ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Tivozanib in Renal Cell Carcinoma

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H&O How has the treatment landscape for renal cell carcinoma (RCC) evolved in recent years?

RF There has been nearly a decade-long period of drug development that has significantly altered the treatment paradigm of metastatic kidney cancer, and the approval of a large number of targeted agents offers patients multiple treatment options. Sorafenib (Nexavar, Bayer) was approved for the treatment of RCC in 2005. We now have 4 tyrosine kinase inhibitors (TKIs): sorafenib, sunitinib (Sutent, Pfizer), pazopanib (Votrient, GlaxoSmithKline), and axitinib (Inlyta, Pfizer); 1 vascular endothelial growth factor (VEGF) ligand inhibitor, bevacizumab (Avastin, Genentech); and 2 mammalian target of rapamycin (mTOR) inhibitors: temsirolimus (Torisel, Wyeth Pharmaceuticals) and everolimus (Afinitor, Novartis) in this disease. This has resulted in progression-free survival times that are more than double that of historical standards, and a significant improvement in survival for these patients, which has dramatically altered the quality and quantity of life for people suffering from kidney cancer. These successes have been primarily in the clear-cell variant of kidney cancer, and this has followed an understanding of the biology of RCC, specifically the genetics, and how to apply targeted therapy to the alterations that the genetics produce.

H&O What is tivozanib (Tivopath, AVEO Pharmaceuticals), and how is it distinguished from other similar agents?

RF Tivozanib bears a structural resemblance to other VEGF-TKIs. Its distinguishing feature is that it is a potent and selective small-molecule inhibitor of the VEGF receptors 1,2, and 3 kinases at subnanomolar concentrations (IC50 of 0.21, 0.16, and 0.24 nM, respectively. Further, the relative selective profile of tivozanib compared with other agents is significantly greater. Tivozanib also exhibits a significantly greater terminal half-life of 4.5 days and has the advantage of once-daily oral dosing. Some of the agents that are currently in use have the capacity to produce both on-target toxicity, such as hypertension, and off-target toxicity, such as hand-foot syndrome. Off-target toxicities commonly associated with other targeted therapies, such as mucositis, fatigue, and hand-foot syndrome, have been notably low in studies of tivozanib, which may underscore a differentiated safety profile and potential for combinability with other therapeutic agents.

H&O Can you discuss the design and setting of the phase III TIVO-1 (Tivozanib Versus Sorafenib in First-Line Advanced RCC) trial?

RF The TIVO-1 trial was a phase III trial that resulted from phase II data in metastatic kidney cancer, suggesting that tivozanib had significant and important activity in this disease. TIVO-1 enrolled patients with clear-cell RCC who had measurable disease and good performance status, and who had undergone a prior nephrectomy. All participants may have had either no or 1 prior therapy, but could not have received VEGF- or mTOR-directed agents. Patients were stratified by region of treatment, prior therapies, and number of metastatic sites. A total of 517 patients were enrolled between February and August of 2010, with 76 sites participating. The primary objective was to demonstrate

superiority of tivozanib when compared to sorafenib. Tivozanib was administered orally at 1.5 mg per day in a 3-weeks-on, 1-week-off regimen. Sorafenib was orally administered at a standard dosing of 400 mg, twice daily. The primary endpoint was progression-free survival, with secondary endpoints including response rate, safety, and overall survival. The primary endpoint was independently assessed by a blinded third party. According to independent review, there was a statistically significant improvement in progression-free survival with tivozanib compared to sorafenib (11.9 months vs 9.1 months, respectively; *P*=.04). This effect was slightly higher in those patients who had received no prior therapy (12.7 months vs 9.1 months). With respect to secondary endpoints, there was a higher proportion of objective responses with tivozanib versus sorafenib (33% vs 23%, respectively). Fewer patients receiving tivozanib required dose interruptions or dose reductions due to adverse events. The major toxicities associated with tivozanib were hypertension, diarrhea, and dysphonia. The most common grade 3/4 toxicities were hypertension for patients treated with tivozanib and hand-foot syndrome for patients who received sorafenib. However, the analysis of overall survival was problematic in this study. At 1 year, 81% of sorafenib patients remained alive compared to 77% of tivozanib patients. However, this was likely due to the fact that more than 60% of the patients randomized to the sorafenib arm crossed over to receive tivozanib or some other therapy upon tumor progression, thereby benefitting from treatment with 2 active kidney cancer drugs. Only 24% of patients in the tivozanib arm went on to a subsequent therapy. One of the challenges moving forward is to determine the true benefit of tivozanib over a long period of time, since most patients with kidney cancer receive multiple agents over the course of their treatment life.

