

IN FOCUS: RENAL CELL CARCINOMA

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Newly Approved Therapies for RCC and Their Effect on the Standard of Care

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H&O What has been the historical standard of care in renal cell carcinoma?

RF Metastatic renal cell carcinoma (RCC) has been treated over the last 20–30 years with immunomodulatory therapy, specifically interferons, and, after its approval in 1992, interleukin (IL)-2. These agents are known to stimulate the immune system and potentially augment clinical responsiveness in kidney cancer. The interferons have remained the standard of care in the outpatient setting because of their ease of administration and physicians' comfort in administering the therapy. Due to difficulty in administration of IL-2 both for the treating physician and the patient, its use has been restricted to certain centers and physicians capable of administering it. IL-2 has been tested extensively, however, and it has been shown that in order to obtain a durable, complete remission from IL-2–based therapy, it is necessary to give high-dose IL-2 treatment.

H&O What new understandings of the biology of RCC led to the development of new therapeutics?

RF Advances have been made in the understanding of the biology of RCC and its relationship to the Von Hippel-Lindau (*VHL*) gene, which is a deletion gene of the short arm of the 3p chromosome that results in overexpression

of angiogenesis and other pathways. Kidney cancer is a unique cancer because clear cell carcinoma of the kidney has a genetic abnormality that is, in approximately 60–70% of patients, similar to a genetic change associated with VHL syndrome. The more common sporadic RCC has the same genetic abnormalities. As a result of this understanding, physicians and researchers have been looking for new ways to inhibit the angiogenesis pathway in RCC, which is the most important pathway with which the VHL gene has been associated. Activation of the angiogenesis pathway can induce cell proliferation and survival, causing the growth of kidney cancer tumor cells. Thus, over the last 3–5 years, attempts have been made to inhibit the angiogenesis pathway, either by inhibiting the ligand to vascular endothelial growth factor (VEGF) or VEGF-A, -B, -C, or -D, inhibiting the receptor to VEGF (VEGFR) using a receptor antibody, or inhibiting the phosphorylation of the tyrosine kinase with tyrosine kinase inhibitors (TKIs). Any inhibitors of these pathways might be associated with clinical benefit in patients with kidney cancer. Additionally, another pathway, the mTOR pathway is associated not only with cell growth and proliferation but has the capacity to be associated with angiogenesis as well. Inhibitors of VEGF, VEGFR, and the mTOR pathway have led to notable results in kidney cancer, resulting in regulatory approval by the US Food and Drug Administration (FDA) of two agents in 2005 and 2006 and research that will potentially lead to new commercially available agents in 2007 and beyond.

H&O Can you describe the newly available agents?

RF The first two agents are the VEGFR TKIs sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer/Onyx), both of whose action in kidney cancer results in inhibition of VEGFR-2. Sorafenib was approved in December 2005 based upon results from randomized trials demonstrating a significant improvement in overall progression-free survival compared to placebo. Sunitinib was approved in January 2006 based on results from phase II trials demonstrating an objective response rate in the 30–40% range with a significant number of patients with stable disease in the second-line setting.

Following these approvals, there were two important plenary session presentations at the June 2006 American

Society of Clinical Oncology (ASCO) annual meeting. One presentation reported results of a comparison between sunitinib and interferon, the standard of care for previously untreated RCC. This presentation showed a significant improvement in the progression-free survival and overall response rates for sunitinib in previously untreated patients as compared to interferon alfa given at a standard dose and schedule. The other important presentation reported results for temsirolimus (Wyeth), a TKI of mTOR, in previously untreated poor-prognosis patients with metastatic RCC. The trial compared interferon to temsirolimus monotherapy and to a combination regimen of the two drugs, and an improvement in survival of 49% was shown for patients treated with temsirolimus 25 mg/week given intravenously, compared to interferon alfa.

At present, clinicians treating RCC are in a dramatically different place from the historical perspective due to the two new commercially available agents, sunitinib and sorafenib, which can be used both in previously untreated and cytokine-failure patients with RCC. It is anticipated that temsirolimus will obtain FDA regulatory approval for the treatment of poor-prognosis untreated patients. A recent press announcement by Roche and Genentech reported the results of a large randomized trial in Europe that compared bevacizumab (Avastin, Genentech) combined with interferon to interferon alone in previously untreated patients with advanced RCC. The results of this trial will probably not be available until the 2007 ASCO meeting, but the available data demonstrate that the progression-free survival of the combination was statistically superior to interferon monotherapy, lending further evidence to the hypothesis that inhibition of the angiogenesis pathway with inhibition of either the VEGF ligand or receptor, or the mTOR pathway, results in significant benefits to patients with RCC.

