immunotherapy. This treatment modality facilitates T cells to express specific CARs on the cell surface which are reinfused to the patient to treat the analogous tumor cells. After showing treatment potential in hematological malignancies, this new therapeutic approach has become a strong candidate as a therapeutic modality for solid neoplasms. Although CAR-T cell therapy has shown promise and clinical benefit compared to previous T-cell modulated immunotherapies, further studies are warranted to overcome unfavorable physiological settings and hindrances such as the lack of specific molecular targets, depletion of CAR-T cells, a hostile tumor microenvironment, and on/off-tumor toxicities. Several approaches are being considered and research is ongoing to overcome these problems. In this comprehensive review, we provide the rationale and preliminary results of CAR-T cell therapy in RCC and discuss emerging novel strategies and future directions.

Keywords: Immunotherapy; Metastasis; Receptors, chimeric antigen; Renal cell carcinoma; T cells

INTRODUCTION

Over 90% of kidney-related malignancies are represented by renal cell carcinoma (RCC) and is the ninth most common neoplasm in the United States [1]. While cytokine-based therapy utilizing interferon and interleukin (IL)-2 and targeted molecular therapies that involve tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF), and mammalian target of rapamycin inhibitors have shown potential in the metastatic disease setting, tumor resistance of the primary or acquired nature has limited effective treatment with these choices [1].

Clinical advancements in the field of immunotherapy resulted in the approval of medications for the treatment of

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advanced RCC [2-5]. Nivolumab, nivolumab plus ipilimumab, avelumab plus axitinib, and pembrolizumab plus axitinib have shown advantages in metastatic RCC (mRCC) regarding survival and response compared to TKIs [2-4]. Nevertheless, treatment outcomes show a diverse spectrum that ranges from complete response (CR) of the tumor to refractory systemic metastasis. Radiographic CR is rare in which only 3% to 9% is achieved in patients who undergo immune checkpoint inhibitor (ICI) therapy [2-4].

The identification of chimeric antigen receptors (CARs) has led to breakthroughs and advancements in immunotherapy. Promising results demonstrated in hematological malignancies have turned the focus of immunotherapy toward solid tumors including RCC. The anti-tumor mechanisms exerted by cytokine agents and ICIs are known to be an immunological response by tumor-reactive T cells. Immunotherapeutic modalities for advanced RCC integrated into this clinical field have encouraged research and development of various antigen-targeted T cell-mediated therapeutic options that can enhance anti-tumor properties while restricting adverse events.

In this review, we provide an overview of the CAR-T cell immunity in the treatment of advanced RCC, summarize clinical outcomes for CAR-T cell involving therapies, and discuss emerging novel therapeutic options to improve the efficacy of CAR-T cell immunotherapy for advanced and mRCC.

OVERVIEW OF THE STRUCTURE AND TREATMENT PLATFORM OF CAR-T CELLS

CAR-T cells are genetically engineered and modified to explicit antigen-specific, non-major histocompatibility complex (MHC)-restricted receptors on their membranes [6]. CAR-T cells are categorized into four generations based on molecule structure. The CAR structure comprises four parts which consist of a single-chain variable fragment (scFv) in the extracellular part of the cell that represents the antigen-binding region, an extracellular hinge region, transmembrane region, and an intracellular signaling domain that is also known as the immunoreceptor tyrosine-based activation motif [6].

The scFV and extracellular hinge region comprise the extracellular target binding domain. This domain binds with tumor antigens, and the intracellular signaling domain is recombined *in vitro* as recombinant plasmids. CAR-expressing T cells are contrived as the recombinant plasmids are subsequently reintroduced into the T cells of the host via transfection technology. Consequently, the newly formed CAR-T cells are expanded and screened *in vitro* and subsequently reinfused.

The intracellular domain consists of the cluster of differentiation (CD) 3z, which is the signal transduction portion of the T-cell receptor (TCR) linked with a costimulatory domain. Moreover, T cells redirected for universal cytokine killing (TRUCK), which are the fourth generation CAR-T cells, have been modified at the molecular level to combine with immune-stimulatory molecules. These include cytokines such as IL-12, IL-15, IL-18, and IL-7R, multiantigen-targeting combinations such as human epidermal growth factor receptor 2 (HER2), ephrin-A2 (EphA2), or knock-in genes, including C-X-C chemokine receptor type 4 (CXCR4), and controlled and inducible systems [7]. Due to the versatile nature of TRUCKs, costimulatory elements and pro-inflammatory molecules can be expressed, increasing the efficacy of CAR-