H&O What are the implications of this study?

RF Future trials of tivozanib are planned, including the TAURUS (TivozAnib Use veRsUs Sutent in advanced renal cell carcinoma [RCC]: Patient Preference) study, which will aim to establish additional data regarding tivozanib when used as first-line therapy in patients with advanced RCC. Other planned tivozanib trials will compare the agent to other active TKIs, which may help to further delineate its role.

One must also be cognizant of the fact that most of us who treat kidney cancer are planning on sequential therapy, identifying which agents will work and which targets are beneficial, and realizing that single-agent treatment is less beneficial than a sequence of agents. Currently, we know that combination therapy is not advantageous when compared to single-agent therapy. Thus, the focus should really be on identifying the biology of the individual patient, their likelihood of response to a targeted agent, and then sequencing those targeted agents in an evidence-based fashion.

Table 1. Ongoing Trials Evaluating Novel Agents in Renal Cell Carcinoma

Drug	Class	Phase	Patient Population
IMA 901	Vaccine	III	First-line
AGS 003	Immuno-therapy	III	First-line
Axitinib	VEGF-TKI	III	Second-line
Dovitinib	FGFR1-3 inhibitor	III	Second/third-line
E7080	Multitargeted TKI	I/II	Second-line
CVX 060	Ang-2 inhibitor	II	Second-line
MDX-1106	PD-1 inhibitor	I	First-line
Brivanib	VEGF receptor and FGFR1-3 inhibitor	II	Second/third-line
BKM-120	PI3K inhibitor	I	Second/third-line
MDX-1106	PD-1 inhibitor	II	Second/third-line

Ang-2= angiopoietin-2; FGFR= fibroblast growth factor receptor; PD-1=programmed death-1; PI3K=phosphatidylinositol 3-kinase; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

H&O What are the biggest remaining challenges in this disease?

RF Great accomplishments have been made over the last decade regarding the development of targeted agents that have activity against RCC. This has led to improved progression-free survival and overall survival. The likelihood that further agents in the same class of drugs is going to have a meaningful impact for patients beyond what has already been accomplished over this decade, in my opinion, is modest. As such, what we need to be looking for are new targets and new treatment approaches. Deciding which one to give to a particular patient and how best to deploy them along with surgical interventions remains a challenge.

H&O What does the future hold?

RF Fortunately, we now have a series of agents in the clinic that are being looked at in phase II and planned phase III trials that may be the next generation of opportunities (Table 1). For example, checkpoint inhibitors, such as antibodies that target programmed death-1 (PD-1), have demonstrated

the possibility for producing important clinical remissions for patients with tolerable toxicity, even in patients who have received prior targeted agents. These agents are now entering phase III trials, and we hope that the next generation of therapies may bring back the role of immune-based treatment, offering the opportunity for the patient's own immune system to control the cancer by controlling the checkpoints that prohibit the immune system from being effective.

Another area of research has been the development of clinical, genetic, and molecular biomarkers that could help identify a subset of patients with the highest response to a given therapy. Clinical trials involving novel agents and application of biomarkers with both predictive and prognostic utility would aid in the appropriate utilization of resources for the best clinical outcomes. Overall, it remains a very exciting time in this field.

Suggested Readings

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