PHARMACY CORNER

Accelerated Approval Granted for Leukemia Treatment

The U.S. Food and Drug Administration (FDA) has granted accelerated approval to nilotinib (Tasigna™, Novartis Pharmaceuticals) for the treatment of newly diagnosed chronic phase Philadelphia chromosome–positive chronic myelogenous leukemia. This *Bcr-Abl* kinase inhibitor had previously been approved for patients demonstrating resistance or intolerance to imatinib (Gleevec™, Novartis Pharmaceuticals).

Nurses should be aware that the recommended dosing is different than for the prior approved uses. Usual dosing in this population is 300 mg orally every 12 hours with capsules taken whole with water and on an empty stomach. The reason for the change is that the 300 mg dosing was shown to have similar efficacy with fewer adverse effects compared to the more familiar 400 mg BID dosing. In data presented to the FDA from a single randomized active-control clinical trial, patients (N = 846) were randomized to receive imatinib 400 mg daily (n = 283), nilotinib 300 mg BID (n = 282), or nilotinib 400 mg BID (n = 281). Major molecular responses (MMR) at 12 months were significantly improved in the nilotinib arms ($p < 0.0001$). In the imatinib arm, 22% of patients (n = 63) achieved MMR compared to 44% (n = 125) in the nilotinib 300 mg arm and 43% (n = 120) in the nilotinib 400 mg arm. Patients should be instructed to avoid eating for at least two hours before and one hour after doses of nilotinib. Failure to follow this instruction could result in elevated blood levels of nilotinib and might have an impact on adverse drug effects. Nurses also should be aware that proton pump inhibitors, as well as other medications that decrease gastric acid, may cause a reduction in bioavailability of nilotinib because the drug capsules have a pH-dependent solubility.

Common adverse drug reactions to nilotinib in evaluable patients receiving 300 mg BID (n = 279) included rash (36%), headache (28%), pruritis (19%), nausea (19%), fatigue (19%), constipation (15%), diarrhea (14%), and vomiting (9%). Neutropenia (12%) and thrombocytopenia (10%) also were observed, and complete blood counts should be monitored every two weeks for two months. If the patient's absolute neutrophil count (ANC) falls below 1,000 cells/mm^3, or if the platelet count falls below 50,000 cells/mm^3, the drug should be stopped until counts rise above those levels. If the counts take longer than two weeks to recover, the dose should be reduced to 400 mg once daily. In addition, if grade 3 elevations in serum lipase, amylase, bilirubin, or hepatic transaminases occur, therapy should be interrupted until levels return to grade 1 or lower. At that point, therapy should resume at 400 mg once daily. For patients with hepatic impairment, initial dosing should be 200 mg BID with plans to increase to 300 mg BID if tolerated.

Nilotinib can worsen electrolyte abnormalities and prolong the QT interval on an electrocardiogram. Any electrolyte abnormalities should be corrected prior to initiation of therapy. The drug is contraindicated in the presence of hypokalemia, hypomagnesemia, or long QT syndrome. Electrolyte levels should be monitored during therapy, and, minimally, electrocardiograms should be obtained at baseline, seven days after initiation of therapy, and following dose adjustments. Additionally, drugs known to be strong CYP3A4 inhibitors or known to also prolong the QT interval should be avoided. Sudden deaths have occurred with patients receiving nilotinib, and cardiac effects of the drug may have had a role.

For more information, visit www.accessdata.fda.gov/drugsatfda_docs/label/2010/022068s004s005lbl.pdf.

New Option Available for Refractory Prostate Cancer

The FDA has granted approval to cabazitaxel (Jevtana Injection™, sanofi-aventis) for the treatment of refractory metastatic prostate cancer in combination with prednisone therapy following treatment with a regimen containing docetaxel (Taxotere™, sanofi-aventis). A microtubule inhibitor, the drug belongs to the class of taxanes and is derived by semisynthesis with molecules extracted from yew needles.

Approval was granted based on favorable findings of an international trial (N = 755) comparing cabazitaxel 25 mg/m^2 with prednisone 10 mg per day to mitoxantrone 12 mg/m^2 with prednisone 10 mg per day. The cabazitaxel arm demonstrated median survival of 15.1 months compared to 12.7 months in the mitoxantrone arm ($p < 0.0001$).

Nurses should be aware that premedication, at least 30 minutes prior to therapy, with an antihistamine (diphenhydramine 25 mg or an equivalent), a corticosteroid (dexamethasone 8 mg or an equivalent), and an H_2-receptor antagonist (ranitidine 50 mg or an equivalent) should be given to reduce the chances of severe hypersensitivity reactions. Severe hypersensitivity reactions can occur within minutes of therapy initiation, and nurses should have necessary equipment and medications available in the event of hypotension or bronchospasm.

Additionally, because severe neutropenia may occur, granulocyte–colony-stimulating factor administration should be considered for patients at high risk for the development of neutropenic fevers. During the clinical trial, five deaths related to infectious complications occurred after treatment with cabazitaxel. Four of the patients had grade 4 neutropenia and one had febrile neutropenia. A sixth death occurred in a patient with neutropenia, but infection was not identified. The drug should not be given to patients with an ANC of less than 1,500 cells/mm^3.

Nurses also should monitor for gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Appropriate supportive care measures and education should be given as required. Also, renal function should be monitored because some cases of renal failure have been observed.