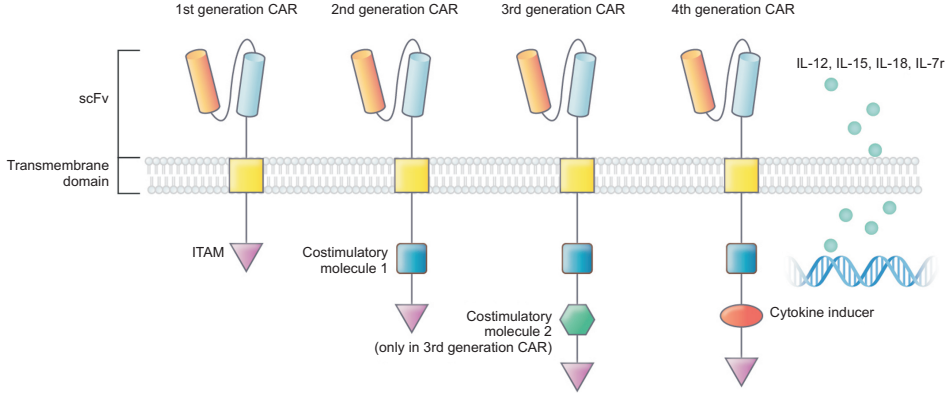

Fig. 1. Molecular structure of different chimeric antigen receptor (CAR) generations. The first-generation CAR only contains immunoreceptor tyrosine based activation motifs (ITAM) in the intracellular domain. Second-generation CARs included the addition of one co-stimulatory molecule and third-generation CARs contain a second co-stimulatory molecule. The fourth generation of CARs was based on second-generation CAR with a constitutive cytokine inducer. These types of CAR-T cells are also known as T cell redirected for universal cytokine-mediated killings. scFv, single-chain fragment variable; IL, interleukin. Adapted from the article of Yu and Kim. Int J Mol Sci 2021;22:640 [7].

T cells. Fig. 1 depicts the molecular structure of the different generations of CAR-T cells.

Lymphocyte harvesting from the patient's peripheral bloodstream via leukapheresis, and subsequent apheresis without the additional insertion of granulocyte colony-stimulating factor marks the initiation of CAR-T cell therapy [8]. The genetically modified T cells are infected with a non-viral CAR vector or a viral vector that has retroviral or lentiviral properties, which has been manipulated to contain genomic DNA. The modified CAR-T cells are transduced back into the host, who usually undergoes lymphodepletion before CAR-T reinfusion after molecular expansion and purification *ex vivo* [8,9]. The CAR-T cells are activated after the infused CAR interacts with the surface antigen presented on the target cell, which leads to target cell lysis along with the production and proliferation of cytokines. Fig. 2 summarizes the CAR-T cell therapy regimen and treatment platform.

In comparison to previous molecular structures of adoptive cell therapy such as TCR and tumor-infiltrating lymphocytes (TIL), CAR-T cells have several properties that are more beneficial in terms of immunotherapy [10,11]. The immune activity of CAR-T cells is not MHC-restricted due to its surface–antigen interaction. This molecular characteristic is essential in the treatment of cancers with low MHC expression that is TCR or TIL resistant, which can respond to CAR-T cell therapy [12]. The majority of TCRs exert low antigen affinity that may induce off-target toxicities, where CAR-T cells exhibit a lower occurrence of these adverse events [13]. CAR-T cells exhibit the antigen-binding activity of T cells and lytic characteristics, making these cells a favorable means of immunotherapy [14].

Immunotherapy with CAR-T cells has shown promising outcomes. Wang et al. [15] studied the curative efficacy of CAR-T cell therapy for hematological cancers, in which a CR rate of approximately 90% was achieved in patients with CD19-positive B-acute lymphoblastic leukemia. However, only one-fourth of the patients with chronic lymphoblastic leukemia showed response to CAR-T cell immunotherapy. An explanation for the difference in CR rates is the exhaustion of T-cell development caused by the coinhibitory cascade activation. Consequently, this exhaustion resulted in suboptimal T-cell expansion and a decrease in T-cell persistence [16]. In a study to elucidate the CAR-T cell immune response, Fraietta et al. [17] analyzed CAR-T cells of the non-responders and concluded that upregulation plays a pivotal role in the exhaustion and apoptosis of T cells. Moreover, the levels of T-cell coinhibitory receptor expression, such as PD-1, T-cell immunoglobulin, lymphocyte activation gene-3, and mucin domain-3 were upregulated in CAR-T cells, which ultimately leads to the inhibition of T-cell activity [18].

NOVEL BIOMARKERS AND PROGNOSTICATORS FOR IMMUNOTHERAPY IN ADVANCED RENAL CELL CARCINOMA

1. Clinical and biological biomarkers

Traditionally, disease progression and prognosis of RCC patients are to be highly dependent on their anatomical location, molecular and clinical characteristics, and the histology of the tumor [19-21]. According to the study results from the Groupe Francais d'Immunotherapie, elevated neutrophil counts, short interval progression for metastasis, and more than one metastatic site were considered factors for RCC progression following immunotherapy [22].

