CCR Drug Updates

Pazopanib in Renal Cell Carcinoma

James E. Ward and Walter M. Stadler

Abstract

Pazopanib is an oral, multitargeted tyrosine kinase inhibitor that has been approved by the U.S. Food and Drug Administration for treatment of patients with advanced renal cell cancer on the basis of a randomized, double-blind, placebo-controlled, phase III trial, which showed that once a day dosing of 800 mg of pazopanib resulted in progression free survival of 9.2 months versus 4.2 months ($P < 0.0001$). Pazopanib thus joins sorafenib and sunitinib as one of the clinically available VEGF receptor (VEGFR)–targeted drugs for the treatment of patients with advanced clear cell renal cell cancer. The mechanism of action, preclinical and clinical data, and a comparison with the other drugs in its class are outlined below.

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Renal cell carcinoma (RCC) accounts for approximately 3% of all malignancies in adults and was estimated to have affected 57,760 new individuals in the United States during 2009 (1). Multiple histologic subtypes of RCC exist. Clear cell RCC is the most common, representing about 70 to 80% of tumors. Although familial RCC syndromes are well described, the vast majority of new cases (96%) are due to sporadic gene mutations (2). Silencing of the von Hippel-Lindau ($VHL$) tumor suppressor gene is now known to be associated with the development of sporadic clear cell RCC. The loss of the $VHL$ gene product leads to increased levels of hypoxia-inducible factor (HIF), which activates the transcription of an assortment of downstream genes including VEGF, platelet derived growth factor beta (PDGF-$\beta$), and TGF-$\alpha$ (2).

Prior to 2005, very few treatments were available for individuals with advanced RCC. However, clarification of the importance of VHL and HIF in patients with sporadic clear cell RCC led to investigation of small molecule tyrosine kinase inhibitors (TKI) of the VEGF pathway, culminating in the approval of sorafenib by the U.S. Food and Drug Administration (FDA) for patients with advanced RCC in December of 2005.1 Since then, an additional five therapies targeting the VEGF and mTOR pathways have been approved, with several others on the horizon.

On October 19, 2009, the FDA approved the use of pazopanib for treatment of individuals with advanced clear cell RCC. This article serves as an update on the preclinical and clinical data supporting the use of pazopanib in this patient population and also provides a comparison of pazopanib to the now-growing number of agents in its class that are approved for use in RCC.

Preclinical Data

Pazopanib is an oral multitargeted TKI, with potent inhibitory activity against VEGF receptor (VEGFR)-1, -2, -3, PDGF receptor (PDGFR)-$\alpha$, PDGFR-$\beta$, and c-Kit. It was synthesized and purified after initial screening of a chemical precursor identified its ability to inhibit VEGFR-2 (3). In vitro kinase assays have established its activity against VEGFR-1 (IC$_{50}$ 10 nmol/L), VEGFR-2 (IC$_{50}$ 30 nmol/L), VEGFR-3 (IC$_{50}$ 47 nmol/L), PDGFR-$\alpha$ (IC$_{50}$ 71 nmol/L), PDGFR-$\beta$ (IC$_{50}$ 84 nmol/L), and c-Kit (IC$_{50}$ 74 nmol/L; ref. 4). Pazopanib also shows less potent inhibition of several other tyrosine kinases. Proliferation assays and receptor phosphorylation assays done using human umbilical vascular endothelial cell (HUVEC) cultures have shown that pazopanib selectively inhibits VEGF-induced cellular proliferation (4).

In vivo studies were done using human tumor xenografts (colon, melanoma, prostate, renal, breast, and lung) in female Swiss nude mice. Animals were treated with 10, 30, or 100 mg/kg of pazopanib administered once or twice daily by oral gavage for 21 days. Compared with a negative control, the administration of pazopanib resulted in a dose-dependent growth inhibition in each of the six human tumor xenografts. The RCC xenograft was the most sensitive to pazopanib, with a maximal growth inhibition of 99% (4).

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Pharmacokinetic studies done in animal models showed excellent oral absorption and an estimated t$_{1/2}$ of approximately 4 hours. Inhibition of VEGF-2 phosphorylation in resected tumor specimens declined once the plasma
concentration dropped below 40 μmol/L, suggesting that a steady-state concentration of ≥ 40 μmol/L was required for optimal in vivo activity (4).

