Novel immunotherapy in metastatic renal cell carcinoma

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Despite the rapid development of therapeutic modalities for metastatic renal cell carcinoma (mRCC) over the past decade to include a number of targeted antiangiogenic therapies and traditional immunotherapy, such as high-dose interleukin-2 and interferon-α, mRCC continues to be associated with poor prognosis. Currently, several novel immunotherapy agents, such as cancer vaccines, adoptive cell therapy, and checkpoint inhibitors, such as programmed cell death-1 (PD-1 present on T cells), one of its ligands (PD-L1 present on antigen-presenting cells and tumor cells), and cytotoxic T-lymphocyte-associated protein-4 pathways, are being studied in mRCC and are showing promise as important steps in the management of this disease. This review summarizes the current landscape of standard and emerging immune therapeutics and other modalities for mRCC.

Keywords: Immune checkpoint inhibitors; Immunotherapy; Renal cell carcinoma; Vaccines

INTRODUCTION

Renal cell cancer (RCC) is not an uncommon malignancy, with an estimated worldwide annual incidence of about 270,000 new cases; approximately 25% to 30% of cases are metastatic at diagnosis [1,2] and 20% to 30% of patients who undergo surgical management for local RCC show relapse [3]. RCC is different from other variable epithelial tumors in that it is inherently resistant to cytotoxic chemotherapy and effective systemic therapeutics did not exist for a long period of time. Despite efficacy of high-dose interleukin-2 (IL-2) and interferon-α (IFN-α) for metastatic RCC (mRCC), the 5-year survival rate was only 10% [4,5]. In the past decade, several agents targeting antiangiogenesis and signal transduction pathways such as sunitinib, pazopanib, temsirolimus, everolimus, and axitinib have replaced the use of cytokines after showing improved clinical benefit and survival, with a median survival to approximately 40 months and a progression-free survival of up to 27 months in randomized prospective clinical trials [6-8].

However, antiangiogenic therapeutics, which mainly target the vascular endothelial growth factor pathway and mammalian target of rapamycin pathways rarely cause durable tumor regressions and most patients will eventually experience disease progression. Currently, the rapidly evolving field of immuno-oncology is yielding novel immunotherapeutic agents. Cancer vaccines, adoptive T-cell therapy, and checkpoint inhibitors are some of the strategies being used in mRCC patients. This review will focus on a brief overview of the current treatment of mRCC using immunotherapy.
TRADITIONAL IMMUNOTHERAPY FOR mRCC

The fields of immuno-oncology have been connected since the late 19th century when the American bone surgeon and cancer researcher, William Coley, showed that an injection of killed bacteria into sites of sarcoma could bring out tumor shrinkage [9]. Following that, Chen and Mellman [10] reported that an adaptive immune response requires presentation and education about its targets, and cancer cell turnover and its associated apoptosis of cells lead to the release of tumor-associated antigens, which are then captured by antigen presenting cells, called the dendritic cells. Dendritic cells migrate to secondary lymphoid organs where effector T cells are being educated and activated. They then infiltrate tumors and recognize and induce the apoptosis of cancer cells expressing specific tumor-associated antigens or mutated proteins [10].

RCC has long been recognized as an immunologically sensitive tumor, with its select successes with IFN-α and high dose IL-2 treatment. IL-2 is a potent stimulator of T-cell proliferation and differentiation, while INF-α has antiangiogenic effects, promoting antigen presentation and dendritic cell maturation. However, their precise mechanism of action is not well known. The efficacy of IFN-α for mRCC patients were first reported in 1989 [11] Subsequent phase III studies of IFN-α showed a 15% response rate and an increase in overall survival from 3 to 7 months [12]. However, most responses to IFN-α were of limited duration and only a small number of patients showed complete responses. In addition, long-term use of IFN-α was difficult due to side effects such as flulike symptoms and liver toxicity. High dose IL-2 was approved in 1992 for treatment of mRCC based on an objective response rate between 10 and 20%; many of the responses were durable [13]. High dose IL-2 showed partial responses in 13% and complete responses in 7%. After treatment, the response lasted for up to 91 months. Despite the response to high dose IL-2, there is a limitation of significant toxicity that can demonstrate in multiple organ systems, most significantly the heart, lungs, kidneys, and central nervous system.