Studies corroborated the role of other prognostic pa-

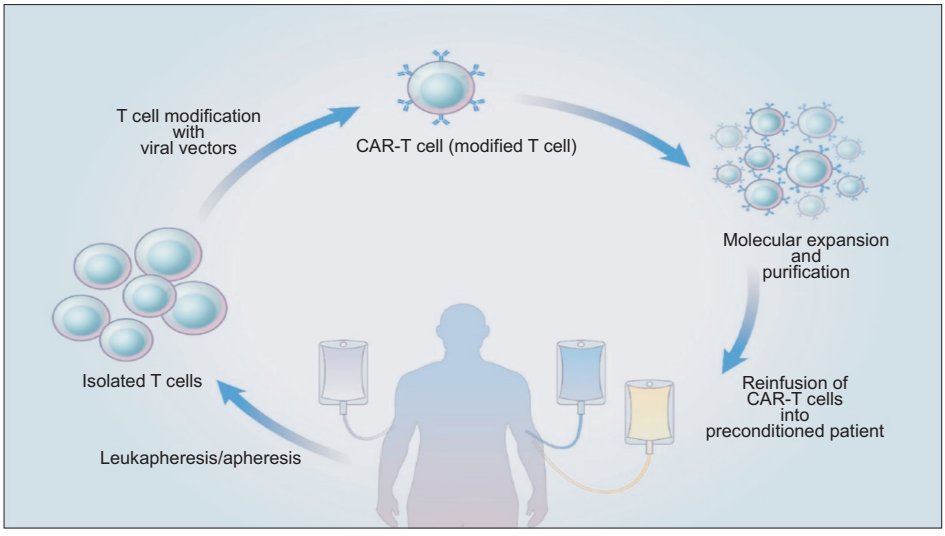

Fig. 2. Schematic drawing of chimeric antigen receptor (CAR)-T cell production. T cells harvested from the peripheral blood are isolated via leukapheresis followed by apheresis. The T cells are transduced by viral/non-viral vectors and genetically modified to express chimeric antigen receptors. Following *ex vivo* expansion and purification, CAR-T cells are reinfused into the patient after lymphodepletion. Adapted from the article of Yu and Kim. Int J Mol Sci 2021;22:640 [7].

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rameters such as the systemic inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) as clinically significant factors and prognosticators [23-25]. Lolli et al. [23] explored the possibility of utilizing the SII as a prognosticator for RCC. The study included 355 RCC patients who received first-line sunitinib. Patients were stratified into high SII and low SII groups. The median progression-free survival (PFS) was 6.3 months for the high SII group, while the low group had a PFS of 18.7 months. The median overall survival (OS) for both groups was 13.5 and 43.6 months, respectively. Moreover, multivariate analysis showed that SII was a reliable biomarker to predict OS (hazard ratio=1.79). In a 2014 study [24], the NLR values of 109 RCC patients treated with sunitinib were evaluated. The study concluded that sunitinib treatment was related to a reduction in NLR as a result of the decreased neutrophil and increased lymphocyte counts. Results showed that NLR was associated with better tumor response and longer cancer-specific survival in RCC patients who were administered sunitinib [24]. After evaluating 103 RCC patients treated with TKIs, Yasuda et al. [25] showed that pretreatment CRP was an independent prognostic factor and concluded that an early 4-week CRP response is predictive of survival in patients who underwent TKI therapy.

2. Molecular biomarkers

Molecular markers are categorized according to histological characteristics and soluble factors [26]. In a study performed by Choueiri et al. [27], carbonic anhydrase IX (CaIX) showed potential as a biomarker, although this finding was limited to RCC patients who underwent sorafenib treatment. The mean tumor shrinkage response after sorafenib treatment significantly differed between high and low CaIX expression cases (-13% vs. +9%) [27]. Other investigations have examined the association between CXCR4 expression and treatment efficacy in mRCC [28,29]. Guo et al. [29] showed that the PFS of sorafenib-treated patients with negative or low CXCR4 expression was longer than those with intermediate or high CXCR4 expressions. Similarly, in an exploratory study, CXCR4 expression levels were shown to be significantly associated with poor response to sunitinib treatment [28,29]. Motzer et al. [30] investigated novel tumor biomarkers as potential candidates for prognosticative purposes and showed that when patients were stratified according to hypoxia-inducible factor 1 alpha (HIF-1α) expression levels, PFS in the high HIF-1α expression group was longer compared to the low HIF-1α expressed group.

3. Immunohistochemical biomarkers

Along with approvals of ICIs, potential prognostic immunohistochemical biomarkers have been identified. ICIs targeting programmed death-1 (PD-1) and its corresponding ligand (PD-L1) have shown potential and are currently widely studied targets. PD-L1 expression is observed in natural killer cells and B cells along with activated T cells and is associated with a poor prognosis for anti-angiogenic medication and shorter survival in mRCC patients who undergo VEGF-TKI treatment [31,32]. Various studies have reported that PD-1 and PD-L1 expression in the RCC setting is associated with poorer outcomes and aggressive clinical features [33]. However, studies are warranted to validate the correlation between the expression of PD-1 and PD-L1 and RCC progression.

