Evolving Role of Novel Targeted Agents in Renal Cell Carcinoma

Review Article [1] | September 01, 2007 | Renal Cell Carcinoma [2], Kidney Cancer [3], Oncology Journal [4], mTOR [5]

The treatment of metastatic renal cell carcinoma (RCC) has changed dramatically over the past few years. An improved understanding of the biology of RCC has resulted in the development of novel targeted therapeutic agents that have altered the natural history of this disease. In particular, the hypoxia-inducible factor (HIF)/vascular endothelial growth factor (VEGF) pathway and the mammalian target of rapamycin (mTOR) signal transduction pathway have been exploited. Sunitinib malate (Sutent), sorafenib tosylate (Nexavar), bevacizumab (Avastin)/interferon alfa, and temsirolimus (Torisel) have improved clinical outcomes in randomized trials by inhibiting these tumorigenic pathways. Combinations and sequences of these agents are being evaluated. Other novel multitargeted tyrosine kinase inhibitors (pazopanib and axitinib) and mTOR inhibitors (everolimus) are in clinical development. Recently reported and ongoing clinical trials will help further define the role of these agents as therapy for metastatic RCC.

In the United States, more than 50,000 new cases of renal cell carcinoma (RCC) and 13,000 associated deaths are predicted for 2007.[1,2] Although surgery is a potential cure for patients with localized RCC, many patients experience recurrence after surgery or have metastatic disease at the time of initial diagnosis. In these patients, few treatment options have been available. A highly vascular disease, RCC is known to be resistant to chemotherapy, with no single agent showing significant antitumor activity.[3,4] Interferon alfa (IFN-α) and interleukin-2 (IL-2, Proleukin) have been widely utilized as treatment for metastatic RCC. However, the majority of patients do not benefit from IFN-α or IL-2, and the few responses seen are not durable—only about 10% of patients remain progression-free at 3 years.[5,6]

An improved understanding of the biology of RCC has resulted in the development of novel targeted agents that are changing the natural history of this disease. In particular, the hypoxia-inducible factor (HIF)/vascular endothelial growth factor (VEGF) pathway and the mammalian target of rapamycin (mTOR) signal transduction pathway have been exploited. Sunitinib malate (Sutent), sorafenib tosylate (Nexavar), bevacizumab (Avastin)/IFN-α, and temsirolimus (Torisel) have improved clinical outcomes in randomized phase III trials (Table 1), leading to the first new drug approvals for the treatment of advanced RCC in almost 2 decades.
Combinations and sequences of these agents are being evaluated. Other novel targeted agents have also demonstrated activity in early studies (Table 2). Given the availability of multiple treatment options, many questions emerge as to how to best integrate these new therapies into the management of metastatic RCC. Ongoing and planned clinical trials should help answer important questions that will allow the selection of patients most likely to respond to these agents. Herein, we review the rapidly evolving role of targeted therapy for RCC.

**Table 1**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>N</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al.</td>
<td>First-line</td>
<td>750</td>
<td>Sunitinib</td>
<td>IFN-α</td>
<td>11.0 vs 5.1 mo$^a$</td>
<td>NA</td>
</tr>
<tr>
<td>Escudier et al.</td>
<td>Second-line</td>
<td>905</td>
<td>Sorafenib</td>
<td>Placebo</td>
<td>24 vs 12 wk$^a$</td>
<td>17.8 vs 14.3 mo$^a$</td>
</tr>
<tr>
<td>Escudier et al.</td>
<td>First-line</td>
<td>649</td>
<td>Bevacizumab + IFN-α</td>
<td>IFN-α</td>
<td>10.2 vs 5.4 mo$^a$</td>
<td>NA</td>
</tr>
<tr>
<td>Hudes et al.</td>
<td>First-line, poor risk</td>
<td>626</td>
<td>Temsirolimus$^b$</td>
<td>IFN-α</td>
<td>3.7 vs 1.9 mo$^a$</td>
<td>10.9 vs 7.3 mo$^a$</td>
</tr>
</tbody>
</table>

$^a$Statistically significant.

$^b$Study contained another arm of temsirolimus + IFN that did not extend survival.

IFN-α = interferon alfa; NA = not available; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma.

