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Chimeric Antigen Receptor-T Cell (CAR-T Cell) Therapy in Advanced Renal Cell Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. Author BMC conceptualized the paper, reviewed the literature, and wrote the paper. Other authors PP, JKI, AG, EV, LM, LKD and RPG reviewed the paper, and provided useful inputs that helped in shaping the paper. All authors read and approved the final manuscript.

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ABSTRACT

With introduction of immunotherapy, the treatment of advanced renal cell carcinoma has undergone a substantial change. Immunotherapeutic agents including nivolumab, ipilimumab, pembrolizumab, have been introduced and approved for therapy of this life-threatening malignancy. Chimeric antigen receptor- T cells produced using adoptive cell transfer genetic engineering technology, have shown significant benefits over previous immunotherapies, but their toxicity profile needs to be carefully weighed. While they have shown significant benefit in hematological malignancies, their role in solid tumors has shown mixed results. Several clinical trials are ongoing to evaluate their safety and efficacy in several malignancies, including advanced renal cell carcinoma.
This paper reviews in brief the immunotherapy and CAR-T cell therapy in renal cell carcinoma.

Keywords: Chimeric antigen receptor; CAR-T cell therapy; renal cell carcinoma.

1. INTRODUCTION

Renal cell carcinoma (RCC) is a life-threatening malignancy, with median age at diagnosis of 64 years [1]. Most common histological subtype is clear cell RCC (ccRCC), accounting for nearly 80% of all RCC; other histologic subtypes being papillary, chromophobe, translocation, and collecting duct tumors [1].

Immunotherapy has shown promising results in treatment of renal cell carcinoma [2]. Nivolumab (OPDIVO, from Bristol-Myers Squibb Company), an anti-programmed death-1 (PD-1) monoclonal antibody, was approved by U.S. Food and Drug Administration (FDA) on November 23, 2015 for treatment of advanced renal cell carcinoma as a second line therapeutic option [1,2]. Later, new combination therapies including immunotherapy drugs were approved by U.S. FDA as first line agents to treat advanced RCC [2]. On April 16, 2018, U.S FDA approved combination therapy with the immunotherapy drugs nivolumab (Opdivo) and ipilimumab (Yervoy) as first-line treatment for patients with advanced RCC [3]. On April 19, 2019, the U.S. FDA approved pembrolizumab plus axitinib, and on 14 May, 2019 avelumab plus axitinib for first-line treatment of patients with advanced renal cell carcinoma (RCC) [4,5]. Again, very recently, On 22 Jan 2021, U.S. FDA approved a combination of nivolumab and cabozantinib (cabometyx) (a tyrosine kinase inhibitor) as first-line therapy in advanced renal cell carcinoma [6,7].

Further advancement in the field of immunotherapy in RCC includes CAR-T cell therapy [2]. CAR-T cell therapy has shown significant benefits over previous immunotherapies, but their toxicity profile needs to be carefully weighed over the benefits [2]. Several CAR-T cell therapies are already approved by U.S FDA for non-Hodgkin lymphoma and leukemia, including axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma, brexucabtagene autoleucel (Tecartus®) for relapsed or refractory mantle cell lymphoma, and tisagenlecleucel (Kymriah®) for relapse (second or later) or refractory B-cell precursor acute lymphoblastic leukemia (ALL) [8]. Recently in February 2021, U.S. FDA approved lisocabtagene maraleucel (Breyanzi®) for the treatment of relapsed or refractory large B-cell lymphoma [8,9]. Very recently, on March 2021, U.S FDA approved idecabtagene vicleucel (Abecma®) for treatment of relapsed or refractory multiple myeloma [10].

CAR-T cell therapy of advanced RCC is still in clinical trials stage [11-13]. In renal cell carcinoma, immunotherapy has shown promising results, so CAR-T cell therapy adds to the hopes, but significant nephrotoxicity of CAR-T cells is an important risk factor to consider [2].

