PHARMACY CORNER

Denosumab Injection Approved for Skeletal Injury Prevention

The U.S. Food and Drug Administration (FDA) has approved denosumab (Xgeva™, Amgen) to help prevent skeletal injuries in patients with solid tumors that have metastasized and caused bone damage. Previous agents approved for this setting include the bisphosphonates zoledronic acid (Zometa®, Novartis Pharmaceuticals) and pamidronate disodium (Aredia®, Novartis Pharmaceuticals). Denosumab is a fully humanized monoclonal antibody that targets receptor activator of nuclear factor k B ligand—a protein involved in the process of bone destruction by osteoclasts.

In a phase III clinical trial reported by Stopeck et al. (2010), denosumab (n = 1,026) demonstrated superiority compared to zoledronic acid (n = 1,020) in increasing time to first skeletal-related events (pathologic fracture, spinal cord compression, or the need for radiation therapy or surgery to the bones) by 18% (hazard ratio [HR] = 0.82, confidence interval [CI] = 0.71–0.95, p = 0.01) in patients with breast cancer and bone metastases.

A suggested benefit of using denosumab versus zoledronic acid is a decreased risk of renal failure associated with therapy. In the clinical trial comparing the two, zoledronic acid was associated with a 2.5% incidence of renal failure versus 0.2% with denosumab.

Hypocalcemia was observed more frequently following denosumab (5%) than zoledronic acid (3.4%). Patients should be treated as indicated with calcium, magnesium, and vitamin D. Of note, patients with decreased creatinine clearance are at increased risk for experiencing hypocalcemia and should be monitored accordingly.

Compared with zoledronic acid, the incidence of osteonecrosis of the jaw was not significantly different between study arms (2% denosumab, 1.4% zoledronic acid, p = 0.39). Precautionary measures should include a dental evaluation and completion of necessary dental work prior to initiating therapy.

Denosumab is given as a monthly 120 mg subcutaneous injection.

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234346.htm.

Stopeck, A.T., Lipton, A., Body, J.J., Steger, G.G., Tonkin, K., de Boer, R.H., . . . Braun, A. (2010). Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *Journal of Clinical Oncology, 28*, 5132–5139. doi: 10.1200/JCO.2010.29.7101

New Option Available for Metastatic Breast Cancer

The FDA has granted approval for eribulin mesylate (Halaven™ Injection, Eisai Inc.) for treatment of patients with metastatic breast cancer previously treated with at least two other chemotherapy regimens—including an anthracycline and a taxane. Eribulin mesylate is a microtubule inhibitor drug that is an analog of a molecule found in the marine sponge *Halichondria okadai*.

Approval was granted based on the E7389-G000-305 study in which patients were randomized 2:1 to receive eribulin mesylate (n = 508) or another single agent chosen by their physician (n = 254). The majority of the control arm received cytotoxic chemotherapy, and the most common agents chosen were vinorelbine, gemcitabine, capecitabine, a taxane, or an anthracycline. A hormonal agent was chosen as the treatment for 2% of the patients in the control arm. The eribulin mesylate arm demonstrated a statistically improved median overall survival of 13.1 months versus 10.6 months in the control group (p = 0.041).

The drug is dosed at 1.4 mg/m^2 IV over 2–5 minutes on days 1 and 8 of 21-day cycles. The dose should be reduced in patients with renal or hepatic impairment. Common adverse reactions include neutropenia, anemia, asthenia or fatigue, alopecia, peripheral neuropathy, nausea, and constipation. For patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, QT prolongation also may occur, and patients should be monitored appropriately. The most common serious adverse reactions during clinical trials included febrile neutropenia (4%) and neutropenia (2%).

Doses should not be given if the patient has an absolute neutrophil count less than 1,000/mm^3, has a platelet count less than 75,000/mm^3, or is experiencing grade 3 or 4 nonhematologic toxicities. The package insert includes directions regarding when to resume therapy following resolution of toxicities, along with reduced dosage guidelines. Doses should not be escalated once they have been reduced.

For more information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm234527.htm.

Accelerated Approval Granted for Astrocytoma Drug

The FDA has given accelerated approval to everolimus (Afinitor®, Novartis Pharmaceuticals) for treating inoperable subependymal giant cell astrocytoma (SEGA) associated with the rare genetic disorder tuberous sclerosis. Everolimus, an oral drug, is a kinase inhibitor that was previously approved for advanced renal cell carcinoma following treatment failure with sorafenib or sunitinib.

The medication may be given without regard to meals, but it should be given at the same time each day. Dosing for SEGA initially is based on body surface area (BSA) and subsequently adjusted, if needed, based on serum drug concentration troughs and other factors.

Starting everolimus dose should follow these guidelines:

- BSA: 0.5–1.2 m^2; dose: 2.5 mg
- BSA: 1.3–2.1 m^2; dose: 5 mg
- BSA: 2.2 m^2 or higher; dose: 7.5 mg

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm231793.htm.

SAFETY CONCERNS

Cardiac Risks Associated With Antiemetic Drug

The IV form of dolasetron mesylate (Anzemet®, sanofi-aventis) should no longer be used for the prevention of chemotherapy-induced nausea and

vomiting. According to the FDA, postmarketing data demonstrated that dolasetron mesylate can have a dose-dependent adverse effect on the electrical activity of the heart by prolonging QT, QRS, and PR intervals. These changes could lead to fatal changes in heart rhythm, such as torsade de pointes. The oral form of dolasetron mesylate may still be used for chemotherapy-induced nausea and vomiting, but stronger language regarding cardiac risks has been added to package labeling. The risk for adverse cardiac changes is greater in patients who have preexisting cardiac comorbidities. Potassium and magnesium abnormalities should be corrected prior to using dolasetron mesylate.