VACCINES

Studies on vaccine therapies in mRCC are ongoing.

1. AGS-003

AGS-003 is a dendritic cell immuno-therapeutic vaccine constructed from autologous blood dendritic cells and generated through electroporation of tumor-derived RNA and CD40 ligands into host immune cells, which was tested in combination with sunitinib [14-18]. Treatment is given by intradermal injection, and the tumor RNA-loaded mature dendritic cells present unique patient-specific tumor antigens via the major histocompatibility complex class I to T cells in tumor-draining lymph nodes. Furthermore, CD40 ligation promotes CD8 positive T-cell recruitment through regional production of IL-12. The phase II study of AGS-003 enrolled 21 patients with an intermediate or poor prognostic risk category of metastatic clear cells [16]. Patients were treated with 1 cycle of sunitinib (4 weeks on, 2 weeks off), followed by concomitant AGS-003 immunotherapy every 3 weeks for 5 doses and then every 12 weeks until tumor progression or the end of the study. Nine patients had a partial response, and four had stable disease. Median progression-free survival and overall survival were 11.2 months and 30.2 months, respectively, and 5 patients lived more than 5 years. Of 21 patients, 13 (62%) achieved a clinical benefit (9 with a partial response and 4 with stable disease). Treatment with AGS-003 was well tolerated, with injection site reactions as the primary adverse event. Remarkably, overall survival was more than 5 years in 5 patients (24%), with 2 patients achieving durable responses for more than 5 years. Based on these promising results, a randomized multicenter phase III ADAPT trial is now ongoing, to determine where there is an overall survival benefit between AGS-003 plus sunitinib in comparison to sunitinib alone in mRCC patients undergoing debulking nephrectomy (NCT01583672) [19].

2. IMA901

IMA901 is a therapeutic vaccine developed from multiple naturally presented tumor-associated peptides (TUMAP) [20-24]. A phase II clinical study investigated the effect of systemic treatment with IMA901 plus granulocyte macrophage-colony stimulating factor with or without cyclophosphamide as an additional immune-modulator before the first vaccination. The disease control rate at 6 months was 31% in the postcytokine group, and 14% at 6 months in the posttyrosine kinase inhibitors [22]. The majority of adverse events reported were local injection site reactions. A multicenter, open-label, randomized, phase III IMPRINT study comparing sunitinib with or without this vaccine for mRCC was recently completed. Unfortunately, the overall survival was not ameliorated with IMA901 plus sunitinib versus sunitinib alone [24].

3. Modified vaccinia Ankara (MVA-ST4; TroVax)

The 5T4 oncofetal antigen is rarely detected in normal
adult tissues but is expressed at high levels by the placenta and by a range of human carcinomas including kidney, colorectal, prostate, ovary, and breast. MVA-5T4 was engineered to stimulate the immune system to destroy cells expressing the 5T4 antigen. About 90% of renal cell tumors overexpress the tumor antigen 5T4 [25-28]. A randomized, double-blind, placebo-controlled phase III study (TRIST trial) assessed overall survival and safety in patients with metastatic clear cell RCC [28]. Patients were randomized to MVA-5T4 (n=365) or placebo (n=368) in combination with sunitinib, IL-2, or IFN-α. No significant difference in overall survival was apparent between the two treatment arms (median 20.1 months MVA-5T4 versus 19.2 months placebo; p=0.55). The adverse events profile was also similar between the treatment arms.

4. Autologous tumor cell lysate (Reniale)

 Principally, autologous tumor cell lysate vaccine stimulates antigen-presenting cells, such as dendritic cells, and these cells stimulate a cytotoxic T lymphocyte response towards tumor associated antigens expressed by RCC, mediating tumor cell destruction [29-31]. Autologous tumor cell lysate vaccine improved progression-free survival in a phase III study of patients with organ confined RCC [32]. The 10-year follow-up analysis revealed that overall survival was comparable between the vaccine group and control patients. However, in subgroup analysis, pT3 RCC patients had overall survival benefit by Reniale (Liponova AG, Hannover, Germany). Additional current studies on non-protein antigens have been limited.

