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

in platelet counts does not occur within four weeks. Eltrombopag is only used to achieve platelet levels necessary to prevent bleeding, and because of safety concerns, the drug should not be used in an attempt to normalize platelet counts.

ITP is a disease process in which the immune system is involved in the destruction of platelets and sometimes appears to produce auto-antibodies whose function inhibits the production of new platelets. First-line therapies include corticosteroids (high-dose dexamethasone or methylprednisolone) and immunoglobulins. Splenectomies also are sometimes performed in patients who are unresponsive or refractory to standard treatments or who develop bleeding complications, and several chemotherapy and biologic therapies also are options in treating patients with refractory ITP.

For more information about eltrombopag, visit www.fda.gov/Cder/Offices/OODP/whatsnew/eltrombopag.htm.

For more information about romiplostim, visit www.fda.gov/bbs/topics NEWS/2008NEW01876.html.

Tapentadol Hydrochloride Treats Moderate to Severe Pain

Tapentadol hydrochloride (Johnson & Johnson Pharmaceutical), an immediate release analgesic with mu-opioid agonist and norepinephrine reuptake inhibitor properties, has received FDA approval for the treatment of moderate-to-severe acute pain in adults. The drug comes in 50, 75, and 100 mg tablets.

The most common adverse reactions included nausea, dizziness, vomiting, somnolence, and headache. Tapentadol hydrochloride is contraindicated in many patients where mu-opioids are contraindicated and in patients who are taking or have received monoamine oxidase inhibitors within the prior 14 days. In the presence of impaired renal or hepatic function, such as in older adults, lower initial doses should be considered. If given concomitantly with other drugs that impair serotonin metabolism or serotonergic drugs, an increased risk exists of developing life-threatening serotonin syndrome.

At this writing, a trade name has yet to be determined, and the FDA still must determine a scheduling classification before tapentadol hydrochloride will be available.

For more information, visit www.fda.gov/bbs/topics/NEWS/2008/NEW01916.html.

Plerixafor Mobilizes Stem Cells for Transplantation

The FDA has granted approval for plerixafor (Mozobil™, Genzyme Corp.) to be used in conjunction with granulocyte-colony–stimulating factor to mobilize stem cells in preparation for autologous hematopoietic stem cell transplantation in patients with non-Hodgkin lymphoma and multiple myeloma. A significant advantage with the use of plerixafor is the dramatic reduction in the time required to harvest an adequate sample of cells (Devine et al., 2008).

For full prescribing information, visit www.genzyme.com.

Devine, S., Vij, R., Rettig, M., Todt, L., McGlauchlen, K., Fisher, N., et al. (2008). Rapid mobiliztion of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. *Blood, 112*(4), 990–998.

SAFETY CONCERNS

Changes Made to Efalizumab

Labeling changes for the recombinant humanized IgG1 monoclonal antibody efalizumab (Raptiva®, Genentech) include warnings regarding life-threatening infections, such as bacterial sepsis, viral meningitis, invasive fungal infections, and progressive multifocal leukoencephalopathy. Efalizumab is used in the treatment of moderate-to-severe psoriasis, but is not approved for use in patients aged 18 years and younger. Risk of permanent suppression of the immune system exists when this drug is used in children.

For additional information, visit www.fda.gov/bbs/topics/NEWS/2008/NEW01905.html.

Phenytoin and Fosphenytoin Sodium Use Carries Risk

According to the FDA, preliminary data suggest phenytoin (Dilantin®, Pfizer) and fosphenytoin sodium (Cerebyx®, Pfizer) use carries an increased risk of Stevens Johnson Syndrome and toxic epidermal necrolysis in patients testing positive for human leukocyte antigen (HLA) allele HLA B*1502. The allele is found almost exclusively in people with ancestry across large portions of Asia.

For more information, visit www.fda.gov/medwatch/safety/2008/safety08.htm#Phenytoin.

Bevacizumab May Increase Risk of Venous Thromboembolism

A review of data from 7,956 patients with cancer in 15 randomized, controlled trials revealed an increased incidence in venous thromboembolism in patients treated with bevacizumab (Avastin®, Genentech) compared to patients in control arms of the trials (relative risk = 1.33, $p < 0.001$) (Nalluri, Chu, Keresztes, Zhu, & Wu, 2008). Bevacizumab is a monoclonal antibody that inhibits angiogenesis (blood vessel formation) by inhibiting vascular endothelial growth factor (VEGF).

Nalluri, S.R., Chu, D., Keresztes, R., Zhu, X., & Wu, S. (2008). Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients. *JAMA, 300*(19), 2277–2285.

NOTEWORTHY

Workgroup Suggests Smoking Be Added as Indication for Pneumococcal Vaccination

Noting a prevalence of invasive pneumococcal disease similar to that of high-risk asthmatics, the Advisory Committee of Immunization Practices (ACIP) Pneumococcal Vaccines Workgroup has recommended that smoking be added as an indication for pneumococcal vaccination in people aged 19–64 years.

To view the ACIP presentation, visit www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-oct08/04-2-pneu.pdf.

Tick-Borne Infection Reported

A confirmed case of red blood cell transfusion-related infection with *Anaplasma phagocytophilum* has been reported by the Centers for Disease Control and Prevention (CDC). *A. phagocytophilum* is a tick-borne infection that causes anaplasmosis. Polymerase chain reaction assays frequently are able to confirm the presence of the organism, but no cost-effective reliable method currently exists

to screen donors for *A. phagocytophilum*. The CDC recommended considering the possibility of anaplasmosis if post-transfusion thrombocytopenia in the presence of fevers occurs, and suspicion of anaplasmosis should be reported to the CDC. Obviously, in the oncology setting, this is more difficult to evaluate because other factors may be contributing to the common symptoms of anaplasmosis. The disease is relatively rare, but incidences are on the rise in the United States. Because symptoms are initially mild, the potential for donor-pool contamination exists because well-meaning donors may be unaware of the disease.

