Improving survival of patients with advanced renal cell carcinoma: a new paradigm

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The primary genetic lesion in most cases of clear-cell renal cell carcinoma (RCC) is silencing of the von Hippel-Lindau disease tumor suppressor gene *(VHL)* by mutation or methylation.[1] Since VHL targets hypoxia-inducible factor 1 (HIF-1) for degradation via a pathway called ubiquitination, lack of the tumor suppressor protein VHL results in upregulation of HIF-1.[2] The resulting overexpression of HIF-1, in turn, leads to the induction of hundreds of genes and proteins that are useful to mammalian cells in their response to hypoxia. These proteins include glucose transporter proteins and many growth factors and their receptors, such as vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis, and platelet-derived growth factor (PDGF). Therapy designed to inhibit VEGF and other HIF-controlled proteins has therefore been pursued as a means of improving survival in RCC.

Initial studies using targeted agents

The first successful targeting attempt in RCC involved the anti-VEGF recombinant human monoclonal antibody bevacizumab (Avastin). Yang et al[3] conducted a randomized phase II trial of bevacizumab in which 116 patients with treatment-refractory, metastatic clear-cell RCC received either placebo or low (3 mg/kg) or high (10 mg/kg) doses of bevacizumab intravenously every 2 weeks. An objective response was seen only in 10% of the high-dose group. This group also showed a significant prolongation in time to disease progression compared with the group receiving placebo (4.8 months vs 2.5 months, respectively; $P < 0.001$ [log-rank test]).

Based on these promising observations, Hainsworth et al[4] studied a combination of bevacizumab (10 mg/kg every 2 weeks) and, to block the epidermal growth factor receptor upregulated by overexpression of HIF, the tyrosine kinase inhibitor erlotinib (150 mg/d; Tarceva) in 58 patients with metastatic clear-cell RCC. The results of this phase II trial were encouraging, with a 25% overall objective response rate, a minor response rate of 22%, and a median survival of 23 months, compared with an expected survival of 15–18 months.

To confirm these findings, Genentech performed a multicenter 100-patient randomized phase II trial of bevacizumab with or without erlotinib. The results were presented at the 2006 Annual Meeting of the American Society of Clinical Oncology (ASCO 2006). Patients in both arms of the trial had a response rate of 14%, a median time to disease progression of about 8 months, and a median survival of 15 months.[5] This study casts serious doubt on the value of erlotinib in RCC; however, it strongly confirms the single-agent activity of bevacizumab in metastatic RCC. Thus, final results of two phase III studies examining the role of bevacizumab in RCC are eagerly awaited.

The first study, conducted by the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group, compared interferon alpha (IFN-α), the current standard of care, with IFN-α plus bevacizumab. This 700-patient phase III trial was completed in July 2005.[6] A study of nearly identical design (sponsored by Roche) is nearing completion in Europe. If both of these trials show a survival benefit for the bevacizumab arm, IFN-α plus bevacizumab will become a new standard of care for metastatic RCC.

Sorafenib

Other methods to target HIF-regulated genes and proteins are also being actively pursued. The first clinical reports appeared in abstract form in 2004 and were recently published.[7,8] Two orally bioavailable small-molecule inhibitors of VEGF and related receptors, sorafenib (Nexavar) and sunitinib (Sutent), were reported to have activity in RCC.

Sorafenib was originally identified as an inhibitor of Raf kinase, an enzyme involved in cellular proliferation, and subsequently found to inhibit the VEGF and PDGF receptor families.[9] Sorafenib (400 mg twice daily) was investigated in an international phase II randomized discontinuation trial in which 202 patients with metastatic RCC were evaluated. The overall percentage of

patients experiencing any tumor regression was 71%, with progression-free survival being clearly superior in the subset of patients who were randomized to remain on sorafenib compared with the group crossed over to the placebo arm (24 weeks vs 6 weeks; $P = 0.0087$).[7] A subsequent European-based, placebo-controlled, randomized phase III trial of sorafenib—the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET)—in 905 cytokine-refractory RCC patients demonstrated a progression-free survival advantage in the sorafenib arm of 24 weeks versus 12 weeks among those given placebo ($P < 0.000001$).[10] This trial also showed a trend in favor of overall survival for the sorafenib arm, but patient crossover between the two arms of the study precluded a definitive survival analysis. Based on these data, the US Food and Drug Administration (FDA) approved sorafenib for the treatment of advanced RCC in December 2005.