ADOPTIVE CELL THERAPY

Adoptive cell therapy, as an encouraging method of immunotherapy, harnesses the cells that can be expanded in vitro and have intrinsic antitumor activity to eliminate malignant cells. Examples include tumor antigen specific cytotoxic T lymphocytes (CTL), lymphokine-activated killer cells, tumor-infiltrating lymphocytes, and cytokine-induced killer cells [33-39]. Adoptive cell therapy for mRCC was reported in 1990 and since then many clinical trials of this therapy in mRCC patients have been completed. A number of studies of adoptive cell therapy for mRCC patients have shown the median survival is only 10.2 months and the 5-year survival rate is less than 15% [39]. However, the worth of adoptive cell therapy for mRCC is still unclear, especially for tumor regression and prolonging survival.

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are being investigated in the majority of solid and hematologic malignancies, and are already approved or under development. Immune checkpoint proteins on CTL cut off costimulatory signals at various stages of immune activation after ligand binding and this gives rise to T-cell anergy and immune suppression. Cutting off these immune checkpoint proteins appears to improve the capability of CTL to mount and maintain an effective T cell response [40-42]. Immune checkpoint inhibitors under investigation include the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, ipilimumab (YERVOY; Bristol-Myers Squibb, New York, NY, USA) and tremelimumab; the programmed cell death protein 1 (PD-1) inhibitors, nivolumab (OPDIVO; Bristol-Myers Squibb, New York, NY, USA, which is US Food and Drug Administration [FDA] approved), pembrolizumab (KEYTRUDA; Merck & Co., Inc, Kenilworth, New Jersey, USA), and pidilizumab; and the programmed cell death protein ligand 1 (PD-L1) inhibitors atezolizumab (TECENTRIQ; Roche, Basel, Swiss), BMS-936559, durvalumab, and avelumab [43] (Table 1).

1. CTLA-4 inhibitors

The immune system is modulated by a series of stimulatory and inhibitory signals that coordinate to show an appropriate response to a pathogenic threat. CTLA-4 is an immune checkpoint on the surface of cytotoxic T cells that counteracts the action of costimulatory receptor CD28 and plays a crucial role in the immune response. Ipilimumab, a human IgG that binds to and blocks CTLA4, was the first drug that was shown to produce a survival benefit in metastatic melanoma [44,45] and it received FDA approval for the treatment of advanced melanoma in 2011. In a phase II study of ipilimumab for mRCC, 5 of 40 responses were noted in the higher dose group (3 mg/kg every 3 weeks) compared to 1 of 21 responses in the lower dose group (3 mg/kg followed by 1 mg/kg every 3 weeks). Adverse events and tumor regression were more frequently observed in the higher dose group [46]. However, phase III trials investigating ipilimumab alone has not yet been studied.

2. PD-1 inhibitors

Programmed cell death-1 (PD-1) (CD279) is a cell surface receptor that consists of the Ig category and is expressed on activated effector T cells as well as natural killer cells and B cells. PD-1 interact with 2 ligands, PD-L1 and PD-L2, which are manifested in various cell types, including tumor cells [43,47,48]. A clinical study demonstrated that
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PD-1/PD-L1 interaction is an important regulator of tumor immune tolerance and tumor growth in RCC. Thompson et al. performed immunostaining on formalin-fixed paraffin-embedded tissue samples and showed that tumor cell PD-L1 membranous expression was seen in 24% of samples and was strongly associated with cancer-specific death (risk ratio 3.92; p<0.001) in RCC patients [48,49]. In another study, PD-L1 expression was detected by immunostaining in RCC patients with fresh frozen tissue available, and PD-L1 expression by tumor cells (>10%), on infiltrating lymphocytes (>50%), or the composite of both makers was strongly associated with poor prognosis [48].

