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Choosing First-line Therapy for Advanced RCC Is Hard—Here's How I Decide

Thomas E. Hutson, DO, PharmD, FACP - *10/22/2012* **More from this author**

The rapid development and approval of several targeted therapies for advanced renal cell carcinoma (RCC) has outpaced our ability to understand how to use them effectively in real-world patients who we see in our clinics. No more clearly is this seen then when one begins the process of selecting initial therapy.

Many First-line Options

The current landscape in first-line therapy for advanced RCC includes 3 approved agents that block the vascular endothelial growth factor (VEGF) pathway: the multitargeted tyrosine kinase inhibitors (TKI) sunitinib and pazopanib and the monoclonal antibody bevacizumab in combination with interferon (IFN)-α. All 3 agents have similar efficacy and overlapping toxicities. For patients with poor-prognosis RCC, temsirolimus, a small molecule inhibitor of the mTOR complex, is approved as first-line therapy. Tivozanib, another highly selective VEGF inhibitor, is now under regulatory review as a therapy in the first line setting. And, this past year, the highly selective VEGF TKI axitinib received US Food and Drug Administration regulatory approval in the second-line setting, whereas a phase III trial has completed evaluating its use as initial therapy. The role of immunotherapy (IFN or high-dose interleukin-2), approved for first-line use, does warrant mention but remains controversial and of limited efficacy for the average patient with an extensive disease burden who we see in clinic.

The Treatment Algorithm

Complicating the decision process even more is that despite receiving broad regulatory approval for all patients with metastatic RCC, the pivotal trials of these new "targeted" agents were conducted in specific patient populations—namely nephrectomized patients with clear-cell histology having specific prognostic features. And, there have been no comparative trials reported to date. Taking this into account, in order to select appropriate therapy using degrees of clinical evidence, patients should be categorized according to histologic subtype (clear cell vs nonclear cell) as well as according to prognostic features (good, intermediate, and poor) using the Memorial Sloan Kettering Cancer Center or similar risk model. Once appropriately grouped, a treatment algorithm based on the results of published clinical trials can be applied to select specific agents for patients with metastatic clear-cell RCC. (For more information on selecting therapy for patients with advanced RCC including an interactive online tool, click here.)

Nonclear Cell RCC

The role of these agents in patients with nonclear-cell RCC is less established, as the limited published data suggest reduced efficacy. On a personal note, if I do not have an available clinical trial for such patients, I have had success using the available agents in patients with papillary and chromophobe RCC. In addition, patients with sarcomatoid elements may benefit from chemotherapy-based regimens (ie, doxorubicin/gemcitabine).

Special Patient Populations

Treating individual patients with unique needs using these new therapies outside of the trial setting can also be challenging. In some patients, dose modifications may be considered for potential drug interactions and for management of severe cases of hematologic or nonhematologic toxicities. In other patients, especially those patients who would otherwise not meet the eligibility criteria for enrollment on clinical trials (end-organ dysfunction, central nervous system metastasis, poor performance score), clinicians should proceed cautiously and consider dose reduction until safety can be established.

My Approach

In my practice, most patients who present with metastatic RCC are started on first-line therapy with either sunitinib or pazopanib. I generally do not use bevacizumab/IFN in clinical practice. Patients with poor-prognosis RCC receive intravenous temsirolimus. The choice of sunitinib or pazopanib is very arbitrary and is primarily made more on insurance coverage than on any real feeling of superior efficacy between these 2 agents. I do believe that many patients appear to tolerate pazopanib better than sunitinib, and this issue is the topic of a soon-to-be-reported phase III trial known as COMPARZ. With that said, I have had patients who have been primary refractory to pazopanib who have responded in the second-line setting to sunitinib, which speaks to the unpredictability of RCC that we have all grown to appreciate.

The choice of first- line therapy for advanced RCC is complicated and requires consideration of the efficacy and toxicity profiles, as well as an understanding of your patient's individual disease specific needs. In my own practice, geographic and economic issues factor in on choice of therapy quite regularly and may be more important than patient or disease specific characteristics.

Your Thoughts?

What factors influence your first-line therapy recommendations for your patients with RCC? Let me know in the comments.

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Dr. Hutson has no significant financial relationships to disclose.

Topics: Renal Cell Carcinoma - Treatment, Genitourinary Cancer - Treatment

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Can pazopanib have any advantage against other TKIs in first line treatment of sarcomatoid RCC?
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- Rash
- Hand-foot syndrome
- Liver toxicity
- Fatigue
- Diarrhea
- Mucositis

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High dose IL-2 can be used in patients with few comorbidities who have disease of clear cell histology and can result in responses more durable than that for TKIs, but with a lower ORR (~20%); unfortunately, there are no predictive algorithms available to guide its use and toxicities can be substantial. Clinical trials for all patients in the first-line setting should still be a priority. The COMPARZ study, designed to demonstrate noninferiority of pazopanib to sunitinib, demonstrated that pazopanib is noninferior to sunitinib and performs better in 11 of 14 QoL assessments.

Eradicator - 10/24/2012

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