Pazopanib (Votrient)

Drug type
- A tyrosine kinase inhibitor (TKI)

Indications
- Advanced renal cell carcinoma
- Advanced soft tissue sarcoma in patients who have received prior chemotherapy

Mechanism of action
- Pazopanib is a multikinase inhibitor. It inhibits vascular epidermal growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3). VEGF is a chemical signal produced by cells that stimulates the growth of new blood vessels; cancers that can express VEGF are able to grow and metastasize.
- Pazopanib also inhibits platelet-derived growth factor receptors, fibroblast growth factor receptors, cytokine receptors, and others.

Dosage and administration
- Renal cell carcinoma
  - 800 mg oral once daily on an empty stomach (at least 1 hour before a meal or 2 hours after a meal)
- Soft tissue sarcomas
  - 800 mg oral once daily on an empty stomach (at least 1 hour before a meal or 2 hours after a meal)
  - Efficacy not demonstrated in adipocytic soft tissue sarcoma or gastrointestinal stromal tumors (GIST)
- Dosage modifications
  - Coadministration with strong CYP3A4 inhibitors (eg, ketoconazole [Nizoral, generics], ritonavir [Norvir], clarithromycin [Biaxin, generics], grapefruit juice): Avoid if possible, but if coadministration is warranted, decrease pazopanib dose to 400 mg/day; further dose reduction may be needed if adverse effects occur
  - Coadministration with strong CYP3A4 inducers (eg, rifampin [Rifadin, Rimactane, generics], carbamazepine): Patients who cannot avoid using strong CYP3A4 inducers should not use pazopanib.
  - Renal impairment
    - No dosage adjustment required
  - Hepatic impairment
    - Baseline moderate impairment: 200 mg oral once daily
    - Severe impairment: Not recommended

Pregnancy and lactation
- Pregnancy category D
- Lactation
  - Unknown whether distributed in breast milk
  - Breastfeeding not recommended

Cautions
- Severe hepatotoxicity, including fatalities, has been reported
- Increases in ALT and AST levels are common (>50% of patients) and warrant caution in patients with existing hepatic impairment
- Hypertension, including hypertensive crisis, have occurred
- Rare occurrences of QT prolongation and torsades de pointes reported during clinical trials
- Hematologic parameter alterations (ie, leukopenia, neutropenia, thrombocytopenia, lymphocytopenia) reported in 31%-37% of patients
- Coadministration with strong CYP3A4 inhibitors may increase pazopanib serum levels
- CYP3A4 inducers decrease pazopanib serum levels
- Events of cardiac dysfunction (decreased LVEF and heart failure) have been observed

- Fatal hemorrhage, arterial and venous thrombotic events, and GI perforation have been observed in randomized clinical trials

Adverse effects

- >10% of patients (percentage of patients who reported experiencing adverse effect)
  - Liver
    - ALT (SGPT) level raised (all grades, 53%; grade 3, 10%; grade 4, 2%)
    - AST/SGOT level raised (all grades, 53%; grade 3, 7%; grade 4, <1%)
    - Diarrhea (52%)
    - Increased glucose (41%)
    - Hypertension (40%)
    - Hair depigmentation (38%)
    - Blood
- Leukopenia (all grades, 37%; grade 3, 0%; grade 4, 0%)
- Increased bilirubin level (all grades, 36%; grade 3, 3%; grade 4, <1%)
- Neutropenia (all grades, 34%; grade 3, 1%; grade 4, <1%)
- Phosphorous decreased (34%)
- Thrombocytopenia (all grades, 32%; grade 3, <1%; grade 4, <1%)
- Lymphocytopenia (all grades, 31%; grade 3, 4%; grade 4, <1%)
  - Decreased sodium levels (31%)
  - Decreased magnesium levels (26%)
  - Nausea (26%)
  - Weakness (22%)
  - Vomiting (21%)
  - Anorexia (22%)
  - Fatigue (19%)
  - Hemorrhage (all grades, 13%-16%; grade 3-5, 2%)
  - Abdominal pain (11%)
- 1%-10% of patients (percentage of patients who reported experiencing adverse effect)
  - Headache (10%)
  - Proteinuria (9%)
  - Weight loss (9%)
  - Alopecia (8%)
  - Dysgeusia (8%)
  - Rash (8%)
  - Hypothyroidism (4% to 7%)
  - Palmar-plantar erythrodysesthesia (6%)
  - Chest pain (5%)
  - Dyspepsia (5%)
  - Skin depigmentation (3%)
  - Prolonged QT interval (<2%)
  - Hepatotoxicity (1%-2%)
  - Facial edema (1%)
  - Rectal hemorrhage (1%)
  - Transient ischemic attack (1%)
  - Hemorrhagic death (0.9%-1%)
- <1% of patients
  - Torsades de pointes
  - Cerebrovascular accident
  - Pancreatitis
- Frequency not defined
  - MI
  - GI fistula/perforation

