The development of vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target of rapamycin (mTOR) inhibitors for the treatment of renal cancer is a real success story. Moving from toxic and minimally efficacious interleukin (IL)-2 and interferon to six US Food and Drug Administration (FDA)-approved agents has significantly benefited our patients, and has led to a dramatic alteration in how oncologists approach this disease. Posadas and Figlin nicely summarize these advances, discuss ongoing research, and provide the data for current treatment recommendations. Nevertheless, and as they point out, these treatments have modest effects on overall survival and limited long-term efficacy. Thus, the importance of continued research and development cannot be overemphasized.

As is typical in any field of scientific endeavor in which major advances have occurred, more questions are raised than answered. It is therefore somewhat ironic that the availability of these therapies has led to a marked curtailment in renal cancer trial enrollment. At our own institution, we accrued more than 40 renal cancer patients annually prior to the development of the new agents, but now are able to accrue fewer than 10 per year. Similarly, the current US Intergroup study of everolimus (Afinitor) with or without bevacizumab (Avastin) in patients with any number of prior VEGFR tyrosine kinase inhibitor treatments is currently accruing so slowly that it is in danger of being closed.

Perhaps more indicting is the type of trials that are currently available. A search of www.clinicaltrials.gov for actively recruiting phase II renal cancer trials reveals that of 74 trials, only 9 include an active comparator and only 12 are investigating a novel target. As has been discussed extensively in the literature, noncomparative phase II trials in a disease such as renal cancer for which active agents are available and for which outcome is highly variable are often difficult, if not impossible, to interpret.

This large number of trials, the relatively small patient population, and the apparent decrease in accrual suggest that there is an urgent need to prioritize the most important questions in metastatic renal cancer. Clearly there is no single set of answers to such a prioritization question, but the following are issues this commentator believes are most critical.

**What are the predictive biomarkers for determining the likelihood of benefit from VEGF pathway and mTOR inhibitors?**

As of today, there are no qualified biomarkers for this purpose, but a number have been considered. The first and most obvious are tumor characteristics; poorly differentiated tumors may be preferentially sensitive to mTOR inhibition. Clearly, modern genetic classifications of renal cancer will also need to be considered. For the VEGF pathway inhibitors, one could ask whether specific stromal phenotypes might be predictive. Finally, as in any therapeutic endeavor, specific host characteristics may be relevant as well. There is heterogeneity in the toxicities associated with these agents, including the development of elevated blood pressure[1]; these toxicities have thus been proposed as potential predictive biomarkers. In addition, certain pharmacogenomic biomarkers may be predictive.

**Is lifelong VEGF pathway inhibition important?**

A number of studies have observed a “flare” response upon discontinuation of VEGF pathway inhibitors.[2] Whether such a flare represents a true tumor growth phenomenon or a tumor edema and blood flow phenomenon remains unclear. Nevertheless, the occurrence of such flare responses has given rise to the hypothesis that long-term VEGF-pathway inhibition may be necessary. This is the fundamental hypothesis behind the ongoing US Intergroup phase III study of everolimus with or
without bevacizumab in patients with prior VEGFR tyrosine kinase inhibitor therapy. On the other hand, it has been noted that intermittent VEGF pathway-directed therapy may be more efficacious than continuous therapy.[3] The obvious corollary to this question is that we need to understand the mechanisms of resistance to VEGF pathway inhibition.

Are there other or better therapeutic targets?

The available data for a large number of VEGF pathway inhibitors as detailed by Posadas and Figlin suggest that more potent VEGF pathway inhibition is unlikely to introduce a paradigm shift. The conclusions regarding mTOR inhibition need to be somewhat more circumspect because the current “rapalog” inhibitors are active only against the mTOR1 complex, and pan-mTOR inhibitors have not yet been fully investigated. Nevertheless, it seems unlikely that the latter will dramatically improve outcomes either.

Are there better ways to target VHL pathway inactivation in clear-cell renal cancer?

von Hippel–Lindau (VHL) pathway inactivation is the pathophysiologic sine qua non of clear-cell renal cancer and should thus be the most important therapeutic target. The VEGF pathway is only one of multiple pathways downstream from VHL inactivation. Unfortunately, the VHL pathway is quite complex and critical to many normal physiologic functions. Whether the pathway could be safely targeted thus remains an important question.

What are the most appropriate therapeutic targets in non–clear-cell renal cancer?

It is now recognized that non–clear-cell cancers include a large number of different subtypes. Some of these tumors do respond to mTOR or VEGF pathway inhibitors, but in general these agents appear to be less active than they are in clear-cell renal cancer. Given the rarity of these diseases, identification of tumor subtypes sensitive to the current therapies, as well as identification of novel therapies, is even more complex than for the clear-cell cancers.

Can we afford the current therapies?

Currently available VEGF- and mTOR-directed therapies have significant clinical and economic toxicities. With regard to the former, the impact on cardiovascular health, functional status, and metabolic diseases has been well described. Many of these toxicities, although tolerable and manageable in the short term, are extremely problematic for patients receiving long-term treatment. Just as important, these medications are currently extremely expensive. It is not clear whether the payer community will continue to support long-term use of these extremely expensive medications or how equitable distribution will be assured.

Conclusions

Posadas and Figlin nicely summarize the advances in renal cancer treatment that have led to the current paradigm shift. They also describe some of the newer potential therapeutic targets. It is hoped that the oncology community will continue to prioritize the research questions and aggressively conduct the necessary clinical trials. Inhibition of the VEGF and mTOR pathways is but a first step.

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