PHARMACY CORNER

Cetuximab and Panitumumab Mystery Solved

Research has provided insight regarding why cetuximab (Erbitux®, Bristol-Myers Squibb, Imclone) works so well with some patients while, at the same time, has little or no benefit for patients with colon cancer testing positive for epidermal growth factor receptor (EGFR) overexpression. By examining gene expression, researchers have found that patients whose tumors exhibited K-*ras* gene mutations derived no benefit with cetuximab compared to best supportive care. Conversely, patients exhibiting "wild-type" K-*ras* expression benefited significantly when treated with cetuximab versus best supportive care. Overall survival improved from 4.8–9.5 months ($p < 0.001$), and progression-free survival improved from 1.9–3.7 months (Karapetis et al., 2008).

Research also has shown that the EGFR-inhibitor panitumumab (Vectibix®, Amgen Inc.) is ineffective in the presence of K-*ras* gene mutations (Weber & McCormack, 2008).

Both drugs are approved for EGFR over expression in colon cancer, but the significance of emerging research is that only patients exhibiting the wild-type K-*ras* gene are likely to benefit from these treatments. Testing for gene expression has the potential of preventing therapies of unlikely benefit and, thereby, avoiding the unnecessary expenses and adverse reactions associated with these drugs.

Karapetis, C.S., Khambata-Ford, S., Jonker, D.J., O'Callaghan, C.J., Tu, D., Tebbutt, N.C., et al. (2008). K-*ras* mutations and benefit from cetuximab in advanced colorectal cancer. *New England Journal of Medicine, 359*(17), 1757–1765.

Weber, J., & McCormack, P.L. (2008). Panitumumab: Metastatic colorectal cancer with wild-type KRAS. *BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals, and Gene Therapy, 22*(6), 403–411.

Denileukin Diftitox Receives Approval

Denileukin diftitox (Ontak®, Eisai Medical Research) has received full U.S. Food and Drug Administration (FDA) approval in the treatment of persistent or recurrent cutaneous T-cell lymphoma (CTCL) expressing the CD25 component of the interleukin (IL)-2 receptor (CD25+). CTCL is a rare form of malignant lymphoma with primary manifestations in the skin.

Approval of denileukin diftitox was based on a phase III randomized, double-blind, placebo-controlled, parallel-group trial (N = 144) comparing placebo (saline) to denilukin diftitox dosed at 9 or 18 mcg/kg per day on days 1–5 every 21 days with a maximum of eight cycles. Overall response rates were greater than placebo (15%) in both the 9 mcg/kg arm (37%, $p = 0.03$ versus placebo) and the 18 mcg/kg arm (46%, $p = 0.03$ versus placebo). Improvements also were seen in progression-free survival and median response duration.

For more information, visit www.ons.org/fda/documents/FDA101508.pdf.

Bendamustine Hydrochloride Now Used to Treat Indolent B-Cell Non-Hodgkin Lymphoma

Previously approved in the treatment of chronic lymphocytic leukemia (CLL), the alkylating agent bendamustine hydrochloride (Treanda®, Cephalon) has received FDA approval for the treatment of indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with a rituximab (Rituxan™, Genentech) regimen. Approval was based on a single-arm trial in which patients received bendamustine hydrochloride 120 mg/m^2 infusions over 60 minutes on days 1 and 2 of 21-day treatment cycles for up to eight cycles. This differs from the recommended dosing for CLL (100 mg/m^2 infusions over 30 minutes on days 1 and 2 of 28-day cycles for up to six cycles).

The new NHL approval was based on overall response rates of 74% and median duration of response of 9.2 months in a single-arm trial of patients with indolent B-cell NHL (N = 100). Safety analysis of bendamustine hydrochloride in patients with NHL previously treated with rituximab (N = 176) revealed the most common nonhematologic toxicities as nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and fever (34%). Myelosuppression also is a significant adverse effect of bendamustine hydrochloride, and three patients died as a result of myelosuppressive-related events (neutropenic sepsis, diffuse alveolar hemorrhage, and cytomegalovirus infection). Hematologic nadirs are most commonly seen in the third week of therapy.

Patients with known hypersensitivity to bendamustine or mannitol should not take bendamustine hydrochloride. The drug should not be used if creatinine clearance is less than 40 ml per minute or in the presence of moderate-to-severe hepatic impairment. For patients experiencing grade 1 or 2 infusion reactions, premedication with antihistamines, antipyretics, and corticosteroids should be considered with subsequent doses.

For more information, visit www.fda.gov/cder/Offices/OODP/whatsnew/Bendamustine_hydrochloride.htm.

Accelerated Approval Granted for Eltrombopag

The FDA has granted acclerated approval to a second thrombopoiesis stimulating agent, eltrombopag (Promacta®, GlaxoSmithKline) for the treatment of chronic immune thrombocytopenic purpura that has not responded to the standard treatments of corticosteroids, immunoglobulins, or splenectomy. Previously, approval was granted to romiplostim (Nplate™, Amgen Inc.) for use in patients with chronic immune thrombocytopenic purpura (ITP) who have failed to respond sufficiently to standard first-line therapies. Because of safety concerns, the drugs are currently only available through restricted access programs to track long-term safety data.

Initial dosing for eltrombopag is 50 mg by mouth daily on an empty stomach for most patients. The dose is cut in half for patients with moderate-to-severe hepatic impairment and in patients of Eastern Asian ancestry. Maximum dosing is 75 mg per day, and the drug should be discontinued if improvement