

RENAL CELL CARCINOMA IN FOCUS

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Pazopanib in Renal Cell Carcinoma

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H&O What is the importance of the approval of pazopanib for treatment of advanced renal cell carcinoma (RCC)? What does it add to the armamentarium for oncologists and urologists treating this disease?

CS Although treatment for advanced RCC has improved in the past few years with the introduction of targeted therapies, the disease remains a challenging one. Pazopanib (Votrient, GlaxoSmithKline) has joined existing targeted therapies to provide physicians with a new oral treatment option for their patients with advanced RCC.

Pazopanib, which was approved by the US Food and Drug Administration in 2009, is indicated both for treatment-naïve and cytokine-pretreated patients with advanced RCC. Pazopanib is an oral medicine that is very well tolerated. The safety profile of pazopanib has been well-characterized and addressed in the product label.

H&O How does pazopanib compare with other oral therapies for advanced RCC (assuming there are other oral therapies for advanced RCC)?

CS There are no head-to-head comparative studies available to make a definitive statement about pazopanib in relation to other medications for RCC.

How pazopanib compares with other vascular endothelial growth factor (VEGF) inhibitors for this indication is under evaluation. An ongoing phase III open-label trial, COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma), is comparing pazopanib to sunitinib (Sutent, Pfizer) in locally advanced

and/or metastatic RCC patients who have had no prior treatment. Approximately 876 patients with treatment-naïve metastatic clear cell RCC will be included.

A second trial, PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer), will address patient preferences between pazopanib and sunitinib. This trial is a randomized, double-blind, crossover study of pazopanib versus sunitinib in patients with metastatic RCC who have received no prior systemic therapy. Approximately 160 patients are planned. More information can be found at www.clinicaltrials.gov.

The study that my colleagues and I published in the February 2010 issue of the *Journal of Clinical Oncology* last month is the first phase III study to include both treatment-naïve and cytokine-pretreated patients compared to placebo in the same trial and the first to show an important improvement in progression-free survival (PFS) in both of these groups (Sternberg CN, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28:1061-1068). Other randomized studies have either looked at only treatment-naïve or cytokine-pretreated patients; in the study with treatment-naïve patients, interferon was used as the comparator.

In our study, 435 adult patients with measurable, locally advanced, and/or metastatic RCC were randomly assigned 2:1 to receive oral pazopanib 800 mg once daily or placebo. Primary endpoint was PFS; secondary endpoints included overall survival, tumor response rate, and safety. Of the patients enrolled, 233 (54%) were treatment-naïve and 202 (46%) were cytokine-pretreated. We found that median PFS was significantly prolonged with pazopanib compared with placebo

in the overall study population (9.2 vs 4.2 months, respectively; hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.34–0.62; $P < .0001$), in the treatment-naïve subpopulation (11.1 vs 2.8 months, respectively; HR, 0.40; 95% CI, 0.27–0.60; $P < .0001$), and in the cytokine-pretreated subpopulation (7.4 vs 4.2 months, respectively; HR, 0.54; 95% CI, 0.35–0.84; $P < .001$). Results showed that the objective response rate was 30% in patients who received pazopanib compared with 3% in those who received placebo ($P < .001$). The median duration of response was longer than 1 year.

In this study, patients who progressed on placebo were offered pazopanib on an extension study.

H&O When do you expect to have overall survival data? Is this considered an interim analysis until those data are final?

CS The interim overall survival data are presented in the recent *Journal of Clinical Oncology* paper. The final overall survival data are expected to be available in the near future and will be presented at a medical congress and submitted for publication to a peer-reviewed journal. The PFS data presented in this paper are final.

H&O What is the clinical role of pazopanib? In what sorts of patients might oncologists and urologists want to use this drug?

CS Physicians should know that there is another option for the treatment of patients with advanced RCC. Pazopanib is indicated both in treatment-naïve and cytokine-pretreated patients with advanced RCC.

H&O What is the mechanism by which pazopanib works?

CS The management of advanced clear cell RCC has changed relatively rapidly over the last few years with the advent of anti-angiogenic biologic agents.

Angiogenesis in general and the VEGF signaling axis in particular is a validated target in RCC. Pazopanib inhibits VEGF receptors (VEGFR-1, 2, and 3) and other tyrosine kinases (PDGFR-a, PDGFR-b, and c-kit).

H&O Are the reported side effects—particularly diarrhea in 52% of patients, hypertension in 40%, and hair color change in 38%—of any concern? Or are they nothing more than one might expect in a drug like this?

CS The side effects are what one might expect with this class of agents. In our study, the most common adverse

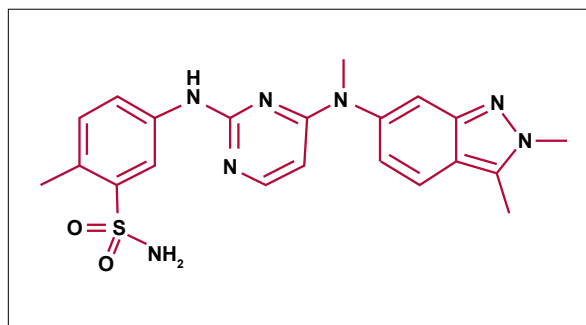


Figure 1. The chemical structure of pazopanib.

events were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. However, there was no evidence of clinically significant differences in the quality of life for patients receiving pazopanib versus those receiving placebo.

H&O What was the significance of studying both patients who were treatment-naïve AND those who were cytokine-pretreated? Why, in particular, study those who were cytokine-pretreated?

CS In this randomized, double-blind trial, a large statistically significant improvement in PFS was observed in the overall population and in the 2 subgroups: treatment-naïve and cytokine-pretreated. The study was initially intended for cytokine-refractory patients, but was rapidly amended after only few patients were entered, as there was a great interest to participate in the study even in patients who were not cytokine-pretreated.

H&O Ultimately, what is the take-home message for practicing oncologists and urologists?

CS Physicians and patients should know that there is another option for the treatment of advanced RCC.

Suggested Readings

Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.

Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist*. 2008;13:1084-1096.

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Sternberg CN, Szczylik C, Lee E, et al. A randomized, double-blind phase III study of pazopanib in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC). *J Clin Oncol*. 2009;27(suppl):Abstract 5021.