H&O What are the known drawbacks to these novel therapies?

RF The major issues related to the administration of these classes of agents in kidney cancer are found when looking at long-term results. Although it is anticipated that these agents will produce a survival benefit in select patient populations, these treatments are noncurative in nature and carry with them the risks and benefits associated with palliative therapy. Unlike high-dose IL-2, which does have the ability to produce a durable remission even when therapy is stopped after 4–6 months, therapy must be continued with these classes of agents in order to continue to obtain the benefit. Furthermore, with angiogenesis inhibitors, oncologists are beginning to see classes of side effects different from those seen heretofore with

cytotoxic chemotherapy. Bevacizumab produces nephrotic syndrome or proteinuria and hypertension, sunitinib produces hypertension and cytopenias, and sorafenib produces mild hypertension and more importantly hand-foot syndrome. Temsirolimus is associated with anorexia as well as cytopenia. Physicians who use these agents for metastatic kidney cancer must recognize that they are palliative and therefore must balance the risks and benefits while attempting to obtain progression-free survival.

H&O How are these side effects managed?

RF The side effect profile of all of these agents does allow for management by standard medical technology, such as antihypertensive agents. A mechanism for management of hand-foot syndrome does not yet exist. The only correct way to manage it is to cease administration of sorafenib, allow the toxicity to resolve, and then restart the drug at a lower dose. Going forward, the oncology community is facing a challenge because with three or four agents available for the treatment of metastatic RCC, it will be important to understand how to pick and choose between the agents as they all have significant and reproducible activity but with different toxicity profiles. These differences are true for monotherapy, but oncologists tend to combine therapies. It is important that the oncology community be careful when considering combinations of these agents because phase I and II trials of combination therapy have shown that some of the combinations are associated with significantly more toxicity than either agent alone.

H&O How do oncologists choose which therapy to use in a specific patient?

RF No head-to-head comparisons in the clinic currently exist (or are planned) to help the practicing oncologist know how to pick each of these agents in comparison to the others. Thus, we are left comparing study to study, which is fraught with problems because of their use of different populations, doses, and schedules. If one practices evidence-based medicine, one is left with the following conclusions. First, sunitinib, when compared with interferon in previously untreated patients with metastatic RCC, is the new standard of care in the outpatient setting. The patient populations treated in the trials that have provided us with this evidence had low- and intermediate-risk according to Memorial Sloan-Kettering risk criteria. In contrast, again using evidence-based literature, poor-risk, metastatic, untreated patients achieve the best benefit from temsirolimus. The trial of bevacizumab and interferon used both low- and intermediate-risk patients;

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thus, if the results, which are not yet available, are comparable to those seen with sunitinib, it will be quite difficult to choose between the combination of bevacizumab and interferon and sunitinib in the untreated population. Finally, the bulk of the evidence in favor of sorafenib is in the second-line setting, though the results of a clinical trial of sorafenib versus interferon in the untreated population are anxiously anticipated in order to see how this agent fits into the picture.

H&O What are the challenges going forward in this setting?

RF First, as mentioned, a challenge facing clinicians is how to choose between several agents for the untreated population with metastatic RCC based on benefit as well as risk. Second, in what sequence does one use these classes of agents? If a patient shows progressive disease on

one agent, what agent should be used next, based on estimations of benefit and risk? And how should the patient who is resistant to frontline therapy be managed? Finally, keeping in mind that each of these agents is palliative in nature, it is ultimately a goal to find ways not only to palliate patients but also to cure them, so how can these classes of agents be combined with other approaches, such as IL-2, other TKIs, and other targeted agents, with the potential goal of cure as opposed to palliation?

Suggested Readings

Bukowski RM, Kabbinavar F, Figlin RA, et al. Bevacizumab with or without erlotinib in metastatic renal cell carcinoma (RCC). *J Clin Oncol.* 2006;24(18S). Abstract 4523.

Hudes G, Carducci M, Tomczak P, et al. A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). *J Clin Oncol.* 2006;24(18S). Abstract LBA4.

Motzer RJ, Hutson TE, Tomczak P, et al. Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFN- α) as first-line systemic therapy for patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol.* 2006;24(18S). Abstract LBA3.



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