REVIEW

Immunotherapy of advanced renal cell carcinoma: Current and future therapies

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ABSTRACT

Previously a malignancy with few therapeutic options, metastatic renal cell carcinoma (mRCC) treatment is rapidly evolving. Although cytokine therapies (interferon- α , interleukin-2) have been used less frequently over the past decade, recent approval of an immune checkpoint inhibitor, nivolumab, has led to a resurgence in immune therapy for mRCC. With greater understanding of the complex and dynamic interaction between the tumor and the immune system, numerous new immunotherapies are being studied for mRCC. In this article, we review the mechanism of action, clinical outcomes and toxicity profiles of both clinically approved and selected investigational immunotherapies. Either alone or in combination, these novel agents are encouraging for the future of mRCC therapy.

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Introduction

Renal cell carcinoma (RCC) accounts for the vast majority of primary renal neoplasms and has a worldwide incidence of over 270,000 new cases annually.¹ For localized disease, surgery presents a potentially curative approach. Unfortunately, 25–30% of patients present with distant metastatic disease, and many develop recurrence in the form of metastasis after surgery.² Treatment of metastatic RCC (mRCC) has evolved significantly over the past 2 decades. Prior to current systemic therapies, dozens of chemotherapeutic regimens were used with poor overall response rates (ORR) of approximately 5%.³

In the 1990s, development of cytokine immunotherapies interleukin-2 (IL-2) and interferon- α (IFN- α) were established as standard of care. Although both treatments had significant acute toxicity profiles, high-dose (HD) IL-2 improved ORR to 15–20% with 7–9% of patients demonstrating complete responses (CR) and is still used in practice today.^{4,5} IFN- α demonstrated a more modest ORR of 10–15% without long-term responses.⁶ Combination IFN- α plus IL2 therapy has slightly improved ORRs with an increase in toxicity.⁷

Development of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs) was the next breakthrough in therapy. In 2005, sorafenib obtained FDA approval for treatment of mRCC after the TARGET study showed prolonged PFS after progression on previous therapy.⁸ Three additional VEGF-TKIs (sunitinib, pazopanib, axitinib) have obtained approval. Bevacizumab, a monoclonal antibody directed against VEGF, is also demonstrated to improve outcomes in combination with IFN- α .^{9,10} In 2009, IFN- α in combination with bevacizumab was granted FDA approval.¹¹ Simultaneously, drugs targeting the mechanistic target of

rapamycin (mTOR) pathway showed improvements in ORR and overall survival (OS). In 2007, temsirolimus became the first mTOR inhibitor (mTORI) to obtain FDA approval in mRCC and is currently recommended as a first-line agent for use in patients with poor prognosis.¹² Everolimus was approved in 2009 in patients who failed previous VEGF-TKI therapy.¹³ More recently, multi tyrosine kinase inhibitors, cabozantinib, and the combination of lenvatinib plus everolimus have shown improved outcomes, compared to everolimus following previous VEGF inhibitors, and were approved.^{14–16}

Checkpoint inhibition has recently advanced the clinical treatment of mRCC. For many decades, RCC has been known to be susceptible to immune therapy with its response to cytokines and abscopal responses to radiotherapy.¹⁷ Recent advances have demonstrated that monoclonal antibodies directed against immune checkpoints, such as programmed death-1 receptor (PD-1), PD-1 ligand (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) can improve outcomes by reducing T cell anergy, and improving host's anti-tumor response. In November 2015, nivolumab, a PD-1 inhibitor, became the first checkpoint inhibitor to obtain US FDA approval with evidence of prolonged overall survival (OS) compared to everolimus after prior antiangiogenic therapy.¹⁸ Although nivolumab is currently the only checkpoint inhibitor approved for mRCC, numerous immunotherapies are under investigation.

Novel cytokines (IL-10, IL-12, IL-15), adoptive cell therapies with NK cells and CD8⁺ cells, cancer vaccines (DCVax and NY-ESO-1) and checkpoint inhibitors (MK-4166, TRX518, urelumab, durvalumab (MEDI4736), MEDI0680 BMS-986016, lirilumab, SGN-CD70A, MGA217, CDX-1127 and tremelimumab) are being studied in phase I investigations. However, this

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review will focus on immunotherapies specifically targeted against mRCC that have at minimum advanced to phase II studies.

