Immunologics and Chemotherapeutics for Renal Cell Carcinoma

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Abstract

Treatment of metastatic renal cell carcinoma remains a challenge for clinicians. Traditional chemotherapy is ineffective and immunotherapy with interleukin-2 is only occasionally beneficial. The development of numerous agents targeting vascular endothelial growth factor and mammalian target of rapamycin signaling pathways that have been studied in phase III trials have resulted in significant improvement in survival for patients with clear cell renal cell carcinoma. Currently available U.S. Food and Drug Administration-approved first line targeted agents include sunitinib, pazopanib, temsirolimus, and bevacizumab (with interferon), while axitinib, everolimus, and sorafenib are most extensively used following progression as second- or third line therapy. Attempts to augment the activity of these agents by combining them together or with chemotherapy or immunotherapy have not yet proven to improve outcomes. As a result, the sequential use of single agents remains the current standard of care.

Keywords
- chemotherapy
- renal cell carcinoma
- VGEF inhibitors
- mTOR inhibitors
- interleukin-2
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to describe the current state of the art medical therapy used in the treatment of renal cell carcinoma.

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Renal cell carcinoma (RCC) is the most common malignancy of the kidneys. It is estimated that about 20% of all patients with RCC present with metastatic disease, and that approximately 30% of patients develop metastatic disease following nephrectomy.[1,2] Surgical resection or ablation of primary tumors may be curative for patients with carcinoma confined to the kidney, and surgical resection of solitary sites of disease can be associated with prolonged disease-free survival in selected individuals. However, metastatic disease is generally incurable and requires systemic therapy. Before the advent of targeted agents, treatment options for metastatic RCC (mRCC) included systemic chemotherapy, which has only minimal efficacy, and cytokine therapy, which produces durable responses in a small proportion of patients at the cost of significant systemic toxicity.[3,4] Over the past decade, several targeted agents have been developed for the treatment of mRCC. In this review, the authors will examine the therapeutic options available today for patients with mRCC.

Immunotherapy

Interferon-α (IFN-α) was first used to treat mRCC in the early 1980s and consistently demonstrated low but reproducible response proportions of 10 to 20% with occasional durable responses. Two randomized trials demonstrated that patients treated with IFN-α compared with vinblastine or

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medroxyprogesterone achieved a small but statistically significant survival benefit.[5] A Cochrane analysis of four randomized trials of IFN-α that included 644 patients found a 26% relative risk reduction of death at 1 year, and an average improvement in survival of 3.8 months.[4] Most patients who did respond achieved partial responses (PRs) that typically lasted less than 12 months. Toxicities of IFN include flu-like symptoms, fatigue, and depression. Based on this survival advantage, IFN has been used as the control arm in numerous clinical trials of targeted therapies, but is rarely administered today as a single agent.

In contrast to IFN, interleukin-2 (IL-2) is still administered today in selected patients. Therapy with high-dose IL-2 results in major responses in 10 to 15% of patients with clear cell histology, with durable responses in 4 to 5% of cases. In a pooled analysis of seven phase II clinical trials including 255 patients treated with two cycles of high-dose IL-2, 15% of patients achieved an objective response with a median duration of 54 months. Among the 9% of patients who achieved a partial remission, the median duration of response was 19 months.[6] Long-term follow-up data for patients with mRCC treated in the initial high-dose bolus IL-2 trials demonstrated that among complete responders, the median progression free survival (PFS) has yet to be reached, and few relapses were observed in patients free of disease for longer than 30 months. Several patients have remained free of disease in excess of 20 years since initiating treatment, suggesting that high-dose IL-2 treatment may have led to cure in a small minority of patients.[7] More recent data from clinical trials in the modern "targeted therapy" era demonstrate a similar or slightly better objective response compared with historical controls, though the putative predictive marker of carbonic anhydrase-9 expression was not validated prospectively.[8]

There are no clear guidelines regarding patient selection, but there are retrospective data to suggest that IL-2 is more efficacious in good and intermediate prognosis patients with clear cell histology with alveolar features.[9] Toxicity associated with high-dose IL-2 results from increased vascular permeability and may require treating patients in an intensive care unit. In the review cited above, the authors reported a 4% treatment-related mortality rate due to complications such as capillary leak syndrome, myocardial infarction, respiratory failure, and gastrointestinal toxicity.[6] These toxicities limit use in the outpatient setting and require hospital-based administration. High-dose IL-2 remains an option today as front line therapy for healthy, good-risk patients as it can result in durable complete responses.

