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Evolving Immunotherapy Approaches for Renal Cell Carcinoma

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Abstract Metastatic renal cell carcinoma (mRCC) continues to be associated with high rates of morbidity and mortality. Renal cell carcinoma (RCC) is typically resistant to cytotoxic chemotherapy, and while targeted therapies have activity and prolong progression-free and overall survival, responses are usually not durable. Modulating the immune system with cytokine therapy, vaccine therapy, cell therapy, and checkpoint inhibitors offers hope of prolonged survival. Standard and emerging immune therapy approaches and combinations of immune therapies and other modalities are reviewed.

Keywords Renal cell carcinoma · Immunotherapy · Cytokines · Adoptive cell therapy · Vaccine therapy · Immune checkpoint inhibitors

Introduction

New cases of RCC worldwide were estimated at 338,000 in 2012 [1]. As many as 30 % of cases were metastatic at diagnosis [2]. Although there are a variety of histologic subtypes including clear cell RCC, papillary subtypes 1 and 2, chromophobe carcinoma, and others, clear cell RCC, the most common subtype, is the focus of most clinical trials. While early stage RCC may be curable with surgical resection, the mortality rate is high with relapsed, unresectable, and metastatic RCC (mRCC). Therefore, mRCC is the subject of intense ongoing preclinical and clinical research.

mRCC is highly chemotherapy resistant. High-dose interleukin-2 (IL-2) and interferon-α (IFN-α) were the standard of care for many years, although the 5-year survival of patients was only 10 % [3, 4]. More recent trials with targeted therapies such as vascular endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors demonstrated improved median survival to ~40 months with a progression-free survival (PFS) of up to 27 months with some therapies, resulting in the widespread use of these drugs for RCC [5]. However, resistance to targeted therapies, the need for continued treatment, and lack of durable complete responses resulted in continued interest in novel immune-modulating agents for the treatment of RCC. Rare cases of spontaneous remissions of RCC led to the theory that the immune system may be able to suppress RCC by antitumor immunity [6]. In addition, presence of tumor-infiltrating lymphocytes (TILs) implicated the immune system as playing a role in the course of the disease [7]. Approaches such as adoptive cell therapy (ACT), T cell modulation, and vaccines have shown promise, while studies of immune checkpoint inhibitors resulted in prolonged survival and are now approved in the second-line setting [8]. Here, we review immune modulating approaches used to date for RCC and discuss future directions for research.

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Approved Cytokine Therapies

Interferon

Cytokine therapy has been used in RCC for over two decades. Responses in patients with mRCC treated with interferon alpha (IFN-α) were first reported in 1989 [9]. Subsequent phase III studies of IFN-α showed a 15 % response rate and an increase in OS from 3 to 7 months [10]. One such study showed that the addition of cytoreductive nephrectomy before treatment with IFN-α increased the OS by 10 months [11]. A randomized trial comparing IFN-γ to placebo did not show benefit in PFS or OS [6]. In a more contemporary phase III trial of 750 patients, IFNα was used as the control arm for comparison to sunitinib. PFS on the interferon arm was 11 months, and the response rate was only 6 %. Moreover, the interferon was poorly tolerated [12]. Consequently, IFN-α monotherapy is rarely used for treating this disease, although it is used in combination with other therapies, as discussed below.

High-Dose IL-2

IL-2 was approved in 1992 for treatment of mRCC based on an objective response rate of 14 %; many of the responses were durable [13]. In 1994, a study of 283 patients treated with high-dose IL-2 who had mRCC or melanoma and had failed first-line therapy was published [14]. Of the mRCC patients, 13 % had partial responses and 7 % had complete responses. Responses continued up to 91 months after treatment. High-dose IL-2 was administered on an inpatient unit to manage toxicities, and a treatment-related mortality rate of 1.1 % was reported. Further assessment of 255 patients with mRCC in several phase II clinical trials with high-dose IL-2 showed response rates of 15 % and complete response rates of 7 %, with a median PFS of 54 months for all responders and 80 months for complete responders. There was a 4 % treatment-related mortality rate [15]. Due to toxicity concerns, IL-2 is typically reserved for patients with an excellent performance status and no cardiac or pulmonary co-morbidities, who are able to tolerate it.

