Drug Monitor

New Treatment Option for Renal Cell Carcinoma

Patients with kidney cancer have seen a dramatic increase in effective treatment options over the past five years. Since December 2005, five drugs (sorafenib, sunitinib, temsirolimus, everolimus, and bevacizumab) have been approved for the treatment of kidney cancer. Now a sixth has been added to the list: pazopanib (Votrient; GlaxoSmithKline, Philadelphia, PA), an oral tyrosine kinase inhibitor approved by the FDA in October 2009 to treat patients with advanced renal cell carcinoma (RCC). RCC is the most common type of kidney cancer; in 2009, approximately 49,000 people were diagnosed with RCC and approximately 11,000 died from the disease.

In a placebo-controlled study of 435 patients with advanced RCC, pazopanib reduced the risk of tumor progression or death by 54%. Median progression free survival (PFS) time was 9.2 months in the group receiving pazopanib, compared with 4.2 months in the group receiving placebo. When the researchers evaluated specific patient groups, they found an even more dramatic difference among those with no prior drug treatment—median PFS time was 11.1 months for those taking pazopanib and 2.8 months for those taking placebo. The manufacturer reports that the overall response rate to pazopanib was 30%, with an average response duration of 59 weeks.

The researchers say that patients taking pazopanib did not experience a significant decline in health-related quality of life. Adverse reactions, which were generally mild to moderate, included gastrointestinal effects, hypertension, and asthenia. The drug was also associated with serious, sometimes fatal, liver toxicity and heart rhythm irregularities, however. Approximately 4% of patients taking pazopanib died, compared with 3% of patients taking placebo, and death was attributed to the study drug in approximately 1.4% of patients in the treatment arm. Because of these risks, the FDA advises health care professionals to monitor patients taking the drug with periodic liver function tests, electrocardiography, and electrolyte studies.

Sources: FDA press release. October 19, 2009.

GlaxoSmithKline press release. June 1, 2009.

Tiotropium for Early-Stage COPD

The benefits of treating chronic obstructive pulmonary disease (COPD) in its later stages have been well established, but less is known about the impact of treatment in the earlier stages. To learn more, researchers from the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial performed a prespecified subgroup analysis of patients with COPD classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II. They found that treatment with the study drug, the long-acting anticholinergic tiotropium, appeared to slow the progression of COPD in these patients.

UPLIFT was a randomized, double-blind, placebo-controlled trial of 5,993 patients with COPD recruited from 487 centers in 37 countries. The patients, aged 40 and older with a smoking history of at least 10 pack-years, were assigned randomly to receive four years of treatment with either once-daily tiotropium or matching placebo, delivered by an inhalation device. The primary endpoints of the study were the yearly rate of decline of mean prebronchodilator forced expiratory volume in one second (FEV_1) and of mean postbronchodilator FEV_1. Secondary endpoints included lung function at each visit, health status, exacerbations (defined as an increase in or a new onset of more than one respiratory symptom, which lasted for at least three days and required treatment with an antibiotic, systemic steroid, or both), all-cause mortality, and mortality from lower respiratory tract conditions.

For the subgroup analysis, the researchers examined data on the 2,739 UPLIFT participants who had GOLD stage II disease at baseline. Although the rate of decline of mean prebronchodilator FEV_1 was not significantly different between the tiotropium group and the placebo group (35 mL per year versus 37 mL per year, respectively; $P = .38$), the difference in the rate of decline of mean postbronchodilator FEV_1 did reach statistical significance (43 mL per year in the tiotropium group versus 49 mL per year in the placebo group; $P = .024$). Additionally, tiotropium was associated with better health-related quality of life scores at all time points and appeared to prolong both the time to a first exacerbation and the time to an exacerbation requiring hospitalization.

The researchers caution that, while their subgroup analysis was planned, its results are subject to the usual methodologic limitations associated with such analyses. Furthermore, since the UPLIFT participants were identified from pulmonary practices, they may have had more severe and

symptomatic disease than other patients with GOLD stage II COPD. Accordingly, the researchers call for a prospective, double-blind, placebo-controlled trial involving patients with GOLD stage II COPD identified from a general practice setting.

In the meantime, however, they say that their findings, coupled with those from recent studies suggesting that annual FEV_1 decline is greater in GOLD stage II than in later stages, should "provide a rational basis for starting treatment in patients with this stage of the disease." The reduction in the rate of decline in postbronchodilator FEV_1 is of particular interest, they add, because it has the potential to alter the natural course of the disease early on.

Source: *Lancet.* 2009;374(9696):1171–1178. doi:10.1016/S0140-6736(09)6129-8.

Comparing Antithrombotic Regimens for Diabetic Patients Undergoing PCI

Patients with diabetes mellitus (DM) are at high risk for ischemic events during percutaneous coronary intervention (PCI) or shortly afterward, due to the metabolic, coagulation, platelet, and endothelial abnormalities associated with the disease. Recent trials have suggested that monotherapy with bivalirudin—a direct-acting, synthetic antithrombotic agent—results in similar efficacy and a lower bleeding risk than the standard combination of unfractionated heparin (UFH) and a platelet glycoprotein (Gp) IIb/IIIa inhibitor in patients undergoing elective or urgent PCI. Only post hoc analyses, however, have compared the regimens specifically in patients with DM. Thus, researchers from Clinica Mediterranea, Naples, Italy and IRCCS Multimedica, Sesto San Giovanni, Milan, Italy conducted the Novel Approaches for Preventing or Limiting Events (NAPLES) trial, a prospective study of 335 patients with DM undergoing elective PCI.

Patients were assigned randomly to receive either bivalirudin monotherapy or UFH plus tirofiban before and during PCI. All patients received aspirin and clopidogrel the day before the procedure and afterward, daily, for at least 30 days when bare metal stents were used or for six months or more when drug-eluting stents were used. The primary endpoint was a composite of death, myocardial infarction (MI), myocardial ischemia requiring urgent surgical or repeat percutaneous coronary revascularization within 30 days of randomization, and in-hospital bleeding (both major and minor).

By the 30-day point, the primary endpoint had occurred less frequently in the bivalirudin group than in the UFH plus tirofiban group (18% versus 32%, respectively; $P = .004$). Non–Q-wave MIs occurred with similar frequency between the two groups (10.2% of the bivalirudin group versus 12.5% of the UFH plus tirofiban group). No patients in either group died, had Q-wave MIs, or needed urgent revascularization.

Significantly fewer patients receiving bivalirudin experienced bleeding events compared with those receiving UFH plus tirofiban (8.4% versus 20.8%, respectively; $P = .002$). The researchers ascribe the difference primarily to the lower rate of minor bleeding, which was 8% in the bivalirudin group and 19% in the UFH plus tirofiban group ($P = .005$). The rate of major bleeding (defined as intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a reduction in hemoglobin of more than 3 g/dL; any reduction in hemoglobin of more than 4 g/dL; or transfusion of at least 2 units of packed red blood cells or whole blood) was comparable between the groups (0.6% in the bivalirudin group versus 2.4% in the UFH plus tirofiban group). Most bleeding events occurred at a femoral vascular access site.

The researchers point out that, while minor bleeding "represents a complication significantly less dangerous than major hemorrhage," it is nevertheless associated with longer hospital stays and higher costs and has negative effects on short- and long-term outcomes. Their findings, they say, demonstrate that bivalirudin monotherapy is a "safe and feasible" strategy for patients with DM undergoing PCI—especially those deemed to be at high risk for bleeding.

Source: *Am J Cardiol.* 2009;104(9):1222–1228. doi:10.1016/j.amjcard.2009.06.035.