2. GENERAL PERSPECTIVE ON IMMUNOTHERAPY

2.1 Immunotherapy in Clinical Practice

- **Naked (unconjugated) monoclonal antibodies**, for example alemtuzumab (anti-CD52), and rituximab (anti-CD20) [14]. Unconjugated monoclonal antibodies don't have any drug or radioactive particle attached. Their mechanism of action in treatment of cancer includes direct cell lysis, induction of apoptosis, complement dependent cytotoxicity, or antibody-dependent cell-mediated cytotoxicity [14].
- **Conjugated monoclonal antibodies,** for example inotuzumab (humanized monoclonal antibody anti-CD22) and brentuximab [14]. In conjugated monoclonal antibodies a chemotherapeutic

agent or radioactive particle is attached [14].

- **Bispecific T-cell engaging antibodies (BiTEs),** for example blinatumomab (anti-CD19). These antibodies link CD3+ T effector cells with target tumor cell and cause target cell lysis [14].
- **Chimeric Antigen Receptor T cells (CAR-T cells),** for example Tisagenlecleucel (Kymriah), and axicabtagene ciloleucel [14]. Tisagenlecleucel and axicabtagene ciloleucel target tumor cells that express CD19, and induce cytotoxicity in them [14]. The first generation of CAR-T cells failed to produce a satisfactory cytokine response and T cell expansion [14]. The second generation CAR-T cells had a co-stimulatory endo-domain that improved expansion and persistence of CAR-T cells [14]. Tisagenlecleucel is a second generation CAR-T cell therapy with a 4-1BB co-stimulatory domain, and targets CD19 [14].

2.2 CAR-T Cell Therapy

Chimeric antigen receptor T cells (CAR-T cells) are produced using an adoptive cell transfer technology. In this method, T cells harnessed from a patient's own blood (autologous) are genetically engineered to produce tumor antigen specific receptors on their surface, called chimeric antigen receptors. These CAR-T cells are multiplied, and then infused into the bloodstream of the patient after the patient has completed a lymphodepleting chemotherapy [15].

The Chimeric antigen receptor directs the CAR-T cells to attack the target cells [16]. Use of CAR-T cell therapy (especially CD-19 directed CAR-T cells) has shown a dramatic response in acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma [14,15].

2.3 CAR-T Cell Therapy Associated Toxicities

2.3.1 Cytokine release syndrome (CRS)

Krishnamoorthy et al observed poor outcomes and significant toxicities with the use of CAR-T cell therapy in 4 solid organ transplant recipients [2 orthotopic heart transplants, 1 deceased donor kidney transplant, and 1 pancreas after kidney transplant (PAK)] who had developed Post Transplant Lymphoproliferative Disorder (PTLD) 10 to 20 years post-transplant [16]. All these 4 patients developed cytokine release syndrome and neurotoxicity that was managed with tocilizumab [16]. Three out of these 4 patients developed acute kidney injury, received renal replacement therapy, and only 1 of these 3 recovered renal functions [16]. Other toxicities in these 3 patients were pancytopenia, pneumonia, and infections [16]. All and 3 of these patients did not survive (chose hospice care or de-escalation of treatment, and died): death occurred on day 15, day 25, and day 42 post CAR-T cell therapy, respectively [16]. The PAK transplant recipient developed acute pancreatitis post CAR-T cell immunotherapy (no acute kidney injury), showed continued response to therapy, with no new lymphomatous tissue involvement (as per assessment till 90 days post-transplant) [16].

Cytokine release syndrome is seen in nearly 40-50% of patients on CAR-T cell therapy [2]. Cytokine release syndrome involves excessive activation of leukocytes, and massive release of inflammatory cytokines [14]. Interleukin-6 (IL-6) is a key mediator in cytokine release syndrome. There are several other cytokines involved, including (but not limited to) interferon gamma (IFN-γ), granulocyte-monocyte colony stimulating factor (GM-CSF), soluble glycoprotein 130 (sgp130), and interleukin-8 (IL-8) [14]. Tocilizumab is a humanized monoclonal antibody against IL-6 receptor, serves as an interleukin-6 receptor inhibitor, and is used in treatment of CRS [14]. The risk factors for cytokine release syndrome in B cell-ALL include high disease burden, lymphodepletion therapy, thrombocytopenia prior to lymphodepletion, and use of higher CAR-T cell dose [14,17].