To improve the therapeutic window of high-dose IL-2, attempts have been made to identify predictive biomarkers that might facilitate patient selection. The SELECT trial failed to find biomarkers that might distinguish those patients most likely to respond to cytokine therapy [16]. Overall, high-dose IL-2 therapy offers the possibility of durable responses; however, treatment toxicity precludes this option for many patients with comorbidities and limits its availability to institutions equipped to monitor and treat the toxicities.

Cytokine-Based Combinations

A trial evaluating the combination of IFN-α with sunitinib in 25 patients showed partial responses in 12 % of patients and stable disease in 80 %; however, the toxicity profile was unfavorable [17]. A similar trial was conducted evaluating the combination of IFN-α and sorafenib, where 19 % of patients achieved an objective confirmed response. An additional 50 % had an unconfirmed partial response or sable disease. Toxicities, however, were limiting [18]. Two phase III trials compared IFNα alone to IFNα and the anti-VEGF antibody, bevacizumab. PFS on the combination therapy was superior, leading to FDA approval of the combination therapy regimen, although OS was not improved [19–22].

The combination of IL-2 with bevacizumab or sorafenib did not show prolonged PFS [23–25]. Finally, the combination of IFN-α with IL-2 was also not shown to be superior to IL-2 alone [26].

Cell Therapy Approaches

Several adoptive cell therapy approaches have been studied, selecting and activating T cells taken from the host tumor environment or from peripheral blood. Examples include lymphokine-activated killer cells, tumor-infiltrating lymphocytes (TILs), and cytokine-induced killer cells (CIK). These approaches have been used since 1990. The original phase I/II trials of lymphokine-activated killer cells showed modest activity [27–31], and a phase III trial published in 1995 comparing IL-2 alone to IL-2 with the addition of lymphokine-activated killer cells showed no difference in response or survival [32]. Several studies with TILs have also shown poor objective response rates [33–39]. While CIK cell therapy showed a PFS of 12 months and OS of 46 months compared with IFN-α plus IL-2 (PFS of 8 months and OS of 19 months), these numbers need to be assessed in the context of subcutaneous IL-2, which is not standard therapy for RCC [40]. Future directions using adoptive cell therapy may include genetic modification of T cells to enhance antitumor activity [41–43].

Vaccine Therapies

Investigations of vaccine therapy for RCC are ongoing. AG3-003 is a dendritic cell-based vaccine, which was tried in combination with sunitinib as a first-line therapy in patients with mRCC [44]. AGS-003 is prepared for individual patients from resected tumor. Autologous dendritic cells are co-electroporated *ex vivo* with tumor RNA and synthetic CD40L. Treatment is administered by dermal injection, and the RNA-loaded dendritic cells present the relevant patient-

specific tumor antigen to T cells in the draining nodal area. CD40L increases CD8+ T cell induction through production of IL-12 [45–47]. In the early phase trial, 21 patients received 1 cycle of sunitinib, followed by AGS-003 every 3 weeks for five doses, and subsequently every 12 weeks until progression. Nine patients had a partial response, and four had stable disease. PFS was 11.2 months and OS was 30.2 months, although five patients lived more than 5 years. There was no reported additive toxicity above the expected for sunitinib. A randomized multicenter phase III trial of AGS-003 plus standard treatment (ADAPT) is ongoing (NCT01582672).

IMA901 is a therapeutic vaccine consisting of nine human leukocyte antigen (HLA)-class I and one HLA-class II-binding tumor-associated peptides. Results from a phase II trial were presented at the 2010 annual meeting of the American Society for Clinical Oncology (ASCO) [48]. Sixty-eight patients with mRCC were randomized to receive intradermal IMA901 with GM-CSF 75 μg with or without low-dose cyclophosphamide 300 mg/m^2 before the first vaccination. In patients who had received prior cytokine therapy, disease control rate was 31 % versus 12 % in patients previously treated with tyrosine kinase inhibitors, and overall survival rate was 54 % at 18 months. A phase III trial with IMA901 and sunitinib has met accrual and results are pending (NCT01265901).