In CheckMate-214, patients with RCC in the advanced setting were administered a combination of nivolumab and ipilimumab and were compared to the sunitinib cohort. At the median follow-up of 42 months, the ICI combination group showed significant superiority over the sunitinib group regarding OS (47.0 vs. 26.6 months; $p<0.001$), PFS (12.0 vs. 8.3 months; $p<0.01$), and overall response rate (ORR) (42% vs. 26%; $p<0.001$) [34]. Moreover, in the phase III JAVELIN Renal 101, when compared to sunitinib monotherapy, patients who received avelumab with axitinib showed a higher (63.2%) PD-L1 expression rate. In this study, patients were assigned in a 1:1 ratio to receive a combination of avelumab with axitinib compared to patients that were administered sunitinib for six weeks. Among PD-L1-positive tumors, the avelumab with axitinib group demonstrated an ORR of 55.2% in comparison to an ORR of 25.5% in the sunitinib group [2]. In both trials, the ORR and OS rates were favorable for immunotherapy notably in the population with PD-L1 expression [35]. Results from both studies emphasized a difference between the International Metastatic RCC Database Consortium prognostic groups, in which the therapeutic benefits from immunotherapy were mostly in the intermediate and high-risk groups [35].

The tumor mutation burden (TMB) is established on the total number of mutations per coding area of the tumor genome. A higher mutation burden provides a molecular environment that is favorable to neo-antigens that enhance tumor immune response [36]. Various studies have shown that the TMB is an inadequate biomarker to identify responders to immunotherapy in clear cell RCC patients but is still under evaluation. The limitations of this biomarker may be due to technical issues such as coverage, lack of procedure standardization along with the DNA amount and analysis time [37,38].

Immunotherapy has shown benefits, especially in neoplasms with an unstable genetic profile demarcated by a high mutational burden. Studies have shown that neoantigens are expressed by tumor cells and can be used as therapeutic targets [39,40]. However, various obstacles limit the effects of immunotherapy such as a low mutational burden and a low infiltration of $CD8^+$ T lymphocytes into specific areas of the tumor tissue [41]. These limitations hinder the clinical application of immunotherapy in various cancers. The concentration and spatial-functional orientation of $CD8^+$ T cells within the tumor are directly associated with treatment response and patient prognosis in many cancers [42,43]. Infiltration of immune cells can be detected by staining tissue samples with hematoxylin and eosin or via immunostaining. Based on the molecular distribution of T lymphocytes in the tumor, three different topographies have currently been defined which are immune active (hot), immune desert (cold), and immune excluded. $CD8^+$ T cells are densely populated in hot tumors while cold tumors may present with other immune molecules or myeloid cells. Immune excluded tumors present cancer cell nests surrounded by T cells, which are incapable of penetration [44]. Although this classification is largely accepted, further clinical studies and quantitative data on the relative frequencies of the three immune landscapes across cancers of different derivations are needed to validate this classification.

The majority of renal cell tumors are associated with gene mutations such as Von Hippel-Lindau (VHL), Polybromo 1 (PBRM1), and SETD2 [45]. Of these molecular alterations, studies show a 40% mutation rate of PBRM1 in the molecular setting of clear cell renal cell carcinoma [46]. It has been reported that the PBRM1 gene encodes the BAF180 protein that is required for the stability of the SWI/SNF chromatin remodeling complex SWI/SNF-B (PBAF) [47]. Alterations and mutations in the PBRM1 gene have shown a correlation with the clinical response of PD-1 blockade therapy [48,49]. However, further studies and clinical data are needed to understand the underlying pathophysiology of PBRM1 gene mutations. Furthermore, the molecular interaction of PBRM1 mutation and its effect on the tumor microenvironment (TME) and immunotherapies are unclear. McGranahan and Swanton [50] reported that the absence or mutation of some genes in tumors may affect the activity of tumor-infiltrating T cells. Moreover, the population density and function of tumor-infiltrating effector T cells influence outcomes of immunotherapy. In general, the higher number of immune infiltrating effector T cells relates to better efficacy of ICIs [51]. Further clinical studies are required to explore the alternations in the PBRM1 gene and resulting outcomes from the mutations of PBRM1 caused in tumors.

Extensive research and development for standardizing prognosticators and clinical biomarkers are ongoing. However, due to the limited amount of supportive data, further prospective trials are needed to elucidate the biological and molecular characteristics of RCC. Moreover, the heterogeneity of the disease and patient population, along with the absence of a clinical stratification system that reflects the efficacy of novel immune-targeted therapy, pose limitations in the translation of the RCC biomarkers into the clinic. Novel molecular classification of RCC subtypes should aid the methods and designs of trials in further validating the prognostic efficacy of potential biomarkers [52].