Generally, CRS is seen days to weeks after infusion with CAR-T cell therapy, unlike CRS after rituximab (unconjugated monoclonal antibody) which appears within hours of the infusion [14].

CRS is associated with fever (usually the first sign) [14]. Multiple organ dysfunction is seen in CRS, with life threatening complications including hypotension unresponsive to fluid resuscitation, cardiac dysfunction, coagulopathy, and respiratory, renal, and hepatic failure [14]. The treatment approach is supportive care fluid resuscitation, and antipyretics for mild CRS [14]. When severity of CRS increases, anti-interleukin-6 (anti-IL6) therapy (for example, tocilizumab and siltuximab) and corticosteroids [14]. Anti-IL6 therapy is preferred over corticosteroids in treatment of CRS, but in very severe cases both may be required [14]. Corticosteroids may

adversely affect the function of T-cells, and diminish persistence and anti-tumor activity of CAR-T cells [14]. If CRS is life threatening, and anti-IL6 therapy is not effective, high dose corticosteroids may be needed [14].

2.3.2 Neurotoxicity [CAR-T cell-related encephalopathy syndrome (CRES) and immune effector cell-associated neurotoxicity syndrome (ICANS)]

It is also known as immune effector cell-associated neurotoxicity syndrome (ICANS) [14]. Initial manifestations of CRES can be subtle neurological signs and symptoms including headache, lethargy, tremor, mild aphasia, apraxia and dysgraphia [14]. As neurotoxicity progresses, severe aphasia, delirium, hallucinations and encephalopathy may manifest [14]. Rarely seizures, coma, and fatal cerebral edema can occur [14].

The underlying mechanism involved for development of CRES is poorly understood [14]. It is believed that CRES occurs either due to direct cytotoxic effect of the CAR-T cell therapy, or due to CRS. Significant inflammation, and early activation of central nervous system endothelial cell (CNS-EC) disrupts the blood-brain barrier (BBB) by increasing its permeability and influx of high levels of inflammatory cytokines into the CNS [14,17]. There are controversies regarding effective management strategy for CRES, other than the use of corticosteroids for treatment of cerebral edema [14].

2.4 Acute Kidney Injury and Tumor Lysis Syndrome

Acute kidney injury may occur due to tumor lysis syndrome or due to CAR-T cell therapy as a part of cytokine release syndrome (CRS) [15,18]. Tumor lysis syndrome occurs when tumors release their contents into patient's blood either due to chemotherapy, or spontaneously. This may result in several metabolic abnormalities including hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and may cause toxic effects including acute kidney injury, cardiac arrythmias, seizures or death [15,18,19].

2.5 On-Target Off-Tumor Toxicity

CAR-T cell therapy, with receptors targeted towards specific tumor antigen can be significantly toxic if these tumor antigens (targeted by CAR-T cells) are expressed in normal cells (even if the level of expression is low). This is called 'on target' toxicity [20]. 'On target' toxicity is a serious concern, and different strategies have been tried, and are being tried to develop CAR-T therapy technique to minimize 'on target' toxicity. This includes split-dose or lesser dose CAR-T cell therapy, saturating CAIX (carbonic anhydrase IX) sites in the liver using anti-CAIX monoclonal antibodies before giving CAR-T cells [20].

2.6 Advanced Renal Cell Carcinoma-Therapeutic Options

Immune checkpoint inhibitors directed against CTLA-4 (example ipilimumab), PD-1 (example pembrolizumab and nivolumab), and PD-L (example, atezolizumab) is an essential component of treatment of patients with advanced RCC [21-25]. For patients having majority of their tumor burden confined to their primary tumor, presenting with stage IV disease, and there are no other IMDC (International Metastatic RCC Database Consortium) risk factors, cytoreductive nephrectomy is considered a preferable option [24]. Patients who need immunotherapy, depending on whether or not the patient has clear cell pathology, and the IMDC risk model for metastatic RCC profile (favorable or poor/intermediate risk, the initial immunotherapy choices include pembrolizumab + axitinib combination therapy; Ipilimumab + nivolumab; anti VEGF tyrosine kinase inhibitors; anti-PD1 monotherapy; and High-dose interleukin-2 (HD-IL2) [24].