For more information, visit www.fda.gov/Drugs/DrugSafety/ucm237081.htm.

Manufacturer Takes Darvon, Darvocet Off the Market

Xanodyne Pharmaceuticals has removed its propoxyphene products Darvon® and Darvocet-N® from the market at the request of the FDA. Propoxyphene, a once commonly used opioid analgesic, has been found to be associated with potentially serious arrhythmias. The FDA also has requested that makers of generic propoxyphene formulations remove their products and advised physicians to cease prescribing of propoxyphene.

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234350.htm.

Epoetin Alfa May Impair Trastuzumab Effectiveness

As reported by Liang et al. (2010), use of the red blood cell growth factor epoetin alfa (Epogen®, Amgen) may decrease the effectiveness of trastuzumab (Herceptin®, Genentech) in treating HER2+ breast cancer. Trastuzumab is a monoclonal antibody that targets HER2 receptors. However, breast cancer cells that overexpress HER2 receptors often also express the receptor for epoetin alfa. Researchers theorized that stimulation of epoetin receptors might counteract the therapeutic effect of trastuzumab. A retrospective study compared patients who were treated with trastuzumab and chemotherapy plus epoetin alfa (n = 37) to a control group in which no epoetin alfa was administered (n = 74). After one year, the epoetin alfa group demonstrated a progression-free survival rate of 19% compared to 40% in the control group.

Liang, K., Esteva, F.J., Albarracin, C., Stemke-Hale, K., Lu, Y., Bianchini, G., . . . Fan, Z. (2010). Recombinant human erythropoietin antagonizes trastuzumab treatment of breast cancer cells via Jak2-mediated Src activation and PTEN inactivation. *Cancer Cell, 18,* 423–435. doi: 10.1016/j.ccr.2010.10.025

NOTEWORTHY

Long-Term Aspirin Regimens Reduce Risk of Many Cancers

Use of aspirin previously has been demonstrated to reduce the risk of colorectal cancer. Rothwell et al. (2011) examined whether this benefit extended to other solid tumors. They reviewed data from seven trials with 23,535 patients and 657 cancer-related deaths and noted a reduction in risk of cancer death, but only when aspirin therapy lasted for more than five years (HR = 0.66, CI = 0.5–0.87, p = 0.003). The 20-year benefits of aspirin therapy versus placebo seemed to increase with duration of treatment (greater than 7.5 years) in three other trials (n = 12,659, cancer deaths = 1,634, HR = 0.69, CI = 0.54–0.88, p = 0.003).

The benefits were seen in esophageal, pancreatic, brain, lung, stomach, colorectal, and prostate cancers. However, for esophageal and lung tumors, the benefits were only seen in adenocarcinomas. The benefits of aspirin do not seem related to dosage but were noted to increase with age. Rothwell et al. (2011) reported a 7.08% reduction in risk for cancer death in patients aged 65 years and older.

One explanation for the delayed benefit of aspirin is that the chemopreventive effects may not be beneficial after cells have undergone the molecular changes that eventually lead to cancer. Cancers often take years to develop, and early changes may occur prior to detectability, past which aspirin is no longer of benefit.

Rothwell, P.M., Fowkes, F.G., Belch, J.F., Ogawa, H., Warlow, C.P., & Meade, T.W. (2011). Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomized trials. *Lancet, 377,* 31–44. doi: 10.1016/S0140-6736(10)62110-1

Computed Tomography Screens May Detect Lung Cancer Earlier

Lung cancer remains the most common cause of cancer-related death for men and women in the United States; however, reliable cost-effective screening methods to detect lung cancer in its early stages have been unavailable. But now, for heavy smokers, this may have changed.

Beginning in August 2002, the National Lung Cancer Screening Trial, sponsored by the National Cancer Institute, examined the effects of screening asymptomatic current and former smokers (30 pack-years or greater history, n = 53,500) by low-dose helical computed tomography (CT) versus chest x-ray (CXR). In this randomized study, those who were screened by CT demonstrated an approximate 20% reduction in mortality (354 deaths) compared to the CXR arm (442 deaths).

Screening was performed on participants three times per year. The advantage of early detection is the potential to provide therapeutic measures before cancers have a chance to metastasize.

For more information, visit www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease.

Graphic Photos, Illustrations May Be Required on Cigarettes

The FDA is considering changes to the warnings that must appear in cigarette packaging and advertisements. The new warning language is proposed to be accompanied by very graphic illustrations and photographs that depict the harmful effects of smoking. A foot with a tagged toe protruding from under a sheet, a graveyard full of headstones, and a body lying in an open casket are a few of the photographs proposed. Other examples are more symbolic and abstract in nature, such as a mother blowing smoke into her infant's face to drive home the message that secondhand smoke is harmful.

The Tobacco Control Act requires the FDA to make final rulings on the proposed warnings by June 22, 2011. Assuming the illustrations are approved, the requirement for the warnings to be used will be 15 months after the final ruling.

To view the proposed warnings, visit www.fda.gov/TobaccoProducts/Labeling/CigaretteProductWarningLabels/ucm2024177.htm.

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