TOXICITIES AND ADVERSE EVENTS ASSOCIATED WITH CAR-T CELL THERAPY

1. Cytokine release syndrome

Clinical studies based on hematological malignancies have reported that cytokine release syndrome (CRS) was the most common toxic reaction occurring in approximately 45% of the study population. The severity varied from low constitutional to life-threatening symptoms such as multi-organ dysfunction. Severe cases of CRS can lead to fulminant hemophagocytic lymphohistiocytosis, in which the features are hyperactivation of lymphocytes and macrophages, upregulation of cytokines, lymphohistiocytic cell infiltration, and immune-related multi-organ failure [53]. The clinical symptoms of CRS are fever, hypotension, hypoxia, high CRP and ferritin levels, and neurologic complications [54]. Increased serum IL-6 levels, which result in hypotension, vasodilation, hypoperfusion, and acute kidney injury, are known to be associated with severe CRS. The association between IL-6 and CRS has been confirmed by the use of the anti-IL-6 receptor antibody tocilizumab which alleviated the symptoms of CRS [55]. Moreover, a correlation between CRS symptom severity and CRP levels has been observed [56]. CRP levels can be used as a biomarker to determine the risk of CRS during CAR-T cell therapy. Furthermore, serum CRP levels have an association with tumor burden, indicating that patients with a lower tumor burden are less likely to develop CRS [57].

2. Tumor lysis syndrome

During the early era of CAR-T cell immunotherapy, symptoms of tumor lysis syndrome (TLS) was first observed by Porter et al. [58] after the administration of CAR-T cells for the treatment of CLL. The syndrome is featured by acute kidney injury with elevated lactate dehydrogenase and uric acid approximately 22 days following the infusion of CAR-T cells

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[59]. Although mild cases of TLS have been reported, investigations are warranted to elucidate the mechanism underlying severe TLS leading to AKI.

3. Neurological toxicities

Neurological toxicity is characterized by delirium, confusion, expressive aphasia, seizure, myoclonus, and obtundation. These symptoms have been reported in patients who received CD19-specific CAR-T cells, and the underlying pathophysiology is unknown. There is a possibility that these adverse events to be elicited by alternative antigen-specific agents. Although neurological toxicity is reversible in most cases, studies are needed to see if this adverse event is triggered explicitly by CD19-specific CAR-T cells or by other tumor-associated antigens [55].

4. On-target/off-tumor toxicity

Molecular targets of CAR-T cell therapy share expression with normal tissue, and on-target/off-tumor toxicity occurs through the interaction of the target antigen expressed on non-cancer tissues. In the clinical trials performed by Lamers et al. [60,61], the development of cholestasis was noted in patients who were administered CaIX-specific CAR-T cells for the treatment of RCC due to CaIX expression in the biliary duct epithelium. The severity of this adverse event was associated with dosage, as shown in the fatal case of a patient who was treated with a high-dose infusion of HER2-specific CAR-T cells. This patient developed respiratory failure and multi-organ failure, which ultimately led to mortality [55]. Subsequent studies using a different HER-2/neu-specific CAR-T cell have proven lower doses safe [62].

5. Anaphylaxis and cell rejection

Most CAR-T cells have antigen recognition domains derived from murine monoclonal antibodies [6,55]. Consequently, several studies have reported CAR-T cell rejection and anaphylaxis on the cellular and humoral level due to the immunogenicity of the foreign molecule [63,64]. Research and development are ongoing to humanize the molecular domains while increasing the durability and efficacy of CAR-T cells [63]. Patient surveillance with prompt recognition and treatment of anaphylaxis are crucial for patients undergoing CAR-T cell immunotherapy. Methodical and organized large-scale studies of relevant biomarkers and early intervention along with the development of optimal treatments for these events are necessary for safe CAR-T cell immunotherapy.

PREVIOUS STUDIES BASED ON T-CELL IMMUNITY IN RENAL CELL CARCINOMA

Spontaneous tumor regression of RCC in the metastatic setting has been reported dating back to the early 20th century [65]. Janiszewska et al. [66] observed that approximately 1% of RCC patients experience spontaneous regression in both primary and metastatic settings. Supported by a clinical study performed in 2005 [67] in which fever accompanied by infection preceded spontaneous tumor regression, systematic activation of the host immunity was suggested as a leading hypothesis.

In a study by Gastl et al. [68], MHC class I was expressed in all RCC tumors, and approximately 90% of the neoplasms retained MHC expression during progression and metastasis, providing clinical evidence proving that kidney tumors elicit immune responses of a cytotoxic nature. Schendel et al. [69] obtained a cytotoxic T lymphocyte (CTL) cell line with a human leukocyte antigen (HLA)-A2 expressing RCC. Results showed that the cultured CTL used a limited number of Vα genes and demonstrated cell lysis in allogeneic HLA-A2 RCC tumors, which demonstrated that RCC tumors are involved in the clonal expansion of T-cells and that RCC cells express common antigen determinants [69]. Subsequent studies focused on the identification of various antigens associated with RCC that could be potential targets for immune T-cell responses. Various molecular and cellular mechanisms such as point mutations, frameshift mutations resulting in open reading frames, and aberrant overexpression of genes and antisense transcripts were revealed as the underlying physiology for these RCC-associated antigens [70-75].