**Table 2**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Manufacturer</th>
<th>Status in RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumub</td>
<td>VEGF A ligand inhibitor</td>
<td>Genentech/Roche</td>
<td>Phase III</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR inhibitor</td>
<td>Novartis</td>
<td>Phase III</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR, PDGFR, c-kit tyrosine kinase Inhibitor</td>
<td>GlaxoSmithKline</td>
<td>Phase III</td>
</tr>
<tr>
<td>Axitinib</td>
<td>VEGFR and PDGFR tyrosine kinase inhibitor</td>
<td>Pfizer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>VEGFR, PDGFR c-kit tyrosine kinase inhibitor</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>VEGF Trap</td>
<td>VEGF ligand inhibitor</td>
<td>Various</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

IFN = interferon; mTOR = mammalian target of rapamycin; PDGFR = platelet-derived growth factor receptor; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor.

**Prognostic Factors and Risk Stratification**

Although pathologic stage (TNM stage) is the most powerful predictor of survival in RCC, other tumor- and patient-related factors have been demonstrated to be significant predictors of outcome.
in multivariate analysis. The widely used Memorial Sloan-Kettering Cancer Center (MSKCC) risk group categorization in untreated patients with metastatic RCC defines the five poor-risk features as a Karnofsky performance status (KPS) < 80, a serum calcium level > 10 mg/dL (corrected for albumin), a hemoglobin below normal, absence of prior nephrectomy, and a lactate dehydrogenase (LDH) > 1.5 times the upper limit of normal.[8,9] In the original MSKCC analysis, the median survivals were 20, 10, and 4 months for good-risk (no risk factors), intermediate-risk (1-2 risk factors), and poor-risk patients (≥ 3 risk factors), respectively.

Similar prognostic factors were subsequently demonstrated to be important for pretreated patients.[10] Pretreatment features associated with a shorter survival were low KPS, low hemoglobin, and high serum calcium. The median time to death in patients with zero risk factors was 22 months, with one of these prognostic factors was 11.9 months, and with two or more risk factors was 5.4 months. The application of the MSKCC risk group categorization or its modification has been widely applied in the pivotal trials of targeted therapy for RCC. Patient selection has allowed for risk group stratification that will enable the practicing oncologist to more appropriately select treatment options for utilizing targeted approaches in the patient cohort most likely to benefit.

**Targeted Therapy for Metastatic RCC**

Loss of VHL gene function correlates with constitutive activation and accumulation of HIF-1α with subsequent transcription of multiple hypoxia-induced genes important in tumor progression, including VEGF and platelet-derived growth factor (PDGF).[11,12] Thus, agents targeting VEGF, VEGF receptor (VEGFR), PDGF, and PDGF receptor (PDGFR) offer a strong biologic rationale as therapy for patients with clear cell RCC.[7] Tumor angiogenesis is also stimulated by growth factors through the phosphatidylinositol-3 kinase (PI3K)-AKT-mTOR signal transduction pathway, and agents that target this pathway can also be expected to have antitumor activity.[13] VEGF-ligand inhibitors, small-molecule receptor tyrosine kinase inhibitors, and mTOR inhibitors have been developed and utilized as therapy for patients with metastatic RCC.

**Sunitinib**

Sunitinib is a highly potent, selective inhibitor of multiple receptor tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-kit, and Flt-3. Sunitinib received US Food and Drug Administration (FDA) regulatory approval in January 2006 based on results from two phase II trials in patients with metastatic RCC that progressed after prior therapy with IFN or IL-2.[14,15] To further evaluate the efficacy of sunitinib in previously untreated patients with metastatic RCC, a large multinational phase III trial was conducted.[16] A total of 750 patients with predominantly good- and intermediate-risk clear cell RCC were randomized to receive either sunitinib or IFN-α. Patients were randomized 1:1 to receive oral sunitinib at 50 mg/d for 4 weeks followed by a 2-week off period (6-week cycles) or IFN-α at 9 million units (MU) subcutaneously 3 times weekly (3 MU per dose given the first week and 6 MU per dose given the second week).