**Clinical Data**

A phase I multicenter, open-label trial (VEG10003) was conducted in 63 patients with relapsed or refractory solid tumors who were enrolled into sequential dose-escalating cohorts, ranging from 50 mg three times weekly to 2,000 mg daily (5).

Sixty-one of the 63 patients experienced at least one adverse event. The majority of these were grades 1 or 2 and reversible upon medication discontinuation. The most commonly reported adverse events were hypertension (33%), diarrhea (33%), hair depigmentation (32%), and nausea (32%). A variety of laboratory abnormalities were noted including cytopenias, as well as abnormal chemistry values. Few were higher than grade 2, although of note, 38% of patients had an increase in aspartate transaminase (AST), and 52% developed proteinuria. The most common grade 3 or 4 toxicity was hypertension, noted in 25% of patients.

Treatment interruptions or dose reductions occurred in 10 out of the 63 patients. Only 2 patients were removed from the study owing to dose-limiting toxicities in cycle 1. Three patients were enrolled at the 2,000-mg per day dosing cohort, the highest in this study. On the basis of the prespecified study criteria, a maximum tolerated dose was not identified.

Pharmacokinetic assessments showed that mean C_{max} and area under the curve (AUC)_{0-24} on day 1 increased in a linear fashion with the dose of pazopanib, with an overall m_{800-mg once daily group at approximately 25 μg/ml, suggesting absorption was saturated. Pazopanib is metabolized by CYP3A4, and inhibitors or inducers of this enzyme may affect serum concentrations and require dose adjustments (6). Other studies suggest the potential for QTC prolongation and the potential for cardiac toxicity, especially when used with other agents that have a similar effect.2

The clinical activity observed in this phase I trial was promising. Three patients achieved a partial response (PR); two of these responses were in RCC patients and one (unconfirmed) was in a patient with a neuroendocrine tumor. Fourteen additional patients achieved stable disease with a duration of ≥ 6 months.

On the basis of these results, a phase II trial in clear cell RCC patients was planned using 800 mg once daily of pazopanib (7). Prior treatment with a noncytokine or nonbevacizumab therapy was disallowed. The trial initially employed a randomized discontinuation design: The entire study population received pazopanib for the first 12 weeks, at which point disease response was assessed; those with evidence of PR and/or complete response (CR) were continued on pazopanib, those with progressive disease discontinued pazopanib, and those with stable disease were randomized to pazopanib or placebo. All of the patients were included in the final data analysis.

Interim analysis of the week 12 data in the first 60 patients enrolled revealed a PR rate of 38%; the trial was converted to a single-arm, open-label study, and patients who had been randomized to placebo were allowed to cross over (8). At this point 191 of 225 consented patients had been enrolled. The final overall response rate (RR) was 35%, including a PR rate of 33.3%, and a CR rate of 1.3% (n = 3). Progressive disease occurred in 10.7% of patients, whereas 9.8% (n = 22) of the patient population was not evaluable. The median estimated progression free survival (PFS) was 52 weeks (9). The majority of patients experienced some tumor shrinkage (Fig. 1).

The safety analysis showed that 221 patients (98%) experienced an adverse event, as defined by the common terminology criteria for adverse events version 3.0 (CTCAE), of which 43% (n = 97) were grade 3 and 10% (n = 22) were grade 4. The most common adverse events of any grade were diarrhea (63%), fatigue (46%), hair depigmentation (43%), nausea (42%), and hypertension (41%). The most common laboratory abnormalities included elevations in alanine transaminase (ALT; 54%) and AST (53%). The most common grade 3 or 4 adverse events were hypertension (8%), increased ALT (6%), increased AST (4%), diarrhea (4%), and fatigue (4%). Dose reductions were required for 31% of patients, with subsequent dose reescalation in 50% of those patients. Two deaths were considered to be treatment related: one due to colonic perforation in the setting of diverticulitis and the second due to dyspnea in the setting of malignant pleural effusions (9).