Cytokine therapy

mRCC evokes an immune response that occasionally results in spontaneous and durable remissions.¹⁹ Early oncologic immunotherapies were non-specific cytokine therapies. While numerous cytokines showed anti-tumor activity against mRCC, IL-2 and IFN- α were the most promising. Neither drug has a well-defined mechanism of action, however, both generate robust T cell responses that non-specifically target RCC cells resulting in anti-tumor activity.²⁰

IL-2 is a cytokine with both immunostimulatory and immunoregulatory roles largely dictated by the biological context it operates within.^{21,22} As an immunostimulator, IL-2 was first noted to stimulate CD8⁺ T cell growth. Later discoveries showed IL-2 aids in differentiation of memory T cells.^{23,24} However, IL-2 also has the capability to downregulate T cell responses by non-specifically facilitating a population of regulatory T cells and promoting activation-induced cell death.²¹ With a complex biology, IL-2 has different immunomodulatory effects in individual patients influencing their response to therapy.²⁵ The anti-tumor effects of IFN- α in mRCC are likely a combination of direct anti-proliferative and indirect immune-mediated effects. IFN- α stimulates natural killer (NK) cells and macrophages while also causing upregulation of MHC-I on tumor cells. IFN- α anti-proliferative properties are due to an antiangiogenic effect mediated indirectly by INF- γ .²⁶

Clinical outcomes

The first large study of HD-IL2 for mRCC was published in 1996 and showed an ORR of 14% with 5% CR.²⁷ Importantly, 8 of 12 patients with CR remained in remission after 2 y implying HD-IL2 could produce durable responses in a small number of mRCC patients. An update of these patients published in 2000 led to FDA approval.⁴ The durability of CR from HD-IL2 was further supported by a large retrospective cohort analysis where only 4 of 23 patients with a CR suffered disease relapse.²⁸ Due to the dose-limiting toxicity of HD-IL2, Yang, et al. performed a randomized clinical trial to compare the outcomes of high and low dose IL-2 for mRCC. They found a greater ORR in the HD-IL2 arm (21% vs. 13%, $p = 0.048$). Additionally, they found response durability and OS in patients with CR was greater with HD-IL2 than low dose IL-2.²⁹ This was supported in the “select” trial from McDermott, et al. who reported an overall objective response rates of 25%, and a median OS of 42.8 months of the entire cohort.²² A recently published patient cohort of nearly 400 patients reported similar ORR but an additional 32% ($n = 125$) obtained stable disease (SD) as the best response. Particularly promising, 50% of patients achieved a survival benefit with HD-IL2 with similar outcomes between patients who obtained partial response (PR) and SD as the best response to HD-IL2.³⁰ Those with CR, PR, SD and PD displayed median PFS of 113.8, 11.8, 9.0 and 3.9 months, respectively. Another retrospective trial of 186 patients with mRCC reported 3-year survival of 44% for patients treated with HD-

IL2.³¹ However, as roughly half of patients treated with HD-IL2 will not have a survival benefit, clinical and pathologic predictors of response to HD-IL2 have been identified. The “select” trial demonstrated that selecting patients with clear cell histology and stratifying by UCLA Sani score improved ORR to HD-IL2.²² Still, it is currently not possible to reliably predict response to HD-IL2 and investigation of predictive biomarkers is ongoing. Given the potential for serious acute toxicities including the historical ~3% fatality with HD IL-2, it remains an option only in a small fraction of well-selected younger patients without significant comorbidities.

In numerous studies, IFN- α provides a small survival benefit with modest toxicity compared to control arms.³² Mean ORR for INF- α as a single agent for mRCC is 15% without the durable CRs seen in treatment with HD-IL2.²⁶ Since IFN- α is available in different countries and clinical settings, it became the standard-of-care control arm for many randomized clinical trials investigating novel agents for mRCC.^{33,34} A randomized clinical trial of 492 patients in receiving INF- α and subcutaneous, low dose IL-2 found no survival benefit for INF- α and low dose IL-2 while inducing significant toxicity. While IFN- α was resurrected with the demonstration of improved PFS in combination with bevacizumab as first-line therapy, it is no longer used as single agent therapy for mRCC given the emergence of VEGF targeted therapies as first-line therapy.^{9,10,35}

Safety

Due to significant acute toxicities, HD-IL2 is limited to experienced academic medical centers. Toxicities are both dose and schedule dependent.³⁶ As IL-2 is a non-specific immunotherapeutic, it strongly stimulates numerous pro-inflammatory cytokines including IL-1, INF- γ , and tumor necrosis factor α (TNF- α).^{37,38} The most significant toxicity of HD-IL2 is a capillary leak syndrome which can result in life-threatening hypotension, edema and pulmonary congestion.³⁶ HD-IL2 produces many grade III and IV toxicities at clinically relevant rates such as fever, cardiac toxicity, neurologic toxicity, nausea, vomiting, diarrhea and skin rashes.³⁹ However, toxicities from HD-IL2 are generally reversible within 2–3 d of discontinuing treatment, and chronic toxicities are rare.