The study was recently updated, and independent review revealed an objective tumor response rate (complete plus partial responses) of 39% for patients receiving sunitinib vs 8% for patients receiving IFN (P < .000001).[17] Median progression-free survival (PFS) was also significantly greater for sunitinib-treated patients (11.0 vs 5.1 months; hazard ratio [HR] = 0.538, P < .000001).[17] Although survival endpoints are still premature, the HR was 0.65 (P < .02) in favor of sunitinib. Severe adverse events (grade 3/4 toxicities) were acceptable, with neutropenia (12%), thrombocytopenia (8%), hyperamylasemia (5%), diarrhea (5%), hand-foot syndrome (5%), and hypertension (8%) being noteworthy in the sunitinib arm, whereas fatigue was more common with IFN-α (12% vs 7%). Adverse events leading to withdrawal from the study occurred in 8% of patients on sunitinib and 13% on IFN-α.

In this study, the previously reported MSKCC risk factor model was shown to predict for PFS in sunitinib-treated patients. On multivariate analysis, pretreatment features predictive of PFS to sunitinib were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, time from diagnosis to treatment < 1 year, and corrected calcium level ≤ 10.0 mg/dL. Utilizing these prognostic factors, a nomogram that predicts the probability of remaining progression-free at 12 months with sunitinib has been developed.[17] Based on the highly statistically significant improvement in PFS and the drug's tolerability, sunitinib has become the new standard of care for the first-line treatment of good- and intermediate-risk metastatic clear cell RCC.

**Sorafenib**

Sorafenib is an oral, biaryl urea molecule that was designed as a c-Raf and b-Raf kinase inhibitor, but was also found to inhibit several receptor tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, Flt3, and c-KIT.[18-21] Sorafenib received FDA regulatory approval in December 2005 as therapy for advanced RCC based on the initial results of a phase III placebo-controlled randomized
The trial randomized 626 patients in a 1:1:1 ratio to 3 arms: IFN-α up to 18 MU subcutaneously 3 years).[32] Excluding nephrectomy and including > 1 metastatic site and time from diagnosis to therapy < 1 year. The results of a multinational randomized phase III trial evaluating temsirolimus with or without IFN as frontline therapy for RCC patients with ≥ 3 of 6 poor-risk features (4 from the MSKCC criteria for angiogenesis and 2 for HIF-1).[31] Temsirolimus received FDA regulatory approval in May 2007 for advanced RCC based on the results of a multinational randomized phase III trial evaluating temsirolimus with or without IFN as a single-agent therapy for patients with metastatic RCC who had previously failed therapy with IFN or IL-2. In order to determine the efficacy of sorafenib in previously untreated patients with metastatic clear cell RCC, a randomized phase II trial of sorafenib vs IFN was conducted, and the final results were recently reported.[25] In this randomized, controlled, double-blind study, 649 patients with metastatic clear cell RCC were randomized 1:1 to receive either IFN (9 MIU three times weekly) and placebo or the combination of bevacizumab (10 mg/kg every 2 weeks) and IFN (9 MIU three times weekly).[30] The treatment arms were well balanced for prognostic factors, and all patients enrolled in the study had previously undergone nephrectomy. Side effects were similar between treatment arms. Bevacizumab-related side effects were generally mild and consistent with previous observations. The addition of bevacizumab to IFN significantly increased PFS (10.2 vs 5.4 months; HR = 0.63, P = .0001) and objective tumor response rates (complete plus partial responses, 30.6% vs 12.4%; P < .0001). A trend toward improved overall survival was also observed (P = .0670). In this trial, only MSKCC good- and intermediate-risk patients benefited, with poor-risk patients having no added improvement in PFS over that seen with IFN alone. These results support the antitumor activity of bevacizumab/IFN as a therapy for patients with metastatic clear cell RCC. Given the similar PFS reported in previous phase II trials of bevacizumab,[28,29] the added benefit of IFN is uncertain. Randomized trials with a single-agent bevacizumab arm are needed to fully define the activity of this agent as a monotherapy.