MVA5T4 is a vaccine targeting cell expressing the 5T4 antigen, which is often expressed on solid tumors. It has been studied in mRCC and shown to illicit an immune response [49]. MVA5T4 or placebo was administered in combination with IL-2, INF-a, or sunitinib. No difference in median OS was appreciated for MVA5T4 (20.4 months) versus placebo (19.2 months; $P = 0.55$). A subsequent survival analysis was performed to quantify antibody response [50]. Patients with a greater 5T4 antibody response had longer survival in the group treated with MVA-5T4.

TG4010 is a virus-based vaccine expressing MUC1, which is over-expressed in RCC and other malignancies. In a phase II trial of 37 patients with tumors expressing the MUC1 antigen, TG4010 was injected weekly for 6 weeks followed by injections every 3 weeks until disease progression. At the time of progression, injections were continued and either IL-2 or IFN-α was added. Five patients had stable disease for more than 6 months on TG4010 alone, and six had stable disease for more than 6 months when cytokine therapy was added. However, no objective response was seen [51].

In the adjuvant setting, a phase III trial of a vaccine containing an autologous tumor lysate did not meet its primary endpoint of a reduction in tumor recurrence or death. However, in a 5- and 10-year follow-up analysis, OS in patients who received the vaccine was 80.6 and 68.9 %, respectively, compared to 79.2 and 62.1 % in patients who did not receive adjuvant treatment. There was a statistically significant benefit in patients with pT3 tumors who received the vaccine [52, 53]. Another adjuvant trial studied Vitespen, a heat shock protein glycoprotein complex, compared with observation alone. This study failed to meet the primary endpoint of increase in disease-free survival, although a subgroup analysis of patients with stage I and II disease showed a non-significant decrease in relapse ($p = 0.056$). This agent has been approved in Russia but not in other countries [54].

Immune Checkpoint Inhibitors

Immune checkpoints are being studied in multiple tumor types and are the targets of multiple drugs approved or under development. Inhibitors of CTLA-4 or the PD-1/PD-L1 axis, the first in this class to be approved for cancer therapy, are discussed below. Many additional immune checkpoint modulators are currently being studied, as discussed below.

CTLA-4 Inhibitors

Immune checkpoint inhibitors block signals from the tumor or TILs, which down-regulate T cell activation. CTLA-4 is an immune checkpoint on the surface of cytotoxic T cells that limits an inflammatory reaction by interfering with binding of B71 on tumor cells to CD28 on T cells, as reviewed [55].

CTLA-4 inhibitors were initially studied in melanoma, and one such inhibitor, ipilimumab, resulted in prolonged overall survival when compared to a peptide vaccine, leading to its approval for advanced melanoma [56]. Given the activity seen in melanoma, activity of ipilimumab was studied in a number of other diseases as well. Pre-clinical evidence to support CTLA-4 inhibitors for RCC was provided by a Spanish study comparing genotypic frequency of CTLA-4 polymorphisms in 117 patients with RCC to 196 healthy controls without malignancy, showing that the presence of the CTLA-4/CT60-AA polymorphism had a hazard ratio of 2.12 for development of renal cancer, while the CTLA-4/A49G-AA polymorphism had a hazard ratio of 1.76 for development of renal cancer. There was also a positive correlation between the presence of either polymorphism and higher grades of RCC [57]. In 2007, a phase II trial of two cohorts of patients with RCC treated with ipilimumab was published [58]. Five of 40 patients in the group receiving ipilimumab at 3 mg/kg every 3 weeks had partial responses, while 1 of 21 patients receiving ipilimumab at a lower dose responded. The study also showed an association between autoimmune toxicities and response. Ipilimumab monotherapy has not been studied in phase III trials for mRCC.

Another anti-CTLA-4 monoclonal antibody, tremelimumab, was administered to mRCC patients at 6, 10, or 15 mg/kg intravenously once every 12 weeks, in combination with sunitinib, 50 mg daily for 4 weeks and then 2 weeks off or 37.5 mg daily as a continuous dose [59]. Two of five patients receiving tremelimumab 6 mg

and sunitinib 50 mg experienced unexpected rapid onset renal failure and one of seven patients receiving tremelimumab 10 mg/kg plus sunitinib 37.5 mg had sudden death. An expansion cohort was treated with tremelimumab 10 mg/kg plus sunitinib 37.5 mg; however, dose-limiting toxicities were seen in three or seven patients. Of the nine patients evaluable, 43 % achieved a partial response, but the regimen was not developed further due to toxicities.