Antivascular Endothelial Growth Factor Therapies

Von Hippel-Lindau (VHL) disease is an autosomal dominant, familial cancer syndrome that predisposes individuals to renal clear cell cancers. Cytogenetic studies identifying loss of one allele of chromosome 3p in renal tumors from patients with VHL disease ultimately resulted in the identification of the *VHL* tumor-suppressor gene. The VHL protein promotes the ubiquitination and destruction of hypoxia-inducible factor (HIF-α). Loss or inactivation of VHL results in increased HIF-α expression and consequently the transcription of numerous proteins that contribute to tumor angiogenesis, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor B chain (PDGF-B) (►**Table 1**). Loss or inactivation of *VHL* also occurs in sporadic clear cell RCCs. Activation of the Akt and mammalian target of rapamycin (mTOR) signaling pathways can also increase HIF-α expression.[10–12]

Based on these molecular insights, numerous therapies that target VEGF and mTOR signaling have been developed, tested in multiple clinical trials, and U.S. Food and Drug Administration (FDA) approved for the treatment of mRCC (►**Table 2**).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against VEGF, and was the first agent that directly targeted VEGF to be studied in mRCC. Compared with placebo, patients with cytokine-refractory mRCC demonstrated a 10% response proportion and a prolonged PFS of 4.8 months (compared with 2.5 months).[13] Two large randomized studies compared bevacizumab in combination with IFN-α, against IFN-α alone, in previously untreated patients with metastatic clear cell RCC. In the AVOREN trial, bevacizumab and IFN resulted in a superior PFS (10.2 vs. 5.4 mo) and overall major response proportion (30.6 vs. 12.4%).[14] A second phase III trial, the Cancer and Leukemia Group B (CALGB) 90206 study, resulted in a median PFS of 8.5 months for patients receiving bevacizumab plus IFN-α compared with 5.2 months for patients receiving IFN-α monotherapy. There was also a significant increase in objective tumor response rate (25.5 vs. 13.1%).[15] The most common toxicities were hypertension and asymptomatic proteinuria, with serious adverse events including thromboembolic events and gastrointestinal perforation. Several studies have examined the potential benefit of

Table 1 Table of genes upregulated by HIF-α[68]

Gene	Effector function
CAIX	pH regulation
SDF1α	Inflammatory cell recruitment
CXCR4	Inflammatory cell recruitment
Cyclin D1	Proliferation
IGF2	Proliferation
VEGFA	Cell Survival and angiogenesis
Erythropoietin	Cell Survival
PDK1	Metabolism/mitochondrial function
Fibronectin 1	Extracellular matrix function
Collagen type 5	Extracellular matrix function
MET	Motility
PDGF	Angiogenesis

Abbreviation: HIF, hypoxia-inducible factor.

Table 2 FDA-approved drugs for mRCC

Cytokine
Recombinant interleukin-2
Inhibitors of *VEGF* signaling
Sunitinib
Pazopanib
Sorafenib
Axitinib
Bevacizumab (with interferon-α)
mTOR inhibitors
Temsirolims
Everolimus

Abbreviations: FDA, U.S. Food and Drug Administration; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin.

combining bevacizumab with other targeted agents (i.e., mTOR inhibitors, antiepidermal growth factor receptor inhibitors), but have failed to improve PFS and typically are associated with increased toxicity.

Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits VEGFr2, PDGFR-β, FLT3, FGFR1, and Raf-1, and was the first FDA-approved kinase inhibitor for mRCC. Early antitumor activity in a series of phase II studies led to the phase III randomized Treatment Approaches in RCC Global Evaluation Trial (TARGET) study of sorafenib compared with placebo for second line therapy in patients with clear cell mRCC who progressed on previous therapy (83% cytokines). Although only 2% of patients had an objective response, 74% of patients overall had some degree of tumor shrinkage. Though the study was initially designed with an overall survival endpoint, following clear demonstration that treatment with sorafenib resulted in a 2.2 month improvement in PFS (5.5 vs. 2.8 months, $p < 0.001$), subjects were unblinded and those on placebo were allowed to cross-over to sorafenib. Likely because of this fact, the 3-month improvement in overall survival (19.3 vs. 15.9 months; hazard ratio [HR] 0.77; 95% confidence interval [CI], 0.63–0.95; $p = 0.02$) did not meet prespecified measures of statistical significance. A separate analysis that censored patients at cross-over demonstrated improved survival compared with sorafenib (17.8 vs. 14.3 months; $p = 0.03$).[16] A randomized phase II trial of sorafenib versus IFN-α in previously untreated patients with clear cell mRCC demonstrated comparable efficacy in the two groups, with a median PFS of 5.7 versus 5.6 months for sorafenib and IFN, respectively.[17] In the more recent AGILE trial of the multikinase inhibitor axitinib compared with sorafenib in previously untreated patients (see below), the median PFS for patients receiving sorafenib was 6.5 months.[18] Today, sorafenib is generally used as second- or third line therapy in patients previously treated with cytokines, other VEGF-targeted agents, or both. Common toxicities in patients treated with sorafenib include hand–foot syndrome fatigue, diarrhea, and hypertension.

Sunitinib

Sunitinib is an oral kinase inhibitor that interacts with PDGFRβ, c-KIT, FLT-3, and VEGFR 1, 2, and 3. Sunitinib was first FDA approved in 2006 following results of two phase II trials in patients with cytokine-refractory mRCC in which patients experienced a response proportion of 41% and a PFS of 8.2 months.[19,20] The efficacy of sunitinib as a first line agent was demonstrated in a pivotal phase III randomized trial of sunitinib versus IFN-α in 750 previously untreated patients with metastatic clear cell RCC.

Treatment with sunitinib resulted in a statistically significant improvement in the major response rate (31 vs. 6%; $p < 0.000001$) and PFS (11 vs. 5 months; HR 0.42; $p < 0.001$). Overall survival was not statistically different between the two groups (26.4 vs. 21.8 months; $p = 0.51$), which was likely due to the effects of subsequent therapies in patients on the control arm. A retrospective analysis of overall survival in patients who did not have subsequent therapy showed a 14-month improvement in survival among patients treated with sunitinib (28.1 vs. 14.1 months for patients receiving IFN-α).[21] Use of sunitinib in the second line setting following treatment with sorafenib as first line is supported by a retrospective study showing a 19.5 month delay in progression.[22] The most common adverse events with sunitinib include cytopenias, diarrhea, hand–foot syndrome, and hypertension. While dosing schedules were different than the standard (for mRCC) 50 mg daily for 28 days followed by 14 days off (repeated every day, or 4 weeks on/2 weeks off) are sometimes employed due to toxicity, it should be noted that an exploratory randomized phase II study did not demonstrate lower toxicity with an alternative regimen (37.5 mg continuously), and there was a trend for better efficacy with the traditional regimen.[23]

Pazopanib

Pazopanib is an oral multitargeted tyrosine kinase inhibitor that targets VEGFR-1, 2, and 3, PDGFR, and c-kit. A phase II study evaluated 225 treated and treatment naive patients with mRCC who received pazopanib (800 mg once daily). The major response rate was 35%, the median PFS was 52 weeks, and the median duration of response was 68 weeks. The main adverse effects were diarrhea and fatigue, and the most common grade 3 or grade 4 side effect was hypertension.[24] A phase III trial of pazopanib randomized 435 untreated or cytokine pretreated patients with mRCC in a 2:1 ratio to receive either pazopanib or placebo. The response proportion for patients treated with pazopanib was 30%, and the median PFS was 9.2 months in the pazopanib group and 4.2 months in the placebo group.[25] There was no statistically significant difference in the overall survival (22.9 vs. 20.5 months; $p = 0.224$, which is likely due to a cross-over effect. Among patients treated with pazopanib, 35% experienced hepatotoxicity, including rare deaths, prompting the FDA to assign a

black box warning for this adverse reaction. Other significant toxicities include anorexia, nausea, vomiting, hair color changes, and hypertension. This study led to FDA approval for pazopanib for patients with mRCC.