Several clinical trials of the anti-PD-1 antibody (nivolumab) have been performed for RCC. Nivolumab (OPDIVO®) is a human IgG4 PD-1 inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. In a phase I study that included 34 patients with mRCC, nivolumab demonstrated objective responses and a controlled safety profile; no maximum-tolerated dose was identified (0.1 to 10 mg/kg every 3 weeks) [51]. A phase II study enrolled 168 patients with clear cell mRCC that had received at least one previous treatment (targeted agents or cytokines). Nivolumab was given at 0.3, 2, or 10 mg/kg every 3 weeks resulted in 20%–22% objective response rates of patients with a progression free survival of 2.7–4.2 months and an overall survival of 18.2–25.5 months. The most common treatment-related adverse event was fatigue (24%, 22%, and 35%, respectively) [52].

In the pivotal open-label, randomized phase III study (Check Mate 025), 821 patients with clear cell mRCC were treated with nivolumab (3 mg/kg every 2 weeks) and it reduced the hazard ratio for death (hazard ratio, 0.73; 95% confidence interval, 0.57–0.93; p=0.002) compared with everolimus (10 mg orally every day), representing a 5.4-month improvement in median overall survival (25 months and 19.6 months, respectively). The objective response rate among patients treated with nivolumab was 25% vs. 5% in the everolimus group (p<0.001). However, the median progression-free survival was similar between groups. The exact mechanism behind the discrepancy between progression-free survival and overall survival is not clear; the authors postulated that there might be a potential delayed benefit in progression-free survival with nivolumab. The clinical benefit provided by nivolumab was independent from PD-L1 expression. Grade 3 or 4 adverse events were also lower with nivolumab compared with everolimus [53].

Table 1. Ongoing clinical trials involving PD-1 and PD-L1 inhibitor use for treatment of metastatic renal cell carcinoma (phase II or III trials)

| Drug Line | NCT number* | Study name |
|-----------|-------------|------------|
| Nivolumab (OPDIVO®) | 2nd NCT02596035 | A Safety Trial of Nivolumab in Patients With Advanced or Metastatic Renal Cell Carcinoma |
| Nivolumab (OPDIVO®) | 1st NCT02446860 | A Study of Anti-PD1 (Nivolumab) Therapy as Pre- and Post-operative Therapy in Metastatic Renal Cell Cancer (ADAPTeR) |
| Nivolumab (OPDIVO®) + Ipilimumab (YERVOY®) | 1st NCT02231749 | Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214) |
| Pembrolizumab (KEYTRUDA®) | 1st NCT02014636 | Safety and Efficacy Study of Pazopanib and MK 3475 in Advanced Renal Cell Carcinoma (RCC; KEYNOTE-018) |
| Pembrolizumab (KEYTRUDA®) | 1st/2nd NCT02348008 | Phase Ib and Phase II Studies of Anti-PD-1 Antibody MK-3475 in Combination With Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium GU14-003 |
| Pembrolizumab (KEYTRUDA®) | 1st/2nd NCT02619253 | A Phase I/II, Open Label, Dose Finding Study to Evaluate Safety, Pharmacodynamics and Efficacy of Pembrolizumab (MK-3475) in Combination With Vorinostat in Patients With Advanced Renal or Urothelial Cell Carcinoma |
| Pembrolizumab (KEYTRUDA®) | 1st NCT02420821 | A Study of Pembrolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma (MM1001) |
| Pembrolizumab (KEYTRUDA®) | 1st NCT01984242 | A Phase II, Randomized Study of Pembrolizumab (Anti-PD-L1 Antibody) Administered as Monotherapy or in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma |
| Pembrolizumab (KEYTRUDA®) | 1st NCT02684006 | A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Carcinoma (JAVELIN Renal 101) |

PD-1, programmed cell death-1; PD-L1, programmed cell death protein ligand 1.

*https://clinicaltrials.gov/
Other PD-1 inhibitors, such as pembrolizumab (KEYT-RUDA, IgG4 monoclonal antibody) and pidilizumab (IgG1 monoclonal antibody), are currently undergoing clinical trials, the majority of which are combination trials. Pembroliizumab, approved for advanced melanoma and non-small-cell lung carcinoma, is currently being tested in two randomized phase II trials with mRCC patients [54]. There are several ongoing trials evaluating pembrolizumab in combination with other drugs.