IFN- α has a different toxicity profile than HD IL-2 in regards to types and timing of toxicity. IFN- α causes acute and chronic toxicities, and the severity of IFN- α toxicity is related to the dose and duration of treatment.⁴⁰ Acutely, IFN- α causes an infusion reaction with fevers, chills and rigors 3–6 hours after administration. It can also cause neutropenia and transaminitis 2–3 d after administration.²⁶ The chronic toxicities of IFN- α are more often dose-limiting and include fatigue, anorexia and neuropsychiatric toxicities.

Checkpoint inhibitors

Tumor inhibition of the host's adaptive immune response facilitates progression of mRCC. With monoclonal antibodies directed against CTLA-4, PD-1 and PD-L1, new therapies reverse immune inhibition which facilitates antitumor activity. While CTLA-4 is expressed exclusively on T cells, PD-1 and PD-L1 are expressed on B and T cells.⁴¹ In addition, PD-1 is

Figure 1. Immunologic targets of CTLA-4 and PD-1.

expressed on NK cells and monocytes while PD-L1 is present on dendritic cells, macrophages and vascular endothelium.⁴² As demonstrated in **Figures 1 and 2**, PD-1 binding to PD-L1 dampens immune response by inhibiting T cell proliferation, cytokine production and cell adhesion. While CTLA-4 inhibits T cell activation via counteracting CD28, PD-1 regulates effector T cell activity in peripheral tissues.⁴³ When a T cell receptor (TCR) binds an antigen, T cells are amplified by CD28 signaling. With stronger affinity for CD28's ligands (CD80, CD86), CTLA-4 competitively inhibits CD28.⁴⁴

Obtaining FDA approval in November 2015, nivolumab is a PD-1 monoclonal antibody and the only checkpoint inhibitor currently approved for mRCC. Pembrolizumab is another PD-1 antibody currently under investigation in 2 phase II trials. Ipilimumab, a monoclonal antibody directed

against CTLA-4, is undergoing a phase III trial with nivolumab. Atezolizumab (MPDL3280A) is a PD-L1 antibody undergoing a phase II trial as monotherapy and in combination with bevacizumab in a phase III trial. Also targeting PD-L1, avelumab (MSB0010718C) is currently undergoing a phase III trial in combination with axitinib or sunitinib (**Table 1**).

Clinical outcomes

The CheckMate 025 study compared nivolumab versus everolimus in patients with mRCC who had received previous anti-angiogenic therapy. Results showed increased median OS (25.0 vs. 19.6 m) with a HR of 0.73 (CI 0.57 to 0.93; $p = 0.002$) and greatly improved ORR (25% vs. 5%,

Figure 2. Mechanisms of action for immune checkpoint inhibitors.

Table 1. Ongoing randomized trials of immunotherapeutic agents.

Cytokine Therapy		
High-dose IL-2 Interferon- α	Cytokine infusion Cytokine infusion	FDA Approved FDA Approved in combination with bevacizumab
Checkpoint Inhibitors		
Nivolumab	PD-1 antibody	FDA Approved Phase II +/- bevacizumab or ipilimumab ¹ Phase III + ipilimumab or sunitinib ²
Pembrolizumab	PD-1 antibody	Phase II + IFN- α or ipilimumab ³ Phase II + pazopanib ⁴
Ipilimumab Atezolizumab (MPDL3280A)	CTLA-4 antibody PD-L1 antibody	Phase III + nivolumab ² Phase III + bevacizumab or sunitinib ⁵
Avelumab	PD-L1 antibody	bevacizumab ⁶ Phase III + Axitinib or Sunitinib ⁷
AGS-003	Cancer Vaccine Dendritic cell (pulsed with autologous tumor) infusion	Phase III + standard therapy ⁸

¹NCT02210117, ²NCT02231749, ³NCT02089685, ⁴NCT02014636, ⁵NCT02420821,

⁶NCT01984242, ⁷NCT02684006, ⁸NCT01582672

$p < 0.001$). There was no significant difference in PFS. Grade 3/4 adverse events (AEs) were less common in the nivolumab arm (19 vs. 37%).¹⁸ Analysis of 56 patients treated with atezolizumab showed ORR 14%, SD in 54% ($n = 30$), PD 30% ($n = 17$) and a 24-week PFS of 48%.⁴⁵ Recently published phase Ia data of atezolizumab in mRCC reported 15% ORR with median OS of 28.9 months. ORR was double (18 vs. 9%) in patients with increased tumor PD-L1 expression.⁴⁶ Phase II testing of ipilimumab showed PR in 6 of 61 patients (10%). However, of those who received high dose ipilimumab, 12.5% achieved PR. Of interest, 30% with irAE achieved PR.⁴⁷ A phase I/II study of pembrolizumab in combination with epacadostat (indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor) for 5 patients with mRCC reported PR and SD in 4 patients each.⁴⁸ Pembrolizumab has been shown to be well-tolerated in phase I testing in combination with bevacizumab or ipilimumab without reported outcome data.^{49,50} At the time of publication, data regarding ORR, PFS and OS for avelumab, are not yet available.