The COMPARZ trial was a noninferiority trial comparing sunitinib and pazopanib in the first line setting in patients with clear cell mRCC. This study showed similar efficacy between the two agents, although pazopanib appeared to be better tolerated than sunitinib with respect to common toxicities such as hand–foot syndrome, hypothyroidism, mucositis, and myelosuppression, but had a higher incidence of hepatoxicity.[26] As a result, pazopanib can also be used in the first line treatment of clear cell mRCC.

Axitinib

Axitinib is a potent, selective, second-generation selective inhibitor of VEGFR 1, 2, and 3. The relative potency of in vitro axitinib is 50 to 450 times greater than that of the first-generation VEGFR inhibitors. Early phase II data for this drug in cytokine and sorafenib pretreated patients was very encouraging, with response proportions of 44% and a PFS of 15.7 months. In cytokine-treated patients, a response rate of 23% and a PFS of 7.4 months in sorafenib-treated patients was noted.[27,28] The pivotal trial that led to FDA approval was the Axis trial, a randomized phase III study that compared axitinib with sorafenib in 723 patients with mRCC who had progressed on first line therapy (the majority with VEGF-targeted therapy, most commonly sunitinib). Patients treated with axitinib had a higher rate of major responses (19 vs. 9%), and a significantly longer PFS (6.7 vs. 4.7 months; HR, 0·665; $p < 0.0001$). The most common adverse events were diarrhea, hypertension, dysphonia, hypothyroidism, and fatigue in patients receiving axitinib.[29] A similar study (the AGILE trial) compared these two agents in previously untreated, clear cell mRCC patients, randomized 2:1 to receive axitinib or sorafenib. The investigators predicted that sorafenib would improve PFS by 5.5 months and axitinib by 9.8 months (a 78% improvement in PFS). However, the study showed that sorafenib improved PFS by 6.5 months, compared with 10.1 months with axitinib, which was not statistically significant (HR, 0.77; $p = 0.38$). Thus, although axitinib was effective and PFS was similar to that seen in patients treated first line with sunitinib and pazopanib, the AGILE 1051 trial did not reach its primary endpoint and was deemed a negative study.[30] As a result, axitinib is generally used as second or third line therapy for patients with clear cell mRCC.

mTOR Inhibitors

Temsirolimus

Temsirolimus is an inhibitor of mTOR, a component of the phosphoinositide 3-kinase signaling pathway that activates pro-proliferative downstream targets such as HIF1α. The mTOR protein is frequently activated in RCC, which can result in increased production of HIF proteins. Suggestion of a clinical benefit in a phase II study of patients with cytokine-refractory RCC with Memorial Sloan-Kettering Cancer Center (MSKCC) poor risk criteria led to the multicentered, phase III ARCC trial of temsirolimus, IFN, or the combination of temsirolimus and IFN in previously untreated patients with mRCC who had three of six poor prognostic features (serum lactate dehydrogenase > 1.5 times the upper limit of normal, a hemoglobin less than the lower limit of the normal, a corrected serum calcium level > 10 mg/dL, a time from initial diagnosis of RCC to randomization of less than 1 year, a Karnofsky performance score of 60 or 70, or metastases in multiple organs). In contrast to most studies, patients with nonclear cell histology were eligible for this trial. Patients randomized to receive temsirolimus alone had a significant improvement in overall survival compared with patients receiving IFN alone (10.9 vs. 7.4 months, HR, 0.73; $p = 0.008$). PFS was also superior in the temsirolimus arm compared with the IFN arm (5.5 vs. 3.1 months; HR, 0.66; 95% CI, 0.53, 0.81). The combination of temsirolimus and IFN did not increase survival.[31] Based on this study, temsirolimus was FDA approved in 2007. Commonly observed toxicities included rash, edema, hyperglycemia, and hyperlipidemia. Hypersensitivity reactions and pneumonitis are also potentially serious adverse reactions to this agent.[31] Of clinical significance, a posthoc subgroup analysis showed that treatment with temsirolimus also resulted in superior clinical benefit in patients with nonclear cell histologies when compared with IFN.[32] As a result, temsirolimus is often used as first line therapy in patients with nonclear cell mRCC, such as papillary RCC.

