

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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New Therapeutic Options for Renal Cell Carcinoma

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H&O Until the present time, what have been the treatment options for renal cell carcinoma?

WS Prior to 2006, the only available therapies for kidney cancer were interferon (IFN) and interleukin (IL)-2. Both of these are immune therapies designed to stimulate the immune system to react against the cancer.

The benefit seen with IFN is modest at best, with clinical trials having demonstrated a small improvement in survival. The toxicities associated with this agent are considerable and include fever, chills, and fatigue.

IL-2 has been found to be most effective at high doses. However, high-dose IL-2 requires hospitalization and support, often in an intensive care unit, because it is associated with high fevers, low blood pressure, and capillary leak syndrome. Only very few patients are eligible for high-dose IL-2 therapy because most elderly patients with kidney cancer have comorbidities that prevent them from tolerating this treatment. Of the 10–15% of eligible patients, only 3–5% experience a complete response and long-term disease control. Still, high-dose IL-2 remains the only therapy reported to lead to complete remissions and long-term disease-free survival.

H&O What new therapies are showing efficacy in the treatment of renal cell carcinoma?

WS Two recently developed oral tyrosine kinase inhibitors—sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer/Onyx)—are approved by the US Food and Drug Administration for the treatment of advanced renal cell carcinoma. Both of these oral agents are better tolerated than either IFN or IL-2 and show a comparative benefit in terms of progression-free survival and response rates.

Sunitinib has been compared to IFN in a randomized phase III study and sorafenib has been compared to placebo in a randomized phase III study and to IFN in a randomized phase II study. The phase III studies show that each of these agents provides dramatic improvement in time to progression and likely improves survival as well. Results reported at the 2006 annual meeting of the American Society of Clinical Oncology (ASCO) show that among 750 patients with advanced kidney cancer, the progression-free survival was 47.3 weeks for those receiving sunitinib versus 24.9 weeks for those receiving IFN. Response rates were 24.8% versus 4.9%, respectively.

H&O What side effects are seen with these agents?

WS The most crucial side effect, which appears to be a class effect for all vascular endothelial growth factor (VEGF) pathway–targeted agents, is hypertension. Increases in blood pressure are very common and significant hypertension occurs in 10–20% of patients who receive these agents. In addition, there is a slight but definite risk of cardiovascular toxicities. Studies of sorafenib show an increased risk of myocardial infarctions and other arterial thrombotic events. With sunitinib, occasional decreases in the cardiac ejection fraction have been observed. Some of these side effects are reminiscent of the arterial thrombotic events seen with bevacizumab (Avastin, Genentech) and, as noted, appear to be important toxicities for this whole class of agents.

In addition to the cardiovascular risk factors, fatigue has also been observed, though not as severe as that seen with IFN. Diarrhea is not uncommon, and some patients experience skin toxicities, with the particular characteristics varying between the agents. Sorafenib is associated with a hand-foot reaction, while sunitinib is associated with changes in hair color due to effects on the hair follicles.

H&O What other pathways are being targeted for treatment of renal cancer?

WS The entire VEGF pathway is an important therapeutic target, and anti-VEGF agents other than sorafenib

and sunitinib are being explored for the treatment of renal cancer. These include VEGF binding agents such as bevacizumab and VEGF-TRAP and other kinase inhibitors. Bevacizumab has, for example, been shown to have response rates and tumor shrinkage rates that are very similar to those reported with sorafenib and sunitinib. How agents that target various components of the VEGF pathway can or should be utilized remains an important question. For example, all the currently investigated tyrosine kinases targeted VEGF receptor and platelet-derived growth factor receptor, but their activity against other kinases varies and thus these agents are not all exactly the same. The therapeutic role of one agent versus another, of combination therapy, and of sequential therapies therefore needs to be defined.

Another important pathway for the treatment of renal cell carcinoma is the mTOR (mammalian target of rapamycin) pathway. Preliminary phase II data suggest that temsirolimus (Wyeth) may be effective, and a phase III study of temsirolimus compared with IFN compared with the combination of both agents presented at the 2006 ASCO annual meeting shows that temsirolimus was associated with a statistically significantly longer survival compared with IFN among patients with advanced renal cell carcinoma. Several other mTOR inhibitors are being developed. Interestingly, preclinical data suggest that the von Hippel-Lindau (VHL) mutation, common in kidney cancer, may predict for sensitivity to mTOR inhibitors; these findings need to be validated in the clinical setting.

H&O Might combinations of these various agents be beneficial for patients?

WS The issue of whether the use of more agents is better is very important, but is not a foregone conclusion. Combination therapy may make sense, and certainly there is a great deal of interest in exploring various combinations. However, it is important to approach combination therapy with caution; more agents in combination may not be better than single agents administered in sequence.

H&O Are studies ongoing to determine what patients might respond to which therapy?

WS While this question is one of the most important pertaining to new agents for the treatment of renal cell carcinoma, such studies are only beginning. Ongoing studies are evaluating the VHL mutation, circulating markers of angiogenesis such as the soluble VEGF receptor, circulating cells, and novel imaging approaches such as dynamic contrast-enhanced magnetic resonance imaging. These are all potentially interesting markers for identifying patients likely to benefit either before therapy is begun or shortly after therapy is initiated.

The value of these markers is especially important because many of these drugs act as growth inhibitory agents and therefore if the computed tomography scan of a patient being treated for kidney cancer shows no change after 2 months, it is impossible to know whether this is due to the natural history of the disease or a true drug benefit. At this point, the use of the markers noted above or others remains theoretical; it has not been proven which, if any, will be useful.

H&O Might any of these agents have a role in the adjuvant or locally advanced settings?

WS It is not yet known whether any of the agents will have a role in the adjuvant or locally advanced settings. Currently, there is an open clinical trial of sunitinib versus sorafenib versus placebo in patients with locally advanced kidney cancer, and a similar study is taking place in Europe of placebo versus short-term or long-term sorafenib in patients with locally advanced disease.

Based on the data from the metastatic setting and what is known about angiogenesis, it is thought that these agents will be effective in these settings, but the data are not yet available. It is important to note that the biology of angiogenesis in macroscopic disease, which is the setting of the current data, is markedly different from the biology of angiogenesis in microscopic disease, which is what is treated in the adjuvant setting. Efficacy in one setting does not prove efficacy in the other.

Also, the risk:benefit ratio in the adjuvant setting needs to be carefully considered. A 4% risk of myocardial infarction in patients with metastatic disease is certainly acceptable, but in the adjuvant setting, in which many patients have already been cured by surgery and many will be treated over the long term, the considerations are different. It is important that the efficacy of these agents in the adjuvant and locally advanced disease settings be studied in a phase III clinical trial, rather than proceeding with treatment on the assumption that these agents will be effective in all settings.

Suggested Reading

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

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Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:2502-2512.

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