At ASCO 2006, Eisen et al[11] presented an update of the TARGET data. That trial continues to shows a strong trend for survival in favor of sorafenib (median survival, 19 months) compared with placebo (median survival, 14.5 months) at both the first and second of four planned interim analyses of the data. A randomized phase II trial of sorafenib versus IFN-α in 100 patients has been completed and was due to be reported at ASC0 2006. To the chagrin of the audience, the data were not mature and were not reported as planned.[12] However, Ryan et al[13] presented a phase II trial of sorafenib plus IFN-α conducted by the Southwest Oncology Group (protocol 0412) showing an objective response rate of 18% with acceptable toxicity. Whether the combination of sorafenib and IFN-α is superior to single-agent sorafenib is unclear from this phase II trial.

Several phase I trials of sorafenib and bevacizumab—a so-called vertical blockade of the VEGF pathway—were reported at ASCO 2006. Sosman et al[14] reported that neither drug could be given at the recommended phase II dose but that responses were seen in 8 of 18 patients with metastatic RCC. Data on the synergistic toxicity and efficacy of sorafenib plus bevacizumab were also presented by a group from the National Cancer Institute.[15] Encouraging responses were seen in RCC and ovarian cancer patients, but significant hypertension and proteinuria were also observed, suggesting synergistic toxicity.

Sunitinib

Sunitinib was identified as an orally active tyrosine kinase inhibitor of the VEGF, PDGF, and c-KIT receptor families.[16] As described in the preceding summary article, two sequential phase II trials of sunitinib (50 mg/d for 4 weeks, followed by a 2-week rest period) in cytokine-refractory, metastatic RCC have been conducted by Motzer et al.[17] Objective response rates of approximately 40% were observed, with additional patients experiencing tumor shrinkage. Based on these data, sunitinib was approved by the FDA for advanced RCC in January 2006. The FDA also approved sunitinib for the treatment of gastrointestinal stromal tumors in patients intolerant of or resistant to imatinib (Gleevec).

At ASCO 2006, results of an international randomized phase III trial of sunitinib versus IFN-α reported by Motzer et al[18] demonstrated a significant advantage of sunitinib over IFN-α in disease progression-free survival (11 months vs 5 months; hazard ratio [HR] = 0.415; $P < 0.000001$) and overall response rate (37% vs 9%; $P < 0.000001$). Altogether, 66% of sunitinib-treated patients remain on study, whereas only 34% of the patients who received IFN-α remain on study. Although survival endpoints were still immature, the HR was 0.65 ($P < 0.02$) in favor of sunitinib. The investigators concluded that sunitinib is the new standard of care for metastatic RCC.

Other studies on sunitinib in RCC reported at ASCO 2006 were equally encouraging. Rini et al[19] presented data showing that sunitinib had substantial activity in metastatic RCC patients who were bevacizumab refractory (defined as disease progression within 3 months of treatment with bevacizumab). The investigators treated 60 patients with sunitinib and found that 74% showed some degree of tumor shrinkage (16% of patients had a partial response, and 58% showed < 50% regression). De Mulder et al[20] reported that continuous oral dosing of sunitinib at a dose of 37.5 mg/d (in contrast to the usual dosing schedule of 50 mg/d for 4 weeks, with a 2-week rest period) was safe and induced tumor shrinkage in 33 (82%) of the first 40 evaluable patients.

Other small-molecule inhibitors

A number of other small-molecule inhibitors of the HIF/VEGF pathways are showing significant promise in metastatic RCC. The mTOR/akt pathway is a nutrient-sensing pathway and is upregulated by HIF. Inhibitors of the mTOR molecule include rapamycin (sirolimus [Rapamune]), everolimus (RAD 001), and temsirolimus (CCI-779). In a phase II trial conducted by Atkins et al,[21] temsirolimus produced a low, but reproducible, response rate (7%) in 111 heavily pretreated patients with RCC and appeared to be effective in patients who had a poor prognosis. Median

time to tumor progression was 5.8 months, and median survival was 15.0 months. On the basis of these results, the manufacturer of temsirolimus (Wyeth) conducted a three-arm phase III trial comparing temsirolimus alone with IFN-α alone and combined temsirolimus/IFN-α therapy. An interim analysis of data from this trial on 626 patients, reported by Hudes et al at ASCO 2006, demonstrated a significant survival advantage of temsirolimus monotherapy (median survival, 10.9 months) over IFN-α alone (median survival, 7.3 months; HR = 0.73; $P < 0.0069$ [log-rank test]).[22] Median survival in the combination therapy arm (temsirolimus plus IFN-α) was 8.4 months (HR = 0.95; $P = 0.69$).