Temsirolimus has also been studied as a second line agent in the INTORSECT trial, which was a multicenter phase III trial comparing temsirolimus to sorafenib in good performance status mRCC patients who progressed on first line therapy with sunitinib therapy. There was no statistically significant difference between the two agents with regard to the primary endpoint of PFS suggesting that these two agents are similar in the second line setting, though the secondary endpoint of overall survival favored sorafenib.[33]

Everolimus

Everolimus is an orally administered mTOR inhibitor that has been evaluated in the second line setting in patients who progressed on first line anti-VEGF therapy. The RECORD-1 trial was a phase III randomized placebo controlled trial of predominantly good or intermediate risk patients who had previously been treated with sorafenib, sunitinib, or both. The study was stopped early due to a significant prolongation of PFS in the everolimus group (4.9 vs. 1.9 months; HR 0.30; 95% CI, 0.22–0.40; $p < 0.0001$). Although only 1% of the patients achieved a partial remission, 63% (vs. 32% in the placebo group) experienced disease stabilization for at least 56 days. Adverse effects of everolimus therapy included rash, asthenia, mucositis, edema, myelosuppression, hyperlipidemia, hypercholesterolemia, hyperglycemia, and drug-induced pneumonitis.[34]

Cytotoxic Chemotherapy

Early clinical trials of single agent chemotherapy consistently showed modest response rates in patients with metastatic

RCC (mRCC). A review of trials of 72 single cytotoxic agent chemotherapies in 3,502 patients with advanced RCC found that only 5.6% of patients achieved an objective response (95% CI, 4.8–6.4%).[3] The highest response rates were found with vinblastine (optical rejection ratio [ORR], 6.7%), 5-FU (ORR, 6.6%), and floxuridine (ORR, 9.7%).[3,35,36] Combination chemotherapy regimens, including gemcitabine combined with 5-FU or capecitabine, docetaxel combined with capecitabine, or oxiplatin have failed to demonstrate significant improvement in outcomes,[37–39] although the combination of gemcitabine and doxorubicin has demonstrated a subset of long-term nonprogressors in patients with previously rapidly progressive or sarcomatoid RCC.[40,41] Chemotherapy is only rarely used today to treat mRCC.

Immunotherapy–Cytotoxic Chemotherapy Combinations

Investigators have attempted to augment the activity of cytokine-based immunotherapy with traditional chemotherapies such as vinblastine, gemcitabine, and fluoropyrimidines. Phase II and phase III trials combining IFN and vinblastine report major responses in 10 to 30% of patients and an overall survival of 17 to 22 months.[42–44] The efficacy of this combination is likely due to cytokine effect, and vinblastine adds little to its efficacy.[45] 5-FU combined with cytokines was perhaps the most promising combination regimen but failed to show a survival benefit in large scale randomized trials.[46–50] In a phase II trial conducted in 1993, Atzpodien et al treated 35 treatment naive, good performance status patients with mRCC with 4 weeks of IFN-α and IL-2, followed by 4 weeks of IFN-α and 5-FU. The authors reported an impressive response proportion of 48.6% with four complete remissions and 14 PRs, and only mild systemic toxicity.[51] The largest and most definitive trial to evaluate this regimen was a phase III prospective randomized trial from the EORTC that was reported in 2010. In this study, 1,006 previously untreated patients with histologically proven mRCC were randomized to receive either IFN-α alone or in combination with IL-2 and 5-FU. Patients receiving combination therapy had significantly higher response rates than controls (23 vs. 16%; $p = 0.0045$), but there was no difference in PFS or overall survival (18.8 vs. 18.6 months).