Safety

Most adverse reactions associated with therapy are immune related including rash, pruritis and diarrhea. Other common AEs include fatigue, nausea and injection site reactions. Comparing their use in large trials, there are more frequent immune-related adverse events (irAEs), particularly hepatitis and colitis, with ipilimumab than PD-1 antibodies.⁵¹⁻⁵⁴ Less extensive data is available for newer anti-PD-L1 agent atezolizumab, but most common AEs are fatigue, decreased appetite, nausea and fever. Most common grade 3/4 AEs are hepatitis, hypoxia and hyperglycemia.⁴⁵ In a phase I study limited to

patients with mRCC, the most common grade 3/4 AEs were hypophosphatemia, fatigue, dyspnea and hyperglycemia.⁵⁵

Cancer vaccines

Autologous dendritic cell based therapy

Durable CR is achievable in a minority of patients treated with IL-2 yet not observed with the targeted VEGF-TKIs and mTORIs, which suggests that immune modulation was essential to CR in mRCC.^{28,56} To avoid the toxicity profile of HD-IL2, AGS-003 is intended to be a personalized, less toxic immunotherapy to complement first-line targeted therapies. AGS-003 are mature autologous dendritic cells co-electroporated with the patient's amplified tumor RNA and synthetic CD40L RNA.⁵⁷ Dendritic cells present antigen to CD4⁺ and CD8⁺ T cells to stimulate cell-mediated immunity.⁵⁸ Normally, CD4⁺ helper T cells express CD40L to interact with CD40 on dendritic cells and result in a cytotoxic T lymphocyte (CTL) response. In mRCC, local and systemic effects from the tumor yield CD4⁺ helper T cells and dendritic cells dysfunctional hindering antigen presentation and an appropriate CTL response.^{59,60} AGS-003 circumvents these tumor effects by presenting RNA-loaded mature dendritic cells with intention to produce a more robust CD8⁺ T cell response.⁵⁷

To date, AGS-003 has been studied in a phase II clinical trial of 22 patients with intermediate or low risk mRCC in combination with sunitinib.⁵⁷ No patients obtained CR, but 9/21 (43%) had a PR and 4/21 had SD. PFS was 11.2 months and median OS was 30.2 months. Generating excitement, 52% of the patients treated with AGS-003 had long-term survival in comparison to 13% for the historical comparison and 24% of patients surpassed 5-year OS.⁶¹ ADAPT (NCT01582672) is the subsequent phase III trial and has been completed but is awaiting publication (Table 1).

In comparison to original immunotherapies for mRCC, AGS-003 has minimal clinical data but is remarkably well tolerated. In the study by Amin, et al., no grade III or IV toxicities were attributed to AGS-003.⁵⁷ Of the 22 patients treated with sunitinib and AGS-003, none experienced treatment-related mortality. All of the AEs attributed to AGS-003 were grade I and were primarily injection site events such as induration, swelling, pain and pruritus. In contrast to the checkpoint inhibitors, no evidence of auto-immunity was noted.

Peptide vaccines

Unfortunately, a phase 3 trial reported that the combination of IMA901, a peptide based off-the-shelf vaccine consisting of 10 different tumor-associated peptides, with sunitinib did not improve outcomes compared to sunitinib alone, in patients with advanced RCC.⁶² In this trial, patients received up to 10 intradermal vaccinations of IMA901 plus GM-CSF and a single infusion of cyclophosphamide 3 d prior to the first vaccination to eradicate regulatory T cells. Additionally, the study did not demonstrate an association between immune responses and clinical outcomes in contrast to the phase 2 trial.⁶³ However, IMA901 exhibited a favorable safety profile with transient injection-site reactions being the most frequent adverse effect.

