Nursing Considerations With Pazopanib Therapy: Focus on Metastatic Renal Cell Carcinoma

Laura Bourdeanu, NP, PhD, Przemyslaw Twardowski, MD, and Sumanta Kumar Pal, MD

The rapid evolution of targeted therapies has had a dramatic impact on multiple domains in oncology, particularly metastatic renal cell carcinoma (RCC). Four agents antagonizing vascular endothelial growth factor–mediated signaling have been approved for the treatment of metastatic RCC, including the monoclonal antibody bevacizumab and the small molecular inhibitors sunitinib, sorafenib, and pazopanib. Pazopanib was approved in 2009 for this disease on the basis of a phase III clinical trial demonstrating a superior progression-free survival compared to placebo in 435 patients with either treatment-naive or cytokine-refractory disease. The trial offered insight related to the toxicity profile associated with this agent. The most common clinical adverse events are diarrhea, hypertension, nausea, anorexia, and vomiting. With respect to laboratory adverse events, hepatotoxicity represents a specific concern with pazopanib. Oncology nurses play a critical role in counseling patients regarding the toxicity profile and management of adverse events in pazopanib treatment.

Enhanced understanding of tumor biology has led to the identification of molecular pathways that are susceptible to pharmacologic targeting. Since 1990, this paradigm has changed the face of cancer therapy. For example, the recognition of HER2 as a driver of breast cancer proliferation triggered the development of the monoclonal antibody trastuzumab (Slamon et al., 1987, 2001; Slamon, Leyland-Jones, & Shak, 1998). In renal cell carcinoma (RCC), modulation of the von Hippel-Lindau gene leads to overproduction of vascular endothelial growth factor (VEGF), which in turn triggers aberrant angiogenesis (blood vessel growth and formation) (Kim & Kaelin, 2004). To date, four drugs targeting VEGF-mediated signaling have been approved for the treatment of metastatic RCC on the basis of randomized, phase III studies: bevacizumab, sorafenib, sunitinib, and pazopanib (Escudier et al., 2007, 2010; Motzer et al., 2009; Rini et al., 2010; Sternberg et al., 2010).

The availability of multiple agents for RCC represents a unique clinical dilemma, as treatment with one agent may cause patients to develop resistance to the others because of the similar mechanism of action. Prior to VEGF-directed therapies, immunotherapy (e.g., interleukin-2, interferon-α) represented the mainstay of treatment for RCC. To date, patients and clinicians must decide among a variety of targeted agents. For instance, the National Comprehensive Cancer Network (2011) guidelines...
offer category 1 (unanimous) recommendations for sunitinib, pazopanib, or bevacizumab as first-line therapy for patients with clear cell, treatment-naive metastatic RCC. Unfortunately, no trials directly comparing those agents have been reported to date. As such, choosing among those agents often involves a balanced discussion of the relative benefits and toxicities associated with each (see Table 1). Recognition and management of those toxicities often entails an integrated approach that includes patients, physicians, and nurses. This article describes clinical usage of pazopanib in RCC, with a focus on nursing considerations.

## Clinical Development of Pazopanib

Preclinical assessment of pazopanib identified in vitro inhibition of VEGF receptor-1, -2, and -3; c-Kit tyrosine kinases; and platelet-derived growth factor receptor, all of which have been associated with tumor growth (Kumar et al., 2007). In murine xenograft studies, both bolus oral dosing and continuous IV dosing led to substantial growth inhibition in all tumors; however, renal cell was the most sensitive (Kumar et al., 2007). Those encouraging studies led to a phase I clinical trial of pazopanib in advanced solid tumors, examining oral dosing of the agent (Hurwitz et al., 2009). With 63 patients included in the analysis, a dose of 800 mg orally per day was selected for subsequent phase II clinical trials. Although phase I studies are not intended to evaluate efficacy, three patients in the analysis had a partial response and 14 had stable disease for more than six months. The most frequent drug-related toxicities in the phase I experience were hypertension, diarrhea, nausea, and hair depigmentation, most of which were mild (grade 1 or 2). Among those, hypertension represented the most frequent grade 3 event (Hurwitz et al., 2009).