Trials performed in the late 20th century confirmed tumor-reactive T-cell responses utilizing systemic cytokine manipulation as a promising modality for mRCC. Interleukins, especially IL-2, were revealed to activate post-TCR signaling in T-cells and the proliferation cascade of CD8+ T cells, which in turn enhances the effector function and survival of T-cells. Results have shown that 15% to 30% of patients who received high-dose IL-2 obtained OR, while CR was reached in 5% to 8% of patients [76-78].

Interferons are a vital constituent of the innate immune response system, which reacts to external infections and neoplasms and plays the priming role in the adaptive immune response of the host. Clinical studies utilizing recombinant IFN-α treatment for patients with mRCC have reported a response rate of 15%. However, CRs of less than 5% were less frequent or durable than IL-2 [79-81].

ONGOING TRIALS IN RENAL CELL CARCINOMA

A phase II, two-arm, open-label dose-escalation and dose-expansion clinical trial (National Clinical Trial [NCT]03393936) is evaluating the safety, tolerability, and therapeutic effects of infused autologous CAR-T cells CCT 301-38 or CCT 301-59 in relapsed or refractory stage IV mRCC patients [82]. The study is designed to evaluate the effectiveness of two CAR-T cells with different molecular targets. Patients with receptor tyrosine kinase-like orphan receptor 2 (ROR2) receive CCT31-59 while RCC patients with AXL-positive biopsy undergo CCT 301-38. In RCC patients, ROR2 expression is associated with genes that regulate mitosis and migration, which include proliferating cell nuclear antigen, cyclin-dependent kinase 1, TWIST genes, and matrix metalloproteinase 2 [83]. The molecular target of the CCT301-38 CAR-T cell is AXL, a cell surface tyrosine kinase receptor and a member of the TAM kinase family with the high-affinity ligand growth arrest-specific protein 6 (GAS6). Abnormal expressions or deviants of the Gas6/AXL axis have been documented in various solid neoplasms including RCC [84]. ROR2-positive biopsy patients will be administered with CCT301-59 while the AXL-positive biopsy arm will receive CCT301-38. During the manufacturing process of CAR-T cells, patients will receive a conditioning regimen after which a cycle of intravenous CCT301-48 or CCT301-59 is administered. A three-plus-three dose-escalation model will evaluate the feasibility of this immunotherapy module.

A phase I/II non-randomized trial evaluated the safety and effectiveness of a retrovirus genetically modified to incorporate the anti-VEGF receptor 2 in mRCC patients (NCT01218867) [85]. Participants received a non-myeloablative lymphocyte-depleting regimen along with a combination treatment of CAR gene-transduced CD8 and peripheral blood mononuclear cell with aldesleukin. Cohort 1 included patients with metastatic melanoma and RCC and cohort 2 represented patients with miscellaneous metastatic tumors. The study was terminated after the results showed no OR. Another phase I/II clinical trial is evaluating CAR-T cell gene transfer (NCT02830724) [86]. The peripheral blood lymphocytes are transduced with an anti-hCD70 CAR-T cell and a high-dose IL-2 combination regimen. CD70 is a type II transmembrane protein expressed on antigen-presenting cells and is induced rapidly on T and B cells during the activation of immune cells. CD70 is upregulated in tumorous conditions where cytotoxic effects on B and T lymphocytes are increased, which results in immune escape. CD70 is highly expressed in ccRCC and renal cell tumors with papillary and sarcomatoid histologies. Moreover, studies have shown that RCC tumors with a high expression of CD70 are correlated with decreased survival, providing the rationale for CD70 to be a target for RCC immunotherapy. The primary objectives are the safety of anti-hCD 70 CAR-T cells and their therapeutic benefits [86].

A single-arm, open-label, multicenter phase I dose-escalation and cohort expansion study of the safety and efficacy of allogenic clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 engineered T cells (CTX 130) in subjects with advanced, relapsed, or refractory ccRCC (COBALT-RCC) recruited patients to observe the effects of CTX 130 (NCT04438083) [87]. CTX130 comprises allogeneic CRISPR/Cas9 gene-edited CAR-T cells modified *ex vivo*, which targets CD70, and is studied as a potential molecular target. Participants will receive CTX 130, with the primary outcome measures of adverse events and ORR [87].

A phase I/II, single-arm, open-label trial (NCT03638206) is testing T cells with engineered CAR vectors targeting the tyrosine-protein kinase MET (c-MET) [88]. Participants will be treated with cyclophosphamide or fludarabine and receive CAR-T cells that have modified CAR vectors that specifically target c-MET expressed in RCC. The primary outcome is the number of adverse events [88].