Drug interactions

- Drugs that inhibit or induce cytochrome P450 3A4 enzymes
- Effects of pazopanib on CYP substrates
  - In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.
  - Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19
  - Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.
- Effect of concomitant use of pazopanib and simvastatin (Zocor, generics)
  - Results from drug-drug interaction trials with cancer patients suggest that ALT elevations can occur.
  - Across monotherapy studies with pazopanib, ALT >3× ULN was reported in 126 of 895 (14%) patients who did not use statins, compared with 11 of 41 (27%) patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for pazopanib or consider alternatives to pazopanib. Alternatively, consider discontinuing simvastatin.
  - Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Continued on page 32

What to tell your patient

- Your doctor has ordered the anti-cancer medicine pazopanib to help treat your illness.
- This medication is only given by mouth in tablet form.
- Pazopanib is used for the treatment of advanced renal cell carcinoma.
- It slows or stops the growth of cancer cells in your body. The length of treatment depends on the types of drugs you are taking, how well your body responds to them, and the type of cancer you have.
- Pazopanib may harm the fetus.
  - You should not plan to have children while receiving chemotherapy or for a while after treatments.
  - Use a reliable method of birth control to prevent pregnancy.
- Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects.
- Important things to remember about the side effects of pazopanib
  - Most people do not experience all of the side effects listed.
  - Side effects are often predictable in terms of their onset and duration.
  - Side effects are almost always reversible and will go away after treatment is complete.
  - There are many options to help minimize or prevent side effects.
  - There is no relationship between the presence or severity of side effects and the effectiveness of pazopanib.
- Common side effects (occur in more than 30% of patients taking pazopanib)
  - Diarrhea
  - Hypertension
  - Hair color changes
  - Low blood counts (low WBCs, low platelets)
  - Elevated liver function tests (AST, ALT)
  - Elevated bilirubin level
  - Blood test abnormalities (low phosporus, low sodium, increased glucose)
- Less frequent side effects (occur in 10%-29% of patients taking pazopanib)
  - Abdominal pain
  - Blood test abnormalities (low magnesium, low glucose or blood sugar levels)
  - Fatigue
  - Headache
  - Nausea
  - Poor appetite
  - Vomiting
  - Weakness
- Always inform your health care provider if you experience any unusual symptoms.
- Contact your nurse or doctor immediately if you should experience either of these side effects.
  - Fever of 100.4°F (38°C) or higher, chills (possible signs of infection)
  - Jaundice or yellowing of the skin or whites of the eyes
- These symptoms require medical attention, but are not an emergency. Contact your nurse or doctor within 24 hours of noticing any of the following side effects.
  - Diarrhea (4-6 episodes in a 24-hour period)
  - Hypertension (systolic BP >150 [top number] or diastolic BP >90 [bottom number])
  - Nausea that interferes with ability to eat and unrelieved with prescribed medication
  - Vomiting more than 4-5 times in a 24-hour period
  - Unusual bleeding or bruising
  - Black or tarry stools, or blood in your stools
  - Blood in your urine
  - Pain or burning with urination
  - Extreme fatigue that prevents you from carrying on self-care activities
  - Mouth sores (painful redness, swelling or ulcers) ■

Prepared by **Bette Weinstein Kaplan**. Reviewed by **Maribel Pereiras, PharmD, BCOP.**