To date, several phase II studies with pazopanib have been published, with encouraging activity seen in advanced breast cancer, ovarian cancer, and soft tissue sarcoma, among other malignancies (Friedlander et al., 2008; Sleijfer et al., 2009; Taylor et al., 2010). A smaller subset of studies has focused on the agent in earlier disease settings, including a phase II assessment using pazopanib as preoperative therapy for stage I and II lung cancer (Altorki et al., 2008). In the context of metastatic RCC, a phase II evaluation employing a randomized discontinuation design was initiated. In a randomized discontinuation design, all patients initially are treated with the drug, and the patients who respond to therapy continue. Patients who do not progress or experience excess toxicity within a predetermined period then are randomized to continuing or discontinuing therapy in a double-blind, placebo-controlled manner. However, the study was modified to an open-label design at the recommendation of the data monitoring committee in light of significant activity (a response rate at 12 weeks of 38% was observed in the first 60 patients enrolled). Of the 225 patients ultimately enrolled in the study, 155 patients (69%) were treatment naive. An overall response rate of 35% was observed, with a median duration of response in excess of one year (68 weeks). As in earlier studies of the agent, diarrhea and hair depigmentation were among the most frequently observed adverse events (Hutson et al., 2010).

Phase III data for pazopanib in metastatic RCC has been reported by Sternberg et al. (2010). The study randomized 435 patients in a 2:1 ratio to receive pazopanib or placebo. Although the study originally was designed to enroll only cytokine-refractory patients, treatment-naive patients later were incorporated, given emerging data for sunitinib and other small-molecule inhibitors in this subpopulation. Ultimately, most patients enrolled were treatment naive (54%). Treatment with pazopanib led to a prolongation in progression-free survival of about five months (9.2 versus 4.2 months, p < 0.0001). As anticipated, a greater absolute benefit in progression-free survival was observed in the treatment-naive subset (11.1 versus 2.8 months, p < 0.0001) as

### Table 1. Comparison of Agents in Metastatic Renal Cell Carcinoma Treatment

<table>
<thead>
<tr>
<th>AGENT</th>
<th>RECOMMENDED DOSE</th>
<th>SIDE EFFECTS</th>
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<tr>
<td>Bevacizumab</td>
<td>10 mg per kg given by IV every 14 days</td>
<td>Gastrointestinal perforation, surgery and wound healing complications, hemorrhage, nongastrointestinal fistula formation, arterial thromboembolic events, proteinuria including nephrotic syndrome, hypertension, reversible posterior leukoencephalopathy syndrome, epistaxis, headache, hypertension, rhinitis, taste alteration, dry skin, rectal hemorrhage, laceration disorder, back pain, exfoliative dermatitis, fatigue, venous thrombosis or embolism, neutropenia, febrile neutropenia, pneumonitis or pulmonary infiltrates, infection with or without grade 3 or 4 neutropenia, and hyponatremia</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>800 mg orally once daily without food</td>
<td>Hepatotoxicity, QT prolongation and torsades de pointes, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation and fistula, diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, vomiting, alopecia, dysgeusia, dyspepsia, facial edema, palmar-plantar erythrodysesthesia, proteinuria, rash, skin depigmentation, and decreased weight</td>
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<tr>
<td>Sorafenib</td>
<td>400 mg (2 tablets) orally twice daily without food</td>
<td>Cardiac ischemia, infarction, hemorrhage, hypertension, hand-foot skin reaction with or without rash, gastrointestinal perforation, wound healing complications, fatigue, weight loss, rash or desquamation, alopecia, diarrhea, constipation, anorexia, nausea, vomiting, abdominal pain, and liver dysfunction</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>50 mg orally daily for 4 weeks, then 2 weeks drug free; repeat cycle</td>
<td>Hepatotoxicity, cardiac toxicity, prolonged QT intervals and torsades de pointes, hypertension, hemorrhagic events including tumor-related hemorrhage, thyroid dysfunction, fatigue, asthenia, fever, diarrhea, nausea, mucositis or stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding</td>
</tr>
</tbody>
</table>

Note. Based on information from Bayer HealthCare Pharmaceuticals Inc., 2009; Genentech, Inc., 2011; GlaxoSmithKline, 2010; Pfizer Inc., 2011.
compared to the cytokine-pretreated population (7.4 versus 4.2 months, p < 0.0001). Pazopanib therapy also resulted in a higher overall response rate versus placebo (30% versus 3%, p < 0.001), with a median duration of response in excess of one year.