Recently, the Food and Drug Administration granted fast track designation to the phase I TRAVERSE trial (NCT04696731) [89]. This study evaluates the safety, efficacy, and cellular kinetics of ALLO-316 in advanced or mRCC patients who underwent prior lymphodepletion therapy that consists of fludarabine, cyclophosphamide, and ALLO-647. ALLO-316 is an allogenic CAR-T cell platform that targets CD70 expressed in RCC.

The study of CaIX-targeted CAR-T cells in the treatment of advanced RCC (NCT04969354) is a two-phased clinical study to analyze the safety and efficacy of CAR-T cells targeting CaIX. In the first phase, patients were randomly divided into four groups. The patients were administered cyclophosphamide, fludarabine, and anti-human CaIX monoclonal antibodies (G250) before CAR-T cell infusion. CAR-T cells with IL-2 were infused into the patients three times per week. After determining the maximum tolerated dosage against CAR-T cells, patients in the second phase underwent chemotherapy and G250 infusion before CAR-T cell therapy. Following 6 months of follow-up, the patients will undergo assessment for five years [90].

An open-label dose-escalation phase I study (NCT05239143) has been recently activated to study the treatment effects of P-MUC1C-ALLO1 in subjects with advanced or metastatic solid tumors which includes RCC. P-MUC1C-ALLO1 is an al-

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Table 1. Active clinical trials with CAR-T cell immunotherapy enrolling renal cell carcinoma patients

Identifier or study title	Clinical phase	RCC setting	Type of CAR-T cell	Costimulatory domain	Primary endpoints	Reference
Safety and efficacy of CCT301 CAR-T in adult subjects with recurrent or refractory stage IV RCC (NCT03393936)	I/II	Recurrent or refractory stage IV RCC	CCT301-59 CCT301-28	ROR2	Safety ORR	[82]
CAR-T cell receptor immunotherapy targeting VEGFR2 for patients with metastatic cancer (NCT01218867)	I/II	Metastatic RCC	Anti-VEGFR2 CAR-T cell	VEGFR2	Complete response and partial response	[85]
Administering peripheral blood lymphocytes transduced with a CD70 binding chimeric antigen receptor to people with CD70 expressing cancers (NCT02830724)	I/II	RCC	Anti-hCD70 CAR-T cell	CD70	Safety	[86]
COBALT-RCC (NCT04438083)	I	Relapsed or refractory RCC	CTX130	CD70	Adverse events and ORR	[87]
Autologous CAR-T/TCR-T cell immunotherapy for malignancies (NCT03638206)	I/II	RCC	CAR-T cell/TCR-T cell	c-MET	Safety and adverse events	[88]
TRAVERSE (NCT04696731)	I	Metastatic RCC	Allogenic CAR-T cell	CD70	Safety and efficacy	[89]
The clinical study of CaIX-targeted CAR-T cells in the treatment of advanced renal cell carcinoma (NCT04969354)	I	Advanced RCC	CAR-T cell	CaIX	Safety and efficacy	[90]
P-MUC1C-ALLO1 allogeneic CAR-T cells in the treatment of subjects with advanced or metastatic solid tumors (NCT05239143)	I	Advanced or metastatic RCC	Allogenic CAR-T cell	Mucin 1 cell surface-associated C-terminal	Maximum tolerated dose and recommended phase II dosage	[91]

CAR, chimeric antigen receptor; RCC, renal cell carcinoma; NCT, National Clinical Trial; ORR, objective response rate; COBALT-RCC, study of the safety and efficacy of allogenic CTX 130 in subjects with advanced, relapsed, or refractory clear cell renal cell carcinoma; CTX130, allogenic clustered regularly interspaced short palindromic repeats-Cas9 engineered T cells; TCR, T-cell receptor; CaIX, carbonic anhydrase IX; P-MUC1C-ALLO1, allogeneic CAR-T cell therapy designed to target cancer cells expressing Mucin 1 cell surface-associated C-terminal antigen.

logeneic CAR-T cell therapy designed to target cancer cells expressing Mucin 1 cell surface-associated C-terminal antigen. Patients will be treated with the aforementioned CAR-T cells and will undergo evaluation for safety, tolerability, and response to the treatment [91]. Table 1 summarizes clinical trials that are ongoing with the continuous research of the therapeutic benefits of CAR-T cells for the treatment of advanced and mRCC patients.