Tyrosine kinase inhibitors, such as cabozantinib, inhibit new vessel formation, and have been found to be effective in treatment of renal cell carcinoma [21]. Cabozantinib was approved by U.S. FDA in 2016 for treatment of patients with advanced RCC who had already received prior antiangiogenic therapy [26]. Later, FDA approved this drug (cabozantinib, Cabometyx) for first-line treatment of advanced Renal Cell Carcinoma on 19 December 2017 [26]. Again, recently, on January 22, 2021, F.D.A approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced renal cell carcinoma (RCC) [6].

2.7 CAR-T Cell Therapy in Renal Cell Carcinoma

Cor H.J Lamers, et al developed first generation CAR-T model against carbonic-anhydrase-IX

Table 1. CAR-T cells clinical trials in renal cancer (either exclusively or together with other malignancies)

Clinical Trial Identifier	Sponsor	Title	Phase	Study start date	Study completion date	Estimated number of subjects	Results Posted?
NCT03638206	Shenzhen BinDeBio Ltd.	Autologous CAR-T/TCR-T Cell Immunotherapy for Malignancies.[24]	I/II	March 1, 2018	March 1, 2023	73	No
NCT03393936	Shanghai PerHum Therapeutics Co., Ltd.	Safety and Efficacy of CCT301 CAR-T in Adult Subjects with Recurrent or Refractory Stage IV Renal Cell Carcinoma.[25]	I/II	March 26, 2018	March 30, 2035	66	No
NCT02830724	National Cancer Institute (NCI)	Administering Peripheral Blood Lymphocytes Transduced with a CD70-Binding Chimeric Antigen Receptor to People With CD70 Expressing Cancers.[26]	I/II	April 6, 2017	January 1, 2028	124 (actual enrolment 2)	No (Recruitment suspended)
NCT01218867	National Cancer Institute (NCI)	CAR T Cell Receptor Immunotherapy Targeting VEGFR2 for patients with Metastatic Cancer.[27]	I/II	November 10, 2010	December 15, 2015	24 (actual enrolment)	Yes. Study terminated (observation: no objective responses)
NCT04633148	Cellex Patient Treatment GmbH	Dose-escalating trial with UniCAR02-T Cells and PSMA Target Module (TMpPSMA) in patients with progressive disease after standard systemic therapy in cancers with positive PSMA marker.[28]	I	November 23, 2020	May 2023	35	No

Abbreviations: *CAR: chimeric antigen receptor. TCR: T-cell receptor. VEGFR: vascular endothelial growth factor receptor. PSMA: prostate specific membrane antigen.*

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NCT03393936-NIH: U.S. National Library of Medicine. Safety and Efficacy of CCT301 CAR-T in Adult Subjects With Recurrent or Refractory Stage IV Renal Cell Carcinoma. Clinical trials.gov. Accessed from: https://clinicaltrials.gov/ct2/show/NCT03393936.

NCT02830724-NIH: U.S. National Library of Medicine. Administering Peripheral Blood Lymphocytes Transduced With a CD70-Binding Chimeric Antigen Receptor to People With CD70 Expressing Cancers. Clinicaltrials.gov. Accessed from: https://clinicaltrials.gov/ct2/show/NCT02830724.

NCT01218867- NIH: U.S. National Library of Medicine. CAR T Cell Receptor Immunotherapy Targeting VEGFR2 for Patients With Metastatic Cancer. Clinicaltrials.gov. Accessed from: https://clinicaltrials.gov/ct2/show/NCT01218867.

NCT04633148- NIH: U.S. National Library of Medicine. Dose-escalating Trial With UniCAR02-T Cells and PSMA Target Module (TMpPSMA) in Patients With Progressive Disease After Standard Systemic Therapy in Cancers With Positive PSMA Marker. Clinicaltrials.gov. Accessed from: https://clinicaltrials.gov/ct2/show/NCT04633148.