Adverse Effects of Pazopanib Monotherapy

The phase III study offered a prime opportunity to assess the specific toxicities associated with pazopanib monotherapy in a large cohort. Clinical manifestations of therapy are described in Figure 1. Diarrhea occurred in about 52% of patients; however, less than 4% of the study population experienced grade 3 or 4 diarrhea. Similarly, hypertension was observed in about 40% of patients treated with pazopanib, with grade 3 toxicity occurring among only 4% of patients. Following those side effects, hair color changes, nausea, anorexia, and vomiting were (in that order) the next most frequently observed toxicities. Importantly, the rates of fatigue, stomatitis, and hand-foot syndrome compare favorably to the rates of the side effects reported in the trials of other antiangiogenic agents for metastatic RCC (Escudier et al., 2007, 2010; Motzer et al., 2009; Rini et al., 2010). Discontinuation rates were relatively low, totaling 12% in the treatment-naive population and 19% in the cytokine-pretreated population.

Several unique laboratory abnormalities associated with pazopanib were characterized further in the phase III trial. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in 53% of patients receiving pazopanib, with grade 3 or 4 elevations of ALT and AST in 12% and 7% of patients, respectively. Of note, the vast majority of transaminase elevations occurred within 18 weeks of pazopanib therapy. Total bilirubin elevations also were observed in a substantial proportion of patients (all grades: 36%; grade 3 or 4: 3%). Because fatal hepatotoxicity events have occurred in association with pazopanib therapy (leading to a black box warning), stringent guidelines have been developed for monitoring liver function tests (LFTs) during the course of treatment. Patients who have baseline moderate hepatic impairment may receive a lessened dose, and therapy should be avoided in patients with severe hepatic impairment. LFTs should be assessed before the initiation of treatment and once every four weeks thereafter for the first four months of treatment. Table 2 outlines specific dose modifications recommended for the agent in the event of LFT abnormalities. Clinicians should refer to the package insert for pazopanib for complete information regarding dose modification in the setting of hepatic dysfunction.

Although an emphasis appropriately has been placed on hepatotoxicity associated with pazopanib, other laboratory abnormalities have been noted with the drug. Hyperglycemia, hyponatremia, hypophosphatemia, and hypomagnesemia have been noted in more than 25% of pazopanib-treated patients, albeit with low rates of grade 3 or 4 toxicity. With respect to hematologic toxicities, leucopenia, neutropenia, thrombocytopenia, and lymphocytopenia represented the most common adverse events, all occurring in more than 30% of pazopanib-treated patients. However, the rate of grade 3 or 4 events again was low.

Anorexia
- Record patient’s weight, appetite, and caloric intake at each visit.
- Discuss the use of appetite stimulants.
- Implement individualized dietary counseling.

Diarrhea
- Observe for clinical signs suggestive of dehydration.
- Counsel patient about the following.
  - Use antimotility agents (e.g., loperamide) as appropriate.
  - Consume sufficient fluids, small frequent meals, and beverages such as Gatorade®, diluted juices, and noncaffeinated drinks.
  - Avoid foods high in insoluble fiber (raw fruits and vegetables, skins, seeds, and legumes), greasy and fried foods, lactose, caffeine, alcohol, and hyperosmotic liquids.
  - Eat high-soluble fiber- or pectin-containing and low-insoluble fiber-containing foods (e.g., rice, noodles, bananas, white toast, skinned turkey or chicken, fish, mashed potatoes).