FUTURE DIRECTIONS IN RENAL CELL CARCINOMA TARGETED CAR-T CELL IMMUNOTHERAPY

1. Single-cell technology

Extensive cellular knowledge of the tumor composition is mandatory for effective immunotherapy [92]. Advances in single-cell technology have provided options to bypass and incorporate intratumor heterogeneity by individually identifying cells composing the neoplasm. A study sequenced single-cell RNA (scRNA) to elucidate the relationship between RCC tumor heterogeneity and lung metastasis [93]. After activating the drug target pathways, the study showed that variability in tumor cells existed between primary and distant metastatic sites. The findings show the potential of single RNA sequencing for the discovery of novel biomarkers and characterizing the cellular components of RCC. Zhang et al. [94] utilized scRNA-sequencing to map molecular atlas for benign and malignant renal tumors. Using a random forest model, the investigators elucidated molecular attributes of the TME in ccRCC, along with the relationship between the tumor epithelia and immune cell infiltration. The results provide insight into the influence of the RCC TME and its response to treatment. Moreover, Hu et al. [95] investigated the intratumor heterogeneity of ccRCC by analyzing scRNA sequencing data and identified 15 major cell types. The results confirmed that T cell exhaustion is a major factor in the immunosuppressive properties of RCC which leads to a poor prognosis. The study concluded that immunosup-

pressive checkpoints such as PD-1, LAG3, and TIM3 could be considered potential targets for immunotherapy. Single-cell technology has broadened the horizons for the diagnosis and treatment of RCC. Su et al. [96] reported that scRNA-sequencing has revealed potential tumor-specific markers for RCC in the clinical setting. Results revealed that novel specific tumor markers for different types of RCC such as SPOCK1, PTGIS, REG1A, CP, and SPAG4 showed potential for prognostication. In addition, by employing these scRNA-sequencing results, predicting drug activation pathways and responses was possible for RCC.

2. Adoptive T-cell therapy

The advantages of adoptive T-cell therapy are the high production number of anti-tumor effector T-cells in treated patients and a favorable response rate. However, the occurrence of adverse events in RCC patients undergoing CAR-T cell therapy emphasizes careful patient screening and target selection [60]. Results of trials with the TCR engineered T-cell therapy targeting New York esophageal squamous cell carcinoma 1, MAGE-A4 cancer-testis antigen, and human papillomavirus proteins for the treatment of various solid neoplasms warrant further advancements in CAR vectors and tumor antigen-specific TCRs [97]. The identification of a tumor antigen that specifically targets RCC is of utmost importance. The focus is on antigen targets associated with durable benefits and significant tumor regression. However, identifying an effective antigen for specific TCR sequences poses a challenge. Currently, cutting-edge technologies such as enhanced detection methods for neoantigen reactive T cells and TCR-epitope pairs are studied for an effective T-cell antigen for the treatment of RCC [98].

3. Imaging studies

As an augmentative method, imaging studies can provide spatial information or images of treatment in a chronological fashion. The advantages of these novel methods are that they are non-invasive and allow assessment at different time points. Since only a limited number of CAR-T cells are infused into the patient, there is a need for an *in vivo* detection technique to access the efficacy and pharmacodynamics. Bensch et al. [99] showed that positron emission tomography (PET) imaging was able to assess the biodistribution of zirconium 89 (89Zr)-labeled atezolizumab in tumors expressing PD-L1 between primary tumors and sites of metastasis. The study revealed that tumors had a heterogeneous uptake, and the clinical response better correlated with the pretreatment PET signal compared to immunohistochemistry or RNA sequenced biomarkers.

Reporter gene cell imaging with radionuclides is now being applied to the field of CAR-T cells [100]. Compared to the direct radioisotope labeling method, the advantages of this approach are the absence of background or non-specific radioactivity, no interruption of CAR-T cell function which includes expansion and phagocytosis, and provision of information on the location or number of cells and their functional status. As an augmentative method to immunotherapy, engineering reporter constructs to CAR-T cells before reinfusion will allow the physician to track the pharmacokinetics of the CAR-T cells.

CONCLUSIONS

The disease spectrum of RCC includes various molecular alterations. Therapeutic options have expanded with advances in immunotherapy and have brought substantial improvement in survival. The potential therapeutic benefits of CAR-T therapy have encouraged investigation into integrating this as a treatment option for RCC patients in the advanced setting. Developments in biomarkers are needed for the better stratification and selection of RCC patients who will benefit from treatment and overcome resistance. The existence of on-target/off-tumor toxicity infers the need for cautious approach in the administration of CAR-T cell therapy for RCC treatment. Nevertheless, with ongoing efforts and breakthroughs of such challenges, CAR-T cell immunotherapy holds great potential in the treatment of RCC in the future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Tae Jin Kim and Kyo Chul Koo. Data acquisition: Tae Jin Kim and Young Hwa Lee. Statistical analysis: none. Data analysis and interpretation: Tae Jin Kim and Kyo Chul Koo. Drafting of the manuscript: Tae Jin Kim. Critical revision of the manuscript: Tae Jin Kim and Kyo Chul Koo. Obtaining funding: none. Administrative, technical, or material support: none. Supervision: Kyo Chul Koo. Approval of the final manuscript: all

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