Chemotherapy plus Targeted Therapies

In vitro studies suggest a synergistic antitumor effect when combining fluoropyrimidines and sorafenib in RCC cell lines. The combination of gemcitabine, 5-FU, and sorafenib led to a response proportion that was 38%, with 86% of patients achieving some measure of disease control in a phase II trial. Responses lasted more than 13 months, with 28% of patients having a PFS of more than 26 months.[52] Capecitabine, gemcitabine, and sorafenib combinations have also shown promise with 16 to 45% of patients responding to treatment, with a PFS of 6.1 to 11.0 months and an overall survival of 18.3 to 25.8 months.[53–55] Gemcitabine and sunitinib combinations have shown similar promise (response rate, 25%; PFS 5.8 months) in both retrospective analyses and early stage clinical trials.[56–58] Sunitnib and sorafenib have also been added to gemcitabine and doxorubicin in patients with sarcomatoid RCC with response rates of up to 60%.[59–61] Till date, no phase III trials evaluating these combinations have been performed. A phase I study of the combination of capecitabine, gemcitabine, and sunitinib in treatment naive patients resulted in significant toxicity without signs of synergistic activity.

Bevacizumab has also been studied in combination with capecitabine and gemcitabine in a retrospective analysis of 28 intermediate or poor prognosis patients; this resulted in a median PFS of 5.9 months and an overall survival of 10.4 months.[62] Patients who were previously treated with tyrosine kinase inhibitors had a better response and patients with sarcomatoid features tended to do poorly on this regimen. A subsequent phase II trial using this regimen in 29 patients had an overall response rate of 24%, composed entirely of PRs. The median overall survival and PFS were 9.8 and 5.3 months, respectively. This study was terminated early due to poor patient accrual.[63]

Novel Therapies

Although newer and more potent and/or more selective multikinase inhibitors have been developed, it is unlikely that another kinase inhibitor targeting the VEGF signaling pathway will lead to a significant clinical improvement; the most recent drug (tivozanib) was not approved by the FDA based upon a single study with improved PFS but no improvement in overall survival. Drugs targeting alternative pathways are needed, and novel immune therapies have shown great promise in early phase clinical trials. Nivolumab (BMS-936558) and MPDL3280A are recently developed monoclonal antibodies in the checkpoint inhibitor pathway that target programmed cell death (PD-1) or PD ligand-1 (PD-L1), a surface antigen expressed by RCC cells that induces immune quiescence and is thought to allow cancers to evade the host immune response.[64] Early results of a phase I expansion study of MPDL3280A showed that patients responded to the drug across multiple dose levels with some patients experiencing prolonged stable disease before achieving major responses. Toxicities were mild and included hypophosphatemia, fatigue, dyspnea, and hyperglycemia.[65] Updated results of a phase I trial of nivolumab in heavily pretreated patients with mRCC had a median duration of response of 12.9 months. The median overall survival had not been reached at the time of presentation, suggesting that this agent produces some durable responses. A randomized phase II study testing different doses in patients with clear cell mRCC refractory to VEGF therapy has been completed, and a phase III trial of this agent compared with everolimus is ongoing (NCT01668784).[66] A phase I trial of nivolumab combined with sunitinib, pazopanib, or ipilumumab is also under investigation.[67]

Conclusions

Treatment of mRCC remains a challenge for clinicians. Traditional chemotherapeutic agents are ineffective in this disease.

Immunotherapy with IL-2 is a viable option for selected patients with good performance status and low burden of disease, and can result in prolonged remissions. Agents targeting VEGF signaling pathways are now considered standard treatment in patients with clear cell mRCC. At present the available first line targeted agents include sunitinib, pazopanib, temsirolimus, and bevacizumab (with IFN). At this time, use of axitinib, everolimus, and sorafenib are most extensively studied in the second- or third line setting. Attempts to augment the activity of these agents by combining them with chemotherapy, immunotherapy, or other targeted agents have as of yet not resulted in improved survival and require further study. Perhaps the most promising new development in RCC is the development of anti–PD-(L)1 antibodies, which have been shown to produce quality responses in heavily pretreated patients with minimal toxicity. More advanced clinical trials using these agents are ongoing.

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