Hair Color Changes
- Prepare the patient for this potential side effect.
- Give necessary information and teach self-care strategies to minimize and cope with hair color changes.
- Give appropriate referrals for cosmetology.

Hypertension
- Refer to other healthcare providers (e.g., internist, cardiologist) who may aid in managing treatment-related hypertension.
- Recommend regular blood pressure monitoring.
- Advise on proper prescribed antihypertensives intake and adverse effects that should be reported.

Nausea and Vomiting
- Instruct on the use of 5-hydroxytryptamine, antagonists (i.e., ondansetron) and related agents to be taken as needed for nausea.
- Assess patient-specific risk factors.
- Instruct patients about antiemetic medications that will be prescribed postchemotherapy and instruct on the importance of taking those drugs on schedule to facilitate an optimal outcome.

Figure 1. Nursing Interventions for Adverse Events Related to Pazopanib Therapy

Note. Based on information from Sternberg et al., 2010.

Nursing Implications

Oncology nurses play an important role in the viability of pazopanib therapy. Nurses should be closely aware of its potential side effects, as denoted in previous sections. Early recognition of side effects through careful monitoring can lead to prompt supportive care measures that may ensure patient safety, as well as improve tolerability and clinical outcome.

Because pazopanib is an oral agent, nurses must educate patients about proper drug administration. Nurses should provide patients with clear, written directions for administering pazopanib, encourage patients to take it at the same time each day, and record in a diary the exact time they took the pills and the number of pills they took. Nurses should review the diaries for missed doses or incorrect administration of the drug to ensure adherence. Patients should be instructed that if a dose is missed, it should be omitted if the next scheduled dose is in less than 12 hours. Pazopanib is available as a 200 mg tablet, and the total daily...
**Table 2. Management of Liver Function Test Abnormalities in Pazopanib Treatment**

<table>
<thead>
<tr>
<th>TEST LEVEL</th>
<th>MANAGEMENT</th>
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<tr>
<td>ALT = 3–8 x ULN</td>
<td>Pazopanib therapy may be continued; however, liver function tests should be monitored weekly until ALT is grade 1 or baseline.</td>
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<tr>
<td>ALT &gt; 8 x ULN</td>
<td>Pazopanib therapy should be interrupted until ALT is grade 1 or baseline. A reduced dose of pazopanib could be considered. The liver function tests should be monitored weekly for eight weeks, with permanent discontinuation of pazopanib if ALT is more than three times ULN.</td>
</tr>
<tr>
<td>ALT &gt; 3 x ULN; total bilirubin &gt; 2 x ULN</td>
<td>Pazopanib therapy should be discontinued permanently, and patients should be monitored until liver function test levels normalize.</td>
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ALT—alanine aminotransferase; ULN—upper limit of normal

Note. Based on information from Sternberg et al., 2010.

Dose is not to exceed 800 mg per day. The medication should be administered without food and should be taken either one hour before or two hours after a meal. Crushing the tablet may hasten the rate of absorption of the drug and increase related toxicities; therefore, this should be avoided.

A thorough medication review should be performed before therapy begins to determine whether the patient is taking any oral agents that may have interactions with pazopanib. The medication list should include prescription drugs, over-the-counter medication, vitamins, minerals, and herbal remedies. Pazopanib pharmacokinetics may be substantially affected by various CYP3A4 inducers and inhibitors. Strong inhibitors of CYP3A4 include medications such as ketoconazole or clarithromycin. When using pazopanib with those agents, a dose reduction may be considered. Rifampin is a strong inducer of CYP3A4; therefore, alternative agents should be considered when administering pazopanib. Caution also should be exercised in concomitantly using any other CYP substrates (including substrates of CYP2D6 or CYP2C8). Prior to initiating treatment, nurses may want to consult a pharmacist or online drug interaction checker such as www.drugs.com/drug_interactions.html.