3. Anti–PD-L1 antibodies

Based on the promising results of PD-1 inhibitors for the management of mRCC inspired more interest in the inhibition of the ligands of PD-1, namely PD-L1. PD-L1 is expressed on several cell types, including resting T cells, B cells, macrophages, dendritic cells, vascular endothelial cells, and pancreatic islet cells; PD-L2 is expressed only on macrophages and dendritic cells. PD-L1 and PD L2 inhibit T-cell proliferation and adhesion, as well as cytokine production [14,47,55]. Atezolizumab (TECENTRIQ), a PD-L1 antibody, has demonstrated encouraging results in a multicenter phase I monotherapy trial in 17 mRCC patients. The objective response rate was 12% and responses lasted 4 to 17 months. Seven mRCC patients (41%) had stable disease for at least 24 weeks [47]. In another recent study to evaluate the safety and clinical activity of atezolizumab, clear cell mRCC patients were evaluable for median overall survival, median progression free survival, and objective response rate (289 months, 56 months and 15%, respectively) [56].

BMS936559 binds human PD-L1 with high affinity and blocks PD-L1 binding to both PD-1 and B7.1. In a phase I study, 207 patients with different tumors were treated with BMS936559, including clear cell mRCC, showed 6%–17% of overall response rates with 2 of 17 patients having an objective response. The treatment was well tolerated; grade 3 or 4 adverse events were observed in 9% of patients [57].

Other PD-L1 inhibitors, durvalumab and avelumab, are currently undergoing clinical trials.

COMBINATION STRATEGIES

Previously mentioned dynamic nature of the immune tumor response and intricacy of the regulation of various immune checkpoints, there is a reason to assist combination immunotherapy strategies to maximize clinical benefit. Therefore, a number of combination strategies such as PD-1/PD-L1 blockade, PD-1 inhibitor with antiangiogenesis inhibitors, PD-1 inhibitor with other immunotherapeutic agents and combination with radiotherapy are currently ongoing clinical trial investigation for mRCC patients. Several recently accomplished trials and ongoing randomized phase III clinical trials are analyzing various treatments to determine whether there is a most favorable sequence of targeted agents and if combination strategy with targeted therapeutic agents benefits mRCC patients. However, the combination of immunotherapeutic agents does have considerable toxicities such as gastrointestinal, hepatic toxicities and careful patient selection be guaranteed [58,59]. Therefore, as we develop novel immunotherapeutics and reasonable rational combinations, much more study should be performed.

CYTOREDUCITIVE NEPHRECTOMY

Elimination of the primary tumor (debulking or cytoreductive nephrectomy) should be performed in all renal cell carcinoma patients where is clinically feasible and justifiable before starting systemic therapy. Randomized many clinical trials showed that renal cell carcinoma patients who receive a cytoreductive nephrectomy treated with IFN-α and immunotherapy had survival benefit compared with those with a not resected primary tumors [60,61]. In the era of immunotherapeutics, the role of cytoreductive nephrectomy is not apparently definite. Currently, 2 prospective randomized phase III studies (CARMENA; NCT00900033 and EORTC 30073) is now in progress and awaiting the results. Even, in the era of novel immunotherapeutic agents, cytoreductive nephrectomy or metastatectomy would still have some roles in highly selected clinically feasible mRCC patients [62].

CONCLUSIONS

New perceptions in cancer immunology have led to the development of new immune modulatory agents. From this perspective, the treatment of mRCC continues to evolve faster than ever before and new targeted agents have been developed with treatment regimens that continue to be optimized. Results from recent clinical trials with immunotherapeutic agents suggest that immunotherapy, such as monotherapy or in combination with other agents, with these agents is capable of producing durable responses and significant overall survival improvement. Thus, in the future, immunotherapy alone or together with other treatments, will likely cause a paradigm shift in the clinical management of mRCC patients. Moreover, further studies are warranted to identify biomarkers that reliably predict treatment benefit from these new therapies.
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