Based on such promising data, the role of mTOR inhibitors in metastatic RCC is likely to increase. Amato et al[23] showed that the orally bioavailable mTOR inhibitor everolimus, when given at a dose of 10 mg/d, induced a response in 7 of 25 patients with metastatic RCC. Importantly, mTOR inhibitors act synergistically with angiogenesis inhibitors, and phase I trials of several combinations are under way, such as one combining bevacizumab with everolimus[24] and another combining valatinib (PTK-787/ZK-222584) with temsirolimus. Temsirolimus, which received fast-track status in 2002, should receive FDA approval in RCC.

In a multicenter phase II trial, treatment with axitinib (AG-013736), another oral tyrosine kinase inhibitor of VEGF, PDGF, and c-KIT, at a dose of 5 mg twice daily led to a 46% response rate in patients with cytokine-refractory, metastatic RCC.[25] Valatinib has shown promising activity in metastatic RCC in a phase I trial[26] but has not yet been studied in a phase II trial. Other tyrosine kinase inhibitors are under development as potential treatment of advanced RCC and other solid tumors, such as breast and colorectal cancer.

Adjuvant therapy

The success of sunitinib and sorafenib in controlling metastatic RCC has logically led investigators to consider their use in the adjuvant setting. A large intergroup trial is now open in the US for resected RCC with intermediate- and poor-risk features suggesting a greater than 50% chance of recurrence. Over 1,000 patients will be randomized to treatment with sorafenib, sunitinib, or placebo for 1 year. Another placebo-controlled trial of 1 year versus 3 years of sorafenib therapy is under way in Europe. Whether even 1 year of continuous therapy will be tolerated remains to be seen.

Managing toxicities

The objective toxicities of sorafenib and sunitinib are described in the preceding summary. As expected of drugs that inhibit VEGF, both sorafenib and sunitinib share toxicities of hypertension and diarrhea and can be controlled, respectively, with angiotensin-converting enzyme (ACE) inhibitors and loperamide (eg, Imodium). (Why diarrhea is a class effect is unclear.) Rare instances of hypertension-associated posterior leukoencephalopathy have been seen with valatinib and bevacizumab but have not yet been reported for sorafenib or sunitinib; attention, however, should be paid in treating hypertension caused by either of these two agents.

This reviewer has had only limited experience prescribing sunitinib, but potential side effects of nonulcerative stomatitis (painful mouth), anemia, and myelosuppression require monitoring and, if necessary, dose delays. The changing hair color and increased hair growth associated with sunitinib is a topic of discussion at many clinic visits. No clinical data are available on the long-term sequelae of the decreased left ventricular ejection fraction that has been reported in 15% of patients treated with sunitinib.

The predominant side effect of sorafenib is skin toxicity. Diffuse, dry, itchy, lichenified skin reactions are common and can be quite bothersome to patients. When skin changes occur on the hands and feet, they can interfere with daily activities. Fortunately, they respond to dose reduction. Interestingly, in contrast to sunitinib, hair loss, not hair growth, can occur with sorafenib. In the large phase III placebo-controlled trial conducted by Escudier et al,[10] discontinuation of study medication was similar between sorafenib (10%) and placebo (8%). Dose interruptions occurred in 20% of sorafenib-treated patients and 5% of placebo-treated patients. Dose reductions, mainly due to hand-foot skin reactions and diarrhea, occurred in 12% of sorafenib-treated patients. These drugs have not been compared head to head in clinical trials, and so their relative toxicities and therapeutic effectiveness with respect to each other are unknown. Patients who experience unacceptable toxicities to either agent should be switched to alternatives.

Conclusion

Sorafenib and sunitinib are exciting new drugs that offer real palliative promise to patients with metastatic RCC. They do not induce complete responses (unlike aldesleukin [Proleukin]), are currently expensive (costing over several thousand dollars per month), and have a spectrum of toxicity that requires frequent nursing or physician intervention and dose reductions (usually to 37.5 mg/d for sunitinib or 200 mg twice daily for sorafenib). Patients also need to be monitored for hypertension and the potential complications of hypertension. Whether

these drugs are partial or completely non–cross-resistant with each other is unknown, but anecdotal reports suggest that they are not fully cross-resistant. It is likely that sorafenib and sunitinib with find promise in other malignancies as well.

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