PD-1 Inhibitors

PD-1 is a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on lymphocytes including cytotoxic T cells. PD-1 binds two ligands, PD-L1 and PD-L2, which are expressed on a number of cell types, including tumor cells. PD-1 is thought to inhibit cytotoxic T cell activity by promoting apoptosis, although the precise mechanism of action of PD-1 remains the subject of intense research [60].

There have now been several clinical trials of the anti-PD-1 antibody nivolumab in RCC. A phase I dose-escalation study with nivolumab monotherapy single dose at doses ranging from 0.3 to 10 mg/kg, included 39 patients with solid tumors [61]. A 15 patient expansion cohort was then tested at 10 mg/kg, and one patient with RCC was included and had a partial response. A second phase I trial of nivolumab in solid tumors which involved continuous dosing of 0.1 to 10.0 mg/kg every 2 weeks included 33 patients with RCC [62]. Responses were seen at various dose levels. Longer term follow-up of these patients revealed that the overall response rate in RCC was 29 %, while an additional 27 % had SD lasting ≥24 weeks [63••]. Median overall survival was 22.4 months. Overall, the drug was very well tolerated; 18 % of patients had reversible grade 3 or 4 toxicities. A phase II study of 168 patients with mRCC treated with nivolumab at doses of 0.3, 2, or 10 mg/kg every 3 weeks confirmed the promising results [64]. Median PFS was 2.7, 4, and 4.2 months, respectively, and median OS was 18.2, 25.5, and 24.7 months, respectively. Eleven percent of patients had grade 3 or 4 toxicities. The results led to CHECKMATE 025, a phase III trial of nivolumab versus everolimus [65••]. In the study, 821 patients previously treated patients with mRCC were randomized to either everolimus 10 mg daily or nivolumab 3 mg/kg every 2 weeks. Median OS was 25 months in the nivolumab arm and 19.6 months in the everolimus arm, while the median PFS was 4.6 and 4.4 months, respectively. The toxicity profile was more favorable in the nivolumab arm; grade 3 or 4 toxicities were seen in 19 %, compared with 36 % in the everolimus arm. While the therapy used on the comparator arm (everolimus) was less active than many other approved targeted therapies for RCC, such as axitinib, sunitinib, and pazopanib, median OS on the treatment arm was clearly superior in an era in which salvage therapies with these VEGF-R inhibitors were available. Based on the results of this trial, nivolumab was approved by the FDA in November 2015 for mRCC as a single agent in the second-line setting.

Clinical trials with other PD-1 antagonists for the treatment of metastatic RCC, including pembrolizumab (IgG4 monoclonal antibody), pidilizumab (IgG1 monoclonal antibody), and others are ongoing, the majority of which are combination trials (please see details below).

PD-L1 Inhibitors

The success of PD-1 antagonists for the treatment of RCC sparked further interest in the blockade of the ligands of PD-1, namely PD-L1 and PD-L2. In 2012, results of a phase 1 study of 207 patients with multiple tumor types including RCC treated with the PD-L1 inhibitor BMS936559 was published [66]. Overall response rates ranged from 6 to 17 %, with 2 of 17 patients with mRCC having an objective response. The drug was well tolerated; only 9 % of patients exhibited grade 3 or 4 toxicities. A phase I study of MPDL3280, an anti-PD-1 IgG1 antibody (now called atezolizumab), was studied in multiple tumor types including mRCC [67••]. In this study, tumors were stained for expression of PD-L1 by immunohistochemistry. Scores of 0, 1, 2, or 3 represented <1, 1–5, 5–10, or >10 % of tumor infiltrating immune cells per tumor area with PD-L1 expression, respectively. Tumor infiltrating immune cells included macrophages, dendritic cells, and lymphocytes. Sixty-three mRCC patients were evaluable for survival with a median OS of 28.9 months and a median PFS of 5.6 months. The overall response rate (ORR) was 15 %. Atezolizumab was similarly well tolerated, with 17 % of patients experiencing grade 3 toxicity.