Bevacizumab

Bevacizumab is a recombinant monoclonal antibody that binds and neutralizes circulating VEGF-A, and has demonstrated activity against metastatic RCC in several clinical trials.[27-29] Two randomized phase III trials of IFN-α with or without bevacizumab in previously untreated patients with metastatic RCC have been conducted—the Cancer and Leukemia Group B (CALGB)-90206 and Roche B017705 (AVOREN) trials. The results from the phase III AVOREN trial were recently reported. In this randomized, controlled, double-blind study, 649 patients with metastatic clear cell RCC were randomized 1:1 to receive either IFN (9 MIU three times weekly) and placebo or the combination of bevacizumab (10 mg/kg every 2 weeks) and IFN (9 MIU three times weekly).[30] The treatment arms were well balanced for prognostic factors, and all patients enrolled in the study had previously undergone nephrectomy. Side effects were similar between treatment arms. Bevacizumab-related side effects were generally mild and consistent with previous observations. The addition of bevacizumab to IFN significantly increased PFS (10.2 vs 5.4 months; HR = 0.63, P = .0001) and objective tumor response rates (complete plus partial responses, 30.6% vs 12.4%; P < .0001). A trend toward improved overall survival was also observed (P = .0670). In this trial, only MSKCC good- and intermediate-risk patients benefited, with poor-risk patients having no added improvement in PFS over that seen with IFN alone. These results support the antitumor activity of bevacizumab/IFN as a therapy for patients with metastatic clear cell RCC. Given the similar PFS reported in previous phase II trials of bevacizumab,[28,29] the added benefit of IFN is uncertain. Randomized trials with a single-agent bevacizumab arm are needed to fully define the activity of this agent as a monotherapy.

Temsirilimus

Temsirolimus, an intravenously administered mTOR inhibitor, regulates nutritional needs, cell growth, and angiogenesis by downregulating or upregulating a variety of proteins, including HIF-1.[31] Temsirolimus received FDA regulatory approval in May 2007 for advanced RCC based on the results of a multinational randomized phase III trial evaluating temsirolimus with or without IFN as frontline therapy for RCC patients with ≥ 3 of 6 poor-risk features (4 from the MSKCC criteria for angiogenesis and 2 for HIF-1). The trial randomized 626 patients in a 1:1:1 ratio to 3 arms: IFN-α up to 18 MU subcutaneously 3
times weekly, temsirolimus at 25 mg/wk intravenously, or a combination of temsirolimus at 15 mg/wk plus IFN-α at 6 MU 3 times weekly. The arms were well balanced, and approximately 70% were poor-risk, 80% had predominantly clear cell histology, and 67% had undergone nephrectomy. The median survival of patients receiving temsirolimus alone was superior to those given IFN-α alone (10.9 vs 7.3 months; HR = 0.73, \(P < .007\)), but the combination arm was not superior to the IFN-α arm (8.4 months; HR = 0.95, \(P = .69\)). The median PFS was statistically superior for both temsirolimus arms (3.7 months) compared to IFN-α (1.9 months). Objective responses occurred in 7%, 9%, and 11% of patients in the IFN-α, temsirolimus, and combination arms, respectively.

Any toxicity ≥ grade 3 was seen in 69% of patients on temsirolimus vs 85% to 87% of patients on the IFN-containing arms (\(P < .001\)). The most common grade 3 toxicity was asthenia, which occurred less frequently in the temsirolimus arm (12%) than in the IFN-α arms (~30%). Rash was more common on the temsirolimus arm (37% vs 5% on IFN-α and 16% on the combination). Adverse events leading to withdrawal from the study occurred in 7%, 14%, and 22% of patients on temsirolimus, IFN-α, and the combination arms, respectively.

Given the significant improvement in median overall survival, temsirolimus should be considered a standard treatment in poor-risk metastatic clear cell RCC, and a potential benefit in a broader population may exist. In this study, the activity of temsirolimus was demonstrated in patients with advanced RCC irrespective of histologic subtype (clear cell and non-clear cell).

**Targeted Agents in Clinical Development**

**Everolimus**

Everolimus (RAD001) is an orally bioavailable rapamycin analog. Preclinical models have demonstrated dose-dependent antitumor activity and additive antiproliferative effects in cancer cell lines,[33,34] and tumor regression has been documented in phase I/II trials in metastatic RCC. Everolimus is currently being compared to placebo in a large multinational phase III trial in patients with metastatic RCC who have failed sorafenib, sunitinib, or both.