Both the physician and nurse should ensure that the patient reports to the clinic regularly for evaluation of toxicity. Although formal guidelines have yet to be established, monthly evaluation of the patient represents the standard at most academic institutions. Nurses must educate patients and their caretakers about the type of side effects that may occur and when to contact the healthcare team. Several potential management strategies for the most commonly encountered pazopanib-specific toxicities are described in this article.

**Diarrhea**

Patients should be counseled regarding appropriate use of antiemetics agents, such as loperamide. Dietary strategies should include consumption of sufficient fluids, small frequent meals, and beverages such as Gatorade®, diluted juices, and noncaffeinated drinks. Patients should be instructed to avoid foods high in insoluble fiber (e.g., raw fruits and vegetables, skins, seeds, legumes), greasy and fried foods, lactose, caffeine, alcohol, and hyperosmotic liquids. Patients should be encouraged to eat high-soluble fiber- or pectin-containing and low-insoluble fiber-containing foods (e.g., rice, noodles, bananas, white toast, skinned turkey or chicken, fish, mashed potatoes). Clinical signs suggestive of dehydration (e.g., hypotension, dizziness) warrant prompt intervention with fluid resuscitation.

**Hypertension**

To date, no formal guidelines for management of hypertension in the context of antiangiogenic therapies have been adopted. Therefore, oncology nurses may serve as important liaisons between oncologists and other care providers (e.g., internists, cardiologists) who may aid in concomitantly managing treatment-related hypertension. Patient education should include recommendations for regular blood pressure monitoring, how to take prescribed antihypertensives correctly, and adverse effects that should be reported. In addition, nurses should instruct patients not to discontinue medications without contacting their practitioner.

**Hair Color Changes**

Nurses should prepare patients for this potential side effect, which (anecdotal) results in a yellowing of the original hair color, by giving them necessary information and teaching self-care strategies to minimize and cope with hair color changes. The interventions are aimed at helping patients move through a potentially devastating experience to a renewed sense of well-being. If warranted, patients should be given appropriate referrals for cosmesis.

**Nausea and Vomiting**

Patients should be instructed on the use of 5-hydroxytryptamine antagonists (i.e., ondansetron) and related agents to be taken as needed for nausea. Based on the limited frequency of grade 3 and 4 events, prophylaxis typically is not warranted. Patient-specific risk factors including age, gender, history of low alcohol use, anxiety, lower social functioning, a history of motion sickness, hyperemesis during pregnancy, and poor control during other chemotherapies must be assessed. Before administering any chemotherapy, nurses should talk with patients about their understanding of the therapy as well as their expectations and provide patients with information about the role of antiemetics. Nurses should instruct patients about antiemetic medications that will be prescribed postchemotherapy, the importance of taking the medications on schedule to facilitate an optimal outcome, and when to call if the drugs are not working.

**Anorexia**

Patients’ weight should be recorded at each visit, with a detailed account of appetite and caloric intake if weight loss is an issue. If any of those parameters are decreasing markedly, a discussion related to use of appetite stimulants (e.g., dronabinol, megesterone acetate) should ensue. Individualized dietary counseling should be implemented.
Conclusion

Of the six targeted therapies approved for the treatment of RCC since 2005, pazopanib is the most recent agent to reach the clinic. Although pazopanib has garnered a recommendation akin to that of sunitinib and bevacizumab for treatment-naïve patients with clear cell metastatic RCC, the side-effect profile of the agent is distinct; the more common side effects include low blood counts and hepatotoxicity, which may lead to potentially life-threatening conditions. Given the lack of trial data to discern the relative efficacy of sunitinib, bevacizumab, and pazopanib, the side effect profile of pazopanib (among other factors) may have an important role in treatment selection. Oncology nurses can play an integral part in the discussion and management of side effects associated with those treatments. As noted, pazopanib is being explored in a variety of different malignancies, with encouraging preliminary activity in certain disease types beyond RCC. With the agent potentially expanding into multiple other domains, the nursing community must become familiar with pazopanib.

Author Contact: Laura Bourdeanu, NP, PhD, can be reached at lbourdeanu@yahoo.com, with copy to editor at CJONEditor@ons.org.

References