Experimental Approaches Building on Success of Immune Checkpoint Inhibitor Monotherapy Studies

Multiple clinical trials of immune checkpoint inhibitor combinations, combinations with targeted therapies, combinations with other classes of drugs, and new co-stimulatory or co-inhibitory modifiers are underway. Examples are shown in Table 1 and discussed in the following sections.

Combinations of PD-1 or PD-L1 Inhibitors and Other Therapies

Combinations with Other Therapies Approved for mRCC

A number of studies are underway with the aforementioned PD-1 or PD-L1 inhibitors and other drugs, both standard drugs approved for mRCC and other immune or targeted therapies. Studies combining PD-1/PDL1 inhibitors with VEGF

Table 1 Ongoing trials with checkpoint inhibitor combinations and combinations with other classes of drugs

Class	Drug	Phase	Estimated enrollment	Primary endpoints	ClinicalTrials.gov identifier
Checkpoint inhibitors + histone deacetyalse inhibitors	Nivolumab + HBI-8000[a]	1b/2	Ib (18)/2 (20 per tumor cohort)	Safety, tolerability and MTD	NCT02718066
	Pembrolizumab + vorinostat[a]	1/1b	42	Safety, tolerability and MTD	NCT02619253
Checkpoint inhibitors + cytotoxic chemotherapy	Nivolumab + irinotecan, temsirolimus, or irinotecan + capecitabine[a]	1b/2	49	Safety and tolerability, MTD	NCT02423954
Checkpoint inhibitors + cytokine therapy	Nivolumab + interferon gamma	1	15	Safety and tolerability, MTD	NCT02614456
Checkpoint inhibitor or stimulator combinations	Atezolizumab + varlilumab	1a/2	55	Safety, tolerability and ORR	NCT02543645
	Nivolumab + varlilumab[a]	1a/2	190	Safety, tolerability and ORR	NCT02335918
	Pembrolizumab + pegylated inteferon alpha-2b and pembrolimumab + ipilimumab[a]	1a/2	343	Safety, tolerability and PFS	NCT02089685
	MEDI4736 + temelimumab[a]	1	105	Safety and tolerability, MTD	NCT01975831
	MEDI4736 ± temelimumab[b]	1b	54	Safety and tolerability, MTD	NCT02762006
	MEDI4736 + temelimumab + polylCLC[a]	1a/2	102	Safety, tolerability and ORR	NCT02643303
	Pembrolizumab + INCB024360	1/2	374	Safety, tolerability and ORR	NCT02178722
	Atezolizumab + CPI444 or CPI444 alone[a]	1/1b	534	Safety and tolerability, MTD	NCT02655822
Checkpoint inhibitors + glutaminase inhibitor	Nivolumab + CD839	1/2	242	Safety, tolerability and ORR	NCT02771626
Checkpoint inhibitors + JAK1 inhibitors or PI3K inhibitors	Pembrolizumab + INCB039110 vs Pembrolizumab + INCB050465[a]	1a/1b	78	Safety and tolerability, MTD, ORR	NCT02646748
Checkpoint inhibitors + vaccine therapy	Pembrolizumab + p53MVA	1	12	Safety and tolerability, MTD	NCT02432963
Checkpoint inhibitors + CSF1R inhibitor	Nivolumab + FPA008	1a/1b	280	Safety and tolerability, ORR	NCT02526017
Checkpoint inhibitors + VEGR inhibitors, VEGF inhibitors, or other anti-angiogenics	Avelumab + axitinib	1b	55	Safety and tolerability, MTD	NCT02493751
	Pembrolizumab + axitinib	1b	60	Safety and tolerability, MTD	NCT02133742
	Pembrolizumab + pazopinib[a]	1/2	228	Safety and tolerability, MTD, OS	NCT02014636
	Avelumab + axitinib vs sunitinib	3	583	PFS	NCT02684006
	Pembrolizumab + levatinib	1/2	150	Safety and tolerability, MTD, ORR	NCT02501096
	Pembrolizumab + Ziv-aflibercept	1	36	Safety and tolerability, MTD	NCT02298959
	Pembrolizumab + bevacizumab	1/2	61	Safety and tolerability, MTD, ORR	NCT02348008
	Atezulizumab + bevacizumab	2	40	ORR	NCT02724878
	Atezulizumab + bevacizumab vs sunitinib	3	830	PFS and OS	NCT02420821
	Atezulizumab alone or ateziluzumab + bevacizumab or vs sunitinib	2	305	PFS	NCT01984242
	Nivolumab + sunitinib, pazopinib, or ipilimumab	1	175	Safety and tolerability, MTD	NCT01472081
		1	60	Safety and tolerability, MTD	NCT02210117