The drug should be given at 25 mg/m^2 IV via a 0.22 micrometer inline filter over one hour every three weeks along with daily prednisone 10 mg orally for up to 10 cycles. If patients experience greater than grade 3 neutropenia, despite growth factor support, or neutropenic fever, doses should be held until the ANC has returned to greater than 1,500 cells/mm^3 and febrile neutropenia

has either resolved or improved. Future doses should be reduced to 20 mg/m^2.

Common reactions reported to the FDA from the trial's cabazitaxel arm (n = 371) include anemia (98%), leukopenia (96%), neutropenia (94%, all grades), thrombocytopenia (48%), diarrhea (47%), fatigue (37%), nausea (34%), vomiting (22%), constipation (20%), asthenia (20%), abdominal pain (17%), hematuria (17%), back pain (16%), anorexia (16%), peripheral neuropathy (13%), pyrexia (12%), dyspnea (12%), dysgeusia (11%), arthralgia (11%), and alopecia (10%). Grades 3–4 neutropenia occurred in 82% (n = 303) of the patients treated. Grades 3–4 anemia only occurred in 11% of the patients, and grades 3–4 thrombocytopenia occurred in 4% of the patients.

For more information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm216214.htm.

SAFETY CONCERNS

Safety of Proton Pump Inhibitors Called Into Question

With the toxicities associated with cancer therapies, the use of proton pump inhibitors (PPIs) may seem benign. They do not, however, come without risk. The FDA is examining the potential for increased fracture risk associated with the use of PPIs based on the results of several epidemiologic studies. The risk for fractures may increase with age (older than 50) and with duration of therapy (one year or longer). Fracture risk also may increase with higher doses of PPI therapy. To view the FDA safety announcement and to review the data summary, visit www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm.

Additionally, according to Howell et al. (2010), suppression of gastric acid production also may result in an increased risk for nosocomial *Clostridium difficile* infection. Examining data from 101,796 discharges over five years from one tertiary care center, the researchers noted that the incidence of *C. difficile* rose with the level of acid suppression. Patients not receiving acid-suppression therapy experienced a 0.3% incidence, patients on H_2-receptor antagonist therapy experienced a 0.6% incidence, and patients on daily PPI therapy had a 0.9% incidence rate. Patients on more than daily PPI therapy experienced a 1.4% incidence of *C. difficile*. Although this study is not conclusive regarding the causal relationship between acid suppression and the risk for contracting *C. difficile*, it does highlight the need to be aware of potentially serious adverse consequences of therapies that appear otherwise benign.

Howell, M.D., Novack, V., Grgurich, P., Soulliard, D., Novack, L., Pencina, M., & Talmor, D. (2010). Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Archives of Internal Medicine, 170,* 784–790. doi: 10.1001/archinternmed.2010.89

Acute Myeloid Leukemia Drug Taken Off the Market

In accordance with an FDA request, gemtuzumab ozogamacin (Mylotarg™, Pfizer Inc.) will no longer be available for new patients in the United States. The drug had been granted accelerated approval in 2000 for the treatment of recurrent acute myeloid leukemia (AML) for patients older than 60 when other chemotherapy agents were no longer viable.

Accelerated approval had been granted based on response rates seen among 142 patients with AML. Subsequently, the trial conducted by Pfizer Inc. to determine the benefit of adding gemtuzumab ozogamacin to standard chemotherapy failed to show a benefit as defined by survival time. Instead, more deaths were observed among the patients receiving the drug.

The drug, a humanized monoclonal antibody attached to a more traditional cytotoxic chemotherapy agent, was somewhat novel in its approach to treating cancer.

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216448.htm.

NOTEWORTHY

Coffee Consumption Has No Significant Ties to Colon Cancer

According to Zhang et al. (2010), consumption of coffee does not appear to be significantly contributory to colon cancer incidence. Data were pooled from 13 studies with a total of 731,441 people who were followed over 6–20 years. Consumption of large amounts of coffee (greater than six cups per day) was associated with a relative risk for colon cancer incidence of 1.07 (95% confidence interval [CI] = 0.89–1.3, p [trend] = 0.68) compared to nonconsumers. However, the researchers did note a modest positive correlation for colon cancer incidence (relative risk 1.28, 95% CI = 1.02–1.61, p [trend] = 0.01) with consumers of large amounts of tea (four or more cups per day).

Zhang, X., Albanes, D., Beeson, W.L., van den Brandt, P.A., Buring, J.E., Flood, A., . . . Smith-Warner, S.A. (2010). Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: Pooled analysis of prospective cohort studies. *Journal of the National Cancer Institute, 102,* 771–783. doi: 10.1093/jnci/djq107

PRODUCTS

Dressing Aims to Reduce Bleeding at Catheter Sites

Known risk factors with the placement of central venous catheters include infection and bleeding. Although serious bleeding at the insertion site is not the typical experience, patients with cancer are at an increased risk when thrombocytopenia and other coagulation disorders are present. A product that attempts to address the bleeding and infection risk associated with central lines is the HemCon GuardIVa™ Antimicrobial Hemostatic IV Dressing (HemCon Medical Technologies, Inc.). As the name implies, the dressing uses a hemostatic compound to help minimize bleeding. The dressing also contains chlorhexadine gluconate to reduce the risks for infection.

For more information, visit www.hemcon.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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