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2 FDA pazopanib prescribing information. Available from: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm187509.htm

![Fig. 1. Waterfall plot of tumor responses in patients with metastatic RCC enrolled in a phase II study of pazopanib 800 mg/d. Reprinted with permission from Hutson et al. (9). © 2010 American Society of Clinical Oncology. All rights reserved.](Image)
One randomized, double-blind, placebo-controlled phase III trial has been done (10). Study participants included patients with advanced or metastatic RCC (predominantly clear cell histology) who had progressed on one prior cytokine-based systemic therapy; the protocol was subsequently amended to include treatment-naïve patients. In total, 435 patients (233 treatment naïve and 202 with a prior therapy) from 80 centers across the globe were enrolled and randomly assigned in a 2:1 fashion to either pazopanib 800 mg daily or placebo. Statistical end-points included PFS (primary endpoint), overall survival (OS), RR, duration of response, and safety.

A total of 290 patients were randomized to receive pazopanib, 227 discontinued treatment at the time of final analysis (78%), and only 6% were lost to follow up or withdrew consent. A total of 145 patients were randomized to receive placebo, 131 discontinued treatment at the time of final analysis, and 3% were lost to follow up or withdrew consent.

An independent review of the data confirmed that pazopanib significantly prolonged PFS compared with placebo in the overall study population (9.2 versus 4.2 months, P < 0.0001). In the treatment-naïve group, the median PFS was 11.1 versus 2.8 months (P < 0.0001); in the cytokine-pretreated population, median PFS was 7.4 versus 4.2 months (P < 0.001). The prespecified subgroup analyses confirmed a prolonged PFS in the pazopanib arm in all categories: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and Memorial Sloan-Kettering Cancer Center (MSKCC) risk. The overall RR (CR+PR) in the pazopanib arm was 30%, 32% in treatment-naïve patients, and 29% in cytokine-pretreated patients. An interim analysis of OS was based on 61% of the events required for final analysis and did not reach statistical significance for either superiority or futility. As yet, final OS data are not available.

The safety data provided similar information as described for the phase II trial. Most adverse events and laboratory abnormalities were grade 1 or 2. The most commonly described events were fatigue, diarrhea, hypertension, hair depigmentation, nausea, anorexia, and vomiting. Although the published study does not comment on development of hypothyroidism, the common occurrence of this toxicity with other VEGFR TKIs suggests that at least some of the fatigue may be attributable to thyroid dysfunction (11). The most common grade 3 or 4 events were hypertension (4%) and diarrhea (3%). Of note, arterial thrombotic events occurred in 3% of patients in the pazopanib arm, compared with none in the placebo arm. Hemorrhagic events occurred in 15% of patients in the treatment arm versus 5% of patients in the placebo arm. The most common laboratory abnormalities were AST and ALT elevation; grade 3 or 4 elevation occurred in 8% and 12% of patients in the pazopanib arm, respectively. Death occurred in 4% of patients in the pazopanib arm compared with 3% in the placebo arm. Four patients were deemed to have fatal adverse events, one each due to ischemic stroke, transaminitis and rectal bleeding, bowel perforation, and abnormal hepatic function. The prescribing information includes a boxed warning about the potential for pazopanib to cause severe and fatal hepatotoxicity.

**Drug Comparison**

On the basis of the data reviewed above, pazopanib was approved by the FDA, and now joins two other VEGFR TKIs, sorafenib and sunitinib, as an option for the treatment of patients with advanced clear cell RCC. These medications share many advantages and disadvantages.

Sorafenib became the first multitargeted TKI available for use in patients with advanced RCC when it was approved by the FDA in December 2005. This approval was based on evidence from multiple clinical trials, including one randomized, double-blind, placebo-controlled, phase III trial of 903 patients with advanced RCC resistant to standard therapies, which at that time included only interleukin 2 (IL-2) and/or IFN-α (12). PFS was significantly prolonged in the sunitinib arm at 5.5 months versus 2.8 months in the placebo arm (P < 0.001). An interim analysis of PFS after 769 of the 903 patients had been enrolled showed significant drug activity and, therefore, the patients randomized to the placebo arm were allowed to cross over to the treatment arm. The final median OS was 17.8 months in the sunitinib group versus 15.2 months in the placebo group, which did not meet statistical significance (P = 0.146). However, when excluding the population of patients who crossed over from the placebo arm, there was evidence of improved survival: 17.8 months versus 14.3 months (P = 0.03; ref. 13). Ten percent of patients in the trial discontinued use of sorafenib because of adverse events. The most commonly reported toxicities were diarrhea, nausea, abdominal pain, rash, fatigue, alopecia, hand-foot syndrome, and hypertension. Common grade 3 and/or 4 toxicities included hand-foot syndrome, hypophosphatemia, and elevated lipase.