Table 1 (continued)

Class	Drug	Phase	Estimated enrollment	Primary endpoints	ClinicalTrials.gov identifier
	Nivolumab vs nivolumab + bevacizumab vs nivolumab + ipilimumab				
	Nivolumab + ipilimumab vs sunitinib	3	1099	PFS and OS	NCT02231749
	Pembrolizumab + MGA271	1	74	Safety and tolerability, MTD	NCT02475213
	Ipilimumab + MGA271	1	84	Safety and tolerability, MTD	NCT02381314

[a] Multiple cancer types including advanced RCC

[b] Drug will be given neoadjuvantly as well as adjuvantly

or VEGF-R targeting therapy include a phase I trial of pazopanib plus pembrolizumab (NCT0201463), the phase Ib study evaluating axitinib plus pembrolizumab (NCT02133742), and the phase Ib/II studies of bevacizumab plus pembrolizumab (NCT02348008). Results from the first 12 patients with mRCC treated on this study were reported at the 2015 ASCO annual meeting [68]. Here, bevacizumab 15 mg/kg was given every 3 weeks together with atezolizumab 20 mg/kg. No grade 3 or 4 adverse events related to atezolizumab were reported, and there was a 40 % objective response rate. This was followed by a randomized phase II trial that has met accrual—patients received atezolizumab alone or in combination with bevacizumab versus sunitinib, and cross-over was allowed (NCT01984242). More recently, results of the phase Ib trial of pembrolizumab plus bevacizumab were presented at the 2016 Genitourinary Cancers Symposium. No grade 3 or 4 drug-related toxicities were reported among the first 12 patients and the phase II component is ongoing [69]. A phase I study of pembrolizumab + ziv-aflibercept (trap-VEGF) is also ongoing (NCT02298959). Atezolizumab is being combined with interferon in a phase I trial that includes patients with mRCC and other diseases (NCT02174172). A study of radiation therapy plus pembrolizumab in patients with RCC (and other malignancies) is ongoing (NCT02318771), with the goal of increasing antigen presentation in the irradiated area.

Combinations of PD-1/PD-L1 Inhibitors and Other Therapies Not Approved for RCC

Combinations of PD-1 Inhibitors and CTLA-4 Inhibitors Dramatic responses were seen in a phase I trial of ipilimumab and nivolumab in patients with advanced melanoma [70]. This led to studies of this combination in mRCC, as one arm in a multi-arm phase I trial of nivolimab in combination with other therapies (CHECKMATE-016) [71] [72]. Patients with mRCC who had any number of previous therapies were randomized to receive either 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3 + I1) or 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1 + I3) every 3 weeks for four doses followed by nivolumab alone 3 mg/kg every 2 weeks until progression. A small cohort of six patients was also treated with 3 mg/kg of both drugs. Overall, response rates were 38 % (N3 + I1) and 43 % (N1 + I3). Stable disease was seen in 40 % (N2 + I1) and 38 % (N1 + I3). Grade 3–4 treatment-related adverse events occurred in 34 % of patients (N3 + I1) and 64 % of patients (N1 + I3). Based on the dramatic response rates of ~40 %, a phase III trial comparing nivolumab 3 mg/kg and ipilimumab 1 mg/kg versus sunitinib 50 mg in the frontline setting (CHECKMATE-214) was conducted (NCT02231749). The lower dose of ipilimumab was selected due to the more favorable toxicity profile. The trial has met accrual, and results are pending.