(CAIX) and treated 3 patients with metastatic renal cell carcinoma (RCC) [disseminated clear cell RCC] expressing CAIX [27]. This was first clinical experience of using CAR-T cell therapy in metastatic RCC [27]. One of the problems they experienced in this trial was 'on-target' toxicity manifested as dose limiting liver enzyme disturbances in 2 out of the 3 patients [20]. The on-target toxicity is due to expression of CAIX antigens in bile duct epithelial cells [20]. Besides being present on RCC, CAIX antigens are expressed in several normal tissues including gastric mucosa epithelium, duodenum, small intestine, and bile duct [28]. Also, hypoxia can induce CAIX expression in many other tissues [28]. To prevent or decrease on-target toxicity, they used a technique of shielding the CAIX sites in the liver but not tumor by applying a CAIX monoclonal antibody (mAb) [intravenous infusion of 5 mg of the anti-CAIX mAb G250, 3 days before each series of CAR-T cell infusions] leaving CAIX antigen in renal cell carcinoma accessible [20]. They applied this technique on the next 9 patients (total 12 subjects were studied) [20]. All these 12 patients had their diseased kidney removed, and had treatment refractory metastasis (mainly in the lungs) [20]. They found that by using anti-CAIX mAb to saturate CAIX sites in liver, they could effectively block the liver toxicity, and also could extend peripheral CAR-T cell persistence. CAR-T cells persisted for up to 4 weeks following first treatment cycle, and 1-3 weeks following second treatment cycle when anti-CAIX mAb was not used. When anti-CAIX mAb was used, the CAR-T cells persisted for 3-5 weeks following both first and second treatment cycles [20].

Li Huizhong, et al developed a second-generation CAR-T model targeting antigen carbonic anhydrase IX (CAIX) that is human renal cell carcinoma specific [29]. They used this CAR-T model together with sunitinib, a multitargeted tyrosine kinase inhibitor that improves T- cell infiltration and type-1 T-cell cytokine response. Sunitinib, as a monotherapy had shown objective response rate of approximately 30%. Li Huizhong, et al. found in their study that the combination therapy (second generation CAR-T cells + sunitinib) significantly improved the efficacy against the established mouse lung metastasis model of human renal cell carcinoma prolonged survival of the recipient mice [29].

Wang Y, et al developed dual targeted CAR-T cells against CAIX and CD70. These CAR-T cells had the ability to target double positive (CAIX+ CD70+) and single positive (CAIX+ CD70-, CAIX- CD70+) tumor cells. The investigators showed that their dual targeted model had superior efficacy and persistence when compared with other CAR-T cell models in clear cell renal cell carcinoma (ccRCC) orthotopic mouse model [30].

Several clinical trials, as outlined in Table 1, are testing/have tested safety and efficacy of CAR-T cell therapy in Renal cell carcinoma [31-35]. While outcomes of these clinical and preclinical studies seems promising, more research is needed to establish whether or not CAR-T cells are safe and effective in treatment of renal cell carcinoma.

3. CONCLUSION

Before the availability of biologic therapy and immunotherapy for RCC, it was very difficult to treat this tumor, especially in advanced stages. The only treatment available was surgery, and RCC was resistant to chemotherapy. Biologics and immunotherapy improved survival, and brought a new hope in treating RCC. CAR-T cells are relatively new in the therapeutic arsenal. They have shown very promising results in treatment of hematological malignancies, and some of these agents (Axicabtagene ciloleucel, Brexucabtagene autoleucel, Tisagenlecleucel, lisocabtagene maraleucel, and idecabtagene vicleucel) have been approved by U.S. FDA for treatment of these malignancies; their effectiveness and benefit in managing solid tumors remains an area of research. CRS, neurotoxicity, nephrotoxicity, tumor lysis syndrome, and other adverse events associated with use of CAR-T cells pose a challenge for researchers. Newer generations of CAR-T cells are being designed and tested to reduce the toxicity profile and provide better outcomes. Several clinical trials are ongoing to test safety and efficacy of CAR-T cell therapy in RCC, and hopefully the research will provide the miracle to the community in near future.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

DISCLOSURE STATEMENT

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Authors have declared that no competing interests exist.

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