PHARMACY CORNER

New Kinase Inhibitor Approved for Renal Cell Carcinoma

The oral multityrosine kinase inhibitor pazopanib (Votrient™, GlaxoSmithKline) has received approval by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma. In a 2:1 randomized, double-blind study comparing pazopanib (n = 290) to placebo and best supportive care (n = 145), pazopanib demonstrated a median progression-free survival (PFS) advantage of 9.2 months versus 4.2 months in the placebo arm.

Common adverse reactions include diarrhea, hypertension, depigmentation of hair, nausea, vomiting, and anorexia. As hepatic toxicities have been observed, liver function tests should be obtained prior to initiation of therapy and weekly for the first four weeks of therapy.

The observation of increased bleeding risk is not surprising as the vascular endothelial growth factor (VEGF) receptor is one of several cell receptor targets affected by pazopanib. Fatal hemorrhagic events have occurred and, as a precautionary measure, treatment should be stopped in patients undergoing surgery. The drug also should not be used in patients with histories of hemoptysis, cerebral hemorrhage, or significant gastrointestinal hemorrhage.

In addition, recommended monitoring includes thyroid function testing as hypothyroidism has occurred while on therapy. Patients should be educated regarding and monitored for the increased risk of arterial thrombotic events associated with this therapy.

Pazopanib is normally dosed at 800 mg per day on an empty stomach at the same time each day. Patients should be instructed to take the medication at least one hour before or two hours after a meal. In the setting of moderate hepatic impairment, normal dosing is 200 mg per day. The drug should not be used in patients with severe hepatic impairment.

For more information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm187509.htm.

Prior to the explosion of targeted agent use in the oncology setting, interleukin-2 was commonly used in the treatment of advanced renal cell carcinoma. Unfortunately, the side effects of this approach often were prohibitory and renal cell carcinoma typically does not respond well to traditional cytotoxic chemotherapy. In addition to pazopanib, other agents frequently used in the treatment of advanced renal cell carcinoma include the kinase-inhibitors sunitinib (Sutent®, Pfizer Inc.) and sorafenib (Nexavar®, Bayer Healthcare & Onyx Pharmaceuticals), the monoclonal antibody bevacizumab (Avastin®, Genentech), and the mTOR inhibitors temsirolimus (Torisel®, Wyeth Pharmaceuticals) and everolimus (Afinitor®, Novartis AG).

Ofatumumab Used to Treat Chronic Lymphocytic Leukemia

Ofatumumab (Arzerra™, GlaxoSmith Kline) has received FDA approval for the treatment of chronic lymphocytic leukemia (CLL) refractory to fludarabine (Fludara®, Berlex Laboratories) and alemtuzumab (Campath®, Berlex Laboratories). To date, no curative treatments exist for CLL and the goal of care typically is to prolong progression-free survival and reduce symptoms through control of the disease.

A monoclonal antibody, ofatumumab works by attaching to the CD20 molecule of B cells in CLL. The immune system then is able to lyse the cells through antibody and complement-dependent pathways.

The drug is given in 12 doses with 300 mg on the initial dose followed a week later by 2,000 mg weekly doses for seven doses. This is followed four weeks later by 2,000 mg every four weeks for four doses. Because of the risk for infusion reactions, premedications 30 minutes to two hours prior to the infusion should include acetaminophen 1,000 mg, an antihistamine (cetirizine 10 mg or equivalent), as well as an IV corticosteroid (prednisolone 100 mg or equivalent). If infusion reactions do not occur, the corticosteroid may be gradually reduced for doses 3–8 and 10–12. Do not reduce the corticosteroid for doses 1, 2, and 9.

All doses should be mixed into a total volume of 1,000 ml of 0.9% normal saline. The first (0.3 mg/ml) and second (2 mg/ml) doses should be initiated at 12 ml per hour. If no infusion reactions occur, the rate can be doubled every 30 minutes until a maximum rate of 200 ml per hour is reached. Subsequent doses (3–12) can be initiated at 25 ml per hour with infusion rates doubled every 30 minutes until a maximum rate of 400 ml per hour is reached.

Common adverse reactions observed during clinical trials included neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

As with another well-known CD20-directed monoclonal antibody, rituximab (Rituxan®, Genentech & Biogen), a risk exists for hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML). Ofatumumab should be discontinued if PML is suspected and in patients who experience reactivation of viral hepatitis. Similar to rituximab, infusion reactions (except for grade 4 reactions) are not an automatic reason to discontinue the drug. With lesser grade reactions, the manufacturer provides guidelines for interruption of the drug followed by re-initiation at a slower rate as symptoms resolve.

For additional information, visit www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf.

SAFETY CONCERNS

Flushing Opioids Recommended as Effective Disposal Method

In an effort to reduce diversion risk and accidental medication overdoses, the FDA is encouraging patients to destroy medications that are no longer in use. For the majority of medications, simply hiding the drug in a less-than-palatable base, such as kitty litter or coffee grounds, prior to disposal is suggested. However, in the case of highly potent opioids such as morphine and hydromorphone, the FDA suggests flushing leftover medication in the toilet as an effective approach to drug destruction. For a complete list of medications the FDA suggests disposing via flush, visit www.fda.gov/Drugs/ResourcesForYou/Consumers/