KEYNOTE-029 is examining the combination of the PD-1 inhibitor pembrolizumab with ipilimumab versus pembrolizumab plus IFN-α for patients with mRCC or melanoma (NCT0208968). Interim results of this trial presented at the ASCO 2015 annual meeting showed acceptable safety in patients receiving pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by pembrolizumab 2 mg/kg every 3 weeks for up to 2 years [73]. Results from the arm with pembrolizumab plus IFN-α are pending.

Combinations of PD-1/PD-L1 Inhibitors with Other Immune Therapies Not Approved for RCC Pembrolizumab is being combined with multiple other experimental therapies. Examples include the combination with an inhibitor of a different immune checkpoint, IDO (NCT0218722 and NCT02646748), pembrolizumab in combination with a modified vaccinia virus Ankara vaccine expressing p53 (NCT02432963), and pembrolizumab in combination with a B7-H3 inhibitor MGA 271 (NCT02475213). Atezolizumab plus the CD27 agonist varlilumab is being studied in a phase

I trial (NCT02543645), and atezolizumab plus CPI-444, an oral small molecule targeting the adenosine-A2A receptor on T-lymphocytes is similarly underway (NCT02655822). While these trials are not specifically for RCC patients, they include cohorts of patients with this disease.

Predictors of Response to Immune Checkpoint Inhibitors

Though immune checkpoint inhibitors have shown promise in mRCC, it remains unclear which patients will benefit from these agents. A study of 91 patients treated with 0.3, 3, or 10 mg/kg of nivolumab every 3 weeks showed that 32 % of evaluable patients whose tumors expressed PD-L1 in >5 % of tumor cells had an improved 2 year OS compared to those without expression (64 versus 48 %) [74]. A different study of all cancer types treated with atezolizumab observed that tumors with PD-L1 expression, particularly in the TILs, were more likely to respond [75]. Several groups have attempted to explain differences in response based on discordant expression of the ligand between primary tumors and metastases. Data from our own institution revealed a weak correlation ($R = 0.24$) between PD-L1 expression in 34 matched pairs of nephrectomy and metastatic sites in patients with clear cell RCC, and expression was higher overall in metastatic than matched primary sites [76]. This suggests that determination of PD-L1 expression in a single biopsy site might not be sufficient. In a similar study, 5 of 33 cases with primary tumors and matched metastases showed discordant expression of PD-L1 [77]. Furthermore, it remains unclear whether PD-L1 expression in tumor cell versus TIL is more predictive of response and whether TIL content should be included in biomarker studies [78]. Future studies are needed to determine which patients will benefit from immune checkpoint blockade, monotherapy, or in combination. In patients unlikely to respond, it remains unclear whether additional immune modulation with radiation, cytotoxic chemotherapy, or biologic chemotherapy will improve response.

Conclusions

Metastatic RCC is often resistant to older therapies including cytotoxic chemotherapy and radiation therapy. Newer-approved targeted therapies including inhibitors of VEGF, VEGF-R, and mTOR have largely resulted in improved response rates and/or PFS, but few studies have shown an improvement in OS. High-dose IL-2 therapy results in durable responses in a subset of patients but remains limited to patients with a good performance status who are able to get treatment at centers equipped to manage toxicities. More recently, a plethora of new immune therapies have been developed and are in clinical trials. The PD-1 inhibitor nivolumab is now approved for the treatment of renal cell carcinoma, and other PD-1 inhibitors are now being studied alone and in combination with additional immune checkpoint inhibitors or targeted therapies. Other immune checkpoint antagonists and agonists are being studied in clinical trials as single agents or in combination with PD-1/PD-L1 inhibitors, and newer vaccine and cell therapy approaches are similarly in development. Companion diagnostic tests for patient selection are needed with the goal of improving the therapeutic index for the various regimens and ultimately increasing overall survival for patients with metastatic RCC.

Compliance with Ethical Standard

Conflict of Interest Susanna A. Curtis declares that she has no conflict of interest.

Justine V. Cohen declares that she has no conflict of interest.

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