Sunitinib, another multitargeted TKI, was approved by the FDA in January 2006. Its utility was studied in a randomized, phase III trial, in which 750 treatment-naïve patients with metastatic RCC received either sunitinib or IFN-α (11). The primary endpoint of PFS was found to be 11 months in patients who received sunitinib versus 5 months in patients who received IFN-α (P < 0.001). OS was also greater in the sunitinib arm, 26.4 months, versus the IFN-α arm, 21.8 months (P = 0.051). Overall RR was 47% in patients receiving sunitinib. Nineteen percent of patients withdrew from the trial because of...
adverse events while on sunitinib. Commonly noted adverse events included diarrhea, fatigue, nausea, hypertension, stomatitis, and hand-foot syndrome. The most common grade 3 toxicities included hypertension, fatigue, diarrhea, and hand-foot syndrome. More recently, and based on postmarketing experience, a boxed warning for the hepatotoxicity has been added to the sunitinib FDA label as well.

Although not a TKI, bevacizumab (a monoclonal antibody against the VEGFR) in combination with IFN-α is also approved by the FDA for use in patients with advanced RCC on the basis of two trials showing improved PFS, versus IFN alone without a clear survival advantage (14, 15). Many other TKIs targeting the VEGFR pathway have shown efficacy in humans and are currently being evaluated in early-stage clinical trials including axitinib (16), cediranib (17), tivozanib (18), and BAY 73-4506 (19).

**Summary**

On the basis of these data, sunitinib has since become established as the frontline treatment in individuals with advanced clear cell RCC. The data presented above provide a rationale for pazopanib to be used in the frontline setting in individuals with advanced clear cell RCC. These data, on the basis of a phase III study, showed a 5-month improvement in PFS in the overall study population and an 8.3-month improvement in PFS in the treatment-naive group. The OS data for pazopanib is not yet available, as opposed to sunitinib, which has shown an improved OS when compared with IFN-α in the frontline setting. The efficacy of pazopanib versus sunitinib is, as yet, unknown; however, this question is currently being addressed in a comparative trial. In general, these medications are well tolerated and their side effect profiles are quite similar (Table 1), including a common trio of diarrhea, hypertension, and fatigue. However, differences do exist; hand-foot syndrome is a common cause of significant adverse events in sunitinib, whereas fatal hepatotoxicity has been shown in pazopanib, which carries a black box warning to this effect.

After many years of disappointing investigation into the use of cytotoxic chemotherapy in patients with RCC, the development of novel therapeutic agents targeting the VEGF pathway represents a scientific breakthrough. Pazopanib now joins the growing number of these drugs with proven efficacy in the treatment of advanced clear cell RCC.

**Disclosure of Potential Conflicts of Interest**

W.M. Stadler: commercial research grant, Novartis, Genentech, Pfizer, ImClone, Amgen; ownership interest, Abbott; consulting, Novartis, Pfizer, Genentech, Aveo.

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**Table 1. Comparison of FDA-approved VEGFR-targeted TKIs for advanced RCC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity</th>
<th>Dosing</th>
<th>Common toxicities</th>
<th>Boxed warnings</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>VEGFR-1,-2,-3, PDGFR-α, PDGFR-β, c-Kit</td>
<td>800 mg once daily continuously</td>
<td>Diarrhea*, hypertension*, hair color changes, GI disturbance, fatigue, abnormal LFTs*</td>
<td>Hepatotoxicity</td>
<td>CYP3A4, CYP2C8, CYP2D6, UGT1A1, OATP1B1</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR-1,-2,-3, PDGFR-α, PDGFR-β, c-Kit, FLT-3</td>
<td>50 mg once daily, 28 days followed by 14 days rest</td>
<td>Fatigue*, diarrhea*, nausea, stomatitis, hypertension*, hand-foot syndrome*</td>
<td>Hepatotoxicity</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR-1,-2,-3, PDGFR-β, FLT-3, c-Kit, c-RAF, B-RAF, mutant B-RAF</td>
<td>400 mg twice daily continuously</td>
<td>Diarrhea*, nausea, rash, fatigue*, hand-foot syndrome*, abdominal pain*, anemia*, alopecia, hypophosphatemia*, elevated lipase*</td>
<td>None</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1, UGT1A9</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; LFT, liver function test.
*Denotes common cause of grade 3 or 4 toxicity.

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References

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