**Pazopanib**

Pazopanib (GW786034) is an orally administered multitargeted inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-kit. A multinational phase II randomized discontinuation trial of pazopanib in 225 patients with metastatic clear cell RCC has completed accrual, and the first interim analysis was recently presented.[35] All patients received 800 mg/d of oral pazopanib for the first 12 weeks, at which point patients who had stable disease were randomized 1:1 to continue pazopanib or receive placebo. Approximately 67% of patients in this study were treatment-naive, and 33% had failed one prior therapy (23% cytokines, 8% bevacizumab, 2% both).

In the first 60 patients enrolled in this study, partial responses were seen in 40% and stable disease in 42% at week 12 by independent review. Based on the significant level of "early" activity, the independent data safety monitoring committee recommended discontinuing the randomized portion of the trial, and all patients received pazopanib. The most common adverse events included transaminase elevation, diarrhea, fatigue, and nausea. A randomized placebo-controlled, multicenter international phase III study evaluating pazopanib in patients with locally advanced and/or metastatic RCC who are untreated or have failed prior cytokine treatment has also recently completed accrual, and the results are anxiously awaited.

**Axitinib**

Axitinib (AG-013736) is an oral multitargeted tyrosine kinase receptor inhibitor against VEGFR-1, VEGFR-2, and PDGFR-β. In a phase II trial in 52 patients with advanced cytokine-refractory RCC treated with 4-week cycles of axitinib at 5 mg twice daily, 24 (46%) achieved a partial response.[36] The median PFS has not been reached after a 12- to 18-month follow-up. Grade 3/4 hypertension was the most important toxicity, observed in 15% of patients. No cases of neutropenia or thrombocytopenia above grade 1 were found.

A phase II trial of axitinib in patients with sorafenib-refractory RCC was recently reported.[37] A total of 62 patients were enrolled in this multi-institutional trial. All patients had received prior sorafenib therapy, and 9 of 62 patients had also received sunitinib. Overall, 57% of patients experienced some degree of tumor regression, with a median PFS > 6.1 months. Partial response was seen in 14% of patients, and 36% had stable disease. Treatment-related grade 3/4 adverse events included hypertension (16%), fatigue (14%), and hand-foot syndrome (14%).

**Future Directions**

Future research is needed to determine the most effective dosing schemes for these agents, as well as their optimal sequencing and combination. The development of biomarkers predictive of response will enable the practicing oncologist to optimize and individualize therapy for patients with RCC. Since disease eventually progresses after treatment with these targeted agents, mechanisms of
resistance need to be elucidated and strategies to overcome this problem must be developed. In addition, the activity of these agents in subsets of patients (non-clear cell histologies, central nervous system metastasis, renal and hepatic failure) not formally evaluated in prospective randomized trials needs to be further defined.

Finally, the role of these agents in adjuvant therapy must be explored. Two large multi-institutional trials evaluating the use of these agents as adjuncts to surgery in patients at high risk for recurrence of surgically resected RCC are currently open to accrual. Based on the results of published phase III trials, a treatment algorithm integrating these new targeted agents into the management of metastatic RCC has begun to emerge (Table 3).

Conclusions
The availability of rationally designed, targeted therapy for metastatic RCC has significantly altered the natural history of this disease. Sunitinib malate, sorafenib tosylate, temsirolimus, and bevacizumab/IFN have demonstrated significant improvements in response rates, PFS, and (in the case of temsirolimus) overall survival, with manageable side effects. A variety of other novel targeting agents are currently under development for the treatment of metastatic RCC. These promising drugs including mTOR inhibitors, VEGF ligand inhibitors, and tyrosine kinase inhibitors. Unfortunately, the development of these agents has outpaced our understanding of how to use them optimally.

As recent studies have shown, broad regulatory approval of a particular agent does not equal broad activity in all patient subsets. Therefore, use of these new agents should be limited to the subsets in which the agent was studied. Further elucidation of the complex signaling pathways believed to be crucial in the pathogenesis of RCC will enable both discovery of new agents and individualized selection of current agents for our patients.

References:


Source URL:
http://www.cancernetwork.com/printpdf/evolving-role-novel-targeted-agents-renal-cell-carcinoma/page/0/1

Links:
[1] http://www.cancernetwork.com/review-article
[4] http://www.cancernetwork.com/oncology-journal
[7] http://www.cancernetwork.com/authors/robert-figlin-md