Combination therapy

There are multiple ongoing clinical trials investigating combination therapy with immunotherapies (Table 1). Strategies differ between using 2 immune checkpoint inhibitors together and by combining VEGF inhibition with an immune therapy. Due to the complexity of the tumor's immune response, inhibition with a PD-1/PD-L1 inhibitor as well as a CTLA-4 antibody may provide a synergistic effect. In a mouse model, simultaneous inhibition of CTLA-4 and PD-1 increased effector T cell infiltration of tumors and significantly increased tumor rejection compared to single inhibition.⁶⁴ Others have shown evidence of synergy via different mechanisms of immune regulation. While blockage of PD-1 reduces regulatory T cell suppression, CTLA-4 inhibition prevents CD4⁺ T cells converting into regulatory T cells. In combination, there is expansion of CD8⁺ T cells and a marked increase in the ratio of CD8⁺ to regulatory T cells.⁶⁴⁻⁶⁶ Indeed, the combination of nivolumab and ipilimumab is already approved for the therapy of melanomas.⁶⁷ Given the toxicities of this combination, a strategy of lower dose of ipilimumab and higher dose of nivolumab was evaluated and appeared more feasible in a phase I trial, and is being evaluated in a phase III trial in comparison with sunitinib.⁶⁸ Given the complexity of immune regulation, targeting both PD-1 and PD-L1 receptors may be superior to a single target. A phase I/II study is investigating the combination of PD-1 inhibitor MEDI0680 with and without PD-L1 inhibitor durvalumab for patients with advanced malignancies including mRCC (NCT02118337).

Although not immunotherapies, there is evidence that VEGF-TKIs attenuate myeloid-derived suppressor cells (MDSCs) leading to diminished regulatory T cells activity and promotion of effector T cells.⁶⁹ Another study showed that a VEGF-TKI modulated tumor macrophages and decreased immunosuppressive tumor cytokines.⁷⁰ This suggests there may be a synergistic effect by combining immunotherapies with angiogenesis inhibitors. Currently there are 6 phase II and III trials investigating the combination of bevacizumab or a VEGF-TKI with an immunotherapy, either vaccine or a PD-1/PD-L1 inhibitor (Table 1). Preliminary data has suggested there may be an improvement in ORR at the cost of increased toxicity when combining pazopanib or sunitinib with PD-1 inhibitors. However, the combination of axitinib or bevacizumab with PD-1/PD-L1 inhibitors appeared feasible and active, which has led to a phase III trials (Table 1).⁷¹⁻⁷³

Combining therapies with HD-IL2 also appears promising. A phase II trial combining entinostat, a novel HDAC inhibitor, and HD-IL2 obtained ORR 39%, the highest reported response rate to HD-IL2 reported till date. The dual therapy was well tolerated and median PFS and OS have not yet been reached.⁷⁴ Adding a dendritic cell vaccine to HD-IL2 for treatment of mRCC has been shown to be well-tolerated.⁷⁵ Concomitant treatment with checkpoint inhibition and adoptive cell therapy is under investigation in metastatic melanoma but not mRCC and is potentially a new avenue for study.^{76,77} Another phase II trial has combined bevacizumab and HD IL-2, although outcomes did not clearly appear better than historical data using HD IL-2 alone.⁷⁸

Conclusion

Recent advances in mRCC treatment correlate to greater understanding of the immune system and its relationship to both the tumor cell and therapeutic agent. Early observations of abscopal responses to localized treatment for mRCC proved the potential for immunotherapy. Subsequently, durable CRs from HD-IL2 confirmed a role for immunomodulation in systemic therapy. However, low ORRs coupled with dose-limiting toxicity limited non-specific immunotherapy to a select subset of patients treated in large, experienced medical centers. As our understanding of interactions between the immune system and mRCC improved, a number of novel immunotherapies have rapidly altered the treatment of mRCC.

Monoclonal antibodies directed against CTLA-4, PD-1 and PD-L1 target tumor inhibition of the adaptive immune response against mRCC. Introduction of these monoclonal antibodies has led to improved ORRs with tolerable toxicity profiles, yet when used as monotherapy do not appear to produce the same durable CRs that made immunotherapy such a promising target. Since immune modulation appears to be essential to durable CRs, new approaches such as autologous dendritic cell based therapy are under investigation. Additionally, pre-clinical studies suggest there is a synergistic effect from combining immunotherapies and angiogenesis inhibitors leading to more avenues for further clinical study. Given the multitude of drug targets and a wide heterogeneity of patients' response to different agents, predictive biomarkers (such as tumor PD-L1 staining) are needed to guide therapy. mRCC is a unique malignancy whose treatment has involved immunomodulation since the early 1980s, and future advancements in therapy may likely follow immunologic discoveries.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Authors' contributions

DMG, AWH, GS, and NA all contributed to the conceptual framework, writing, and revisions of the manuscript.

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