For more information, visit www.cdc.gov/mmwr/preview/mmwrhtml/mm5742a1.htm.

No Reduced Cancer Benefit Found With the Use of Folic Acid, Vitamin B_6, and Vitamin B_{12}

The Women's Antioxidant and Folic Acid Cardiovascular (WAFAC) study (Zhang et al., 2008) noted no benefit in reducing cancer risk through the use of folic acid, vitamin B_6, and vitamin B_{12}. The study examined cancer incidence in women at high risk for cardiovascular disease, and participants were randomized to receive either placebo (n = 2,721) or a combination of 2.5 mg folic acid, 50 mg vitamin B_6, and 1 mg vitamin B_{12} (n = 2,721) for 7.3 years, ending in July 2005. The incidences of invasive cancer were similar between the two groups with 192 occurrences in the placebo arm and 187 in the treatment arm.

Zhang, S.M., Cook, N.R., Albert, C.M., Gaziano, J.M., Buring, J.E., & Manson, J.E. (2008). Effect of combined folic acid, vitamin B_6, and vitamin B_{12} on cancer risk in women: A randomized trial. *JAMA, 300*(17), 2012–2021.

Vitamin D Use Did Not Reduce Breast Cancer

A large randomized, double-blinded, placebo-controlled trial failed to demonstrate a reduction in breast cancer incidence with daily supplementation of 1,000 mg calcium plus 400 IU vitamin D3 in postmenopausal women followed over an average of seven years (N = 36,282) (Chlebowski et al., 2008). Despite the negative findings, study limitations reveal areas for additional research in relation to vitamin D's potential role in preventing breast cancer. Because this study was limited to postmenopausal women, the effect of starting vitamin D supplementation earlier in life remains an area to explore. Additional studies also may address whether higher doses of vitamin D are required to achieve the desired reduction in breast cancer risk.

Chlebowski, R.T., Johnson, K.C., Kooperberg, C., Pettinger, M., Wactawski-Wende, J., Rohan, T., et al. (2008). Calcium plus vitamin D supplementation and the risk of breast cancer. *Journal of the National Cancer Institute, 100*(22), 1581–1591.

Statin Use May Complicate Prostate Cancer Screening

Researchers caution that the use of statin medications may complicate the detection of prostate cancers by lowering prostate-specific antigen (PSA) levels. For every 10% reduction in low-density lipoprotein (LDL) levels after initiation of statin therapy, PSA was noted to drop an average of 1.64 ($p = 0.001$). The reductions were noted to be most significant in patients with initially high LDL levels and in patients with PSA levels that would have been an indication for biopsy at prestatin levels (Hamilton, Goldberg, Platz, & Freedland, 2008).

Hamilton, R.J., Goldberg, K.C., Platz, E.A., & Freedland, S.J. (2008). The influence of statin medications on prostate-specific antigen levels. *Journal of the National Cancer Institute, 100*(21), 1511–1518.

Late Congestive Heart Failure May Occur One Year After Stem Cell Transplantation

The development of congestive heart failure (CHF) in patients who received hematopoietic stem cell transplantations may occur even one year after transplantation. Interested in identifying independent risk factors, Armenian et al. (2008) examined data from 60 patients out of a cohort of 2,938 treated at the City of Hope National Medical Center in Duarte, CA, who developed CHF one year or more after transplantation. Not surprisingly, the presence of two or more comorbidities and greater lifetime exposure to anthracyclines (250 mg/m^2 or greater) were identified as independent risk factors for the development of CHF one year or more after transplantation. The median time-to-development of CHF in the patients was three years, but in some cases it occurred much later.

The anthracyclines include doxorubicin, daunorubicin, idarubicin, and epirubicin.

Armenian, S.H., Sun, C., Francisco, L., Steinberger, J., Kurian, S., Wong, F.L., et al. (2008). Late congestive heart failure after hematopoietic stem cell transplantation. *Journal of Clinical Oncology, 26*(34), 5537–5543.

PRODUCTS

Docking Station Helps Reduce Risk of Infection in Tubing

Reuse of IV administration sets for intermittent dosing schedules requires the application of a sterile cap to the end of the tubing to prevent contamination when the set is not in use.

An alternative to single-use sterile caps is the PadLock Set Saver® (Baxa Corporation), which is designed as a docking station for the tubing set when disconnected from the patient. Benefits claimed by Baxa include the reduced need for replacement of contaminated IV administration sets and the ability to reuse the same administration set for up to 96 hours.

For more information and to view a demonstration video, visit www.baxa.com/padlock.

Patient Record Storage Offered on Flash Drive

Providing an alternative for patients in storing medical records, My Critical Medical Information Plus™ is a system that combines the use of a secure server as well as personal flash drives that can be worn on a key chain or necklace.

The advantage of the flash-drive approach is that information is more easily accessible in the event of catastrophic events that interfere with more traditional approaches to medical record retrieval.

For more information, visit www.criticalmedicalinformation.com.

Description of products does not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Michael Smart, RN, BSN, OCN®, can be reached at nursemrsmart@aol.com, with copy to editor at ONFEditor@ons.org.

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