PHARMACY CORNER

Patch Targets Nausea, Vomiting

A transdermal formulation of the 5-HT$_3$ inhibitor Sancuso™ (granisetron, ProStrakan Group) has received U.S. Food and Drug Administration (FDA) approval. The patch provides an alternative for patients with dysphagia or for whom daily IV administration is not feasible. The patch is applied to the upper, outer arm. Sancuso is delivered over five days and is indicated for the prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately to highly emetogenic chemotherapy.

The most common adverse reaction associated with Sancuso was constipation (8.7%); some patients experienced mild skin sensitivity from the adhesive patch. Nurses should be aware that any 5HT$_3$ inhibitor may mask symptoms of a progressive ileus or gastric distention.

Zoledronic Acid Helps Prevent Bone Loss

Treatment of younger women with chemotherapy often results in early menopause. A significant consequence of the resulting estrogen deficiency is the onset of early osteoporosis and an increased fracture risk. As reported by Hershman et al. (2008), loss of bone mass in women with early breast cancer may be preventable with the use of the bisphosphonate zoledronic acid (Zometa™, Novartis Pharmaceuticals). Premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer (N = 101) were randomized to receive either placebo or 4 mg zoledronic acid by IV every three months. Eighty-five women completed the 12-month study. Although women in the placebo group demonstrated significant decreases in bone mineral density of the lumbar spine and hip, women treated with zoledronic acid maintained stable bone mineral density ($p < 0.0001$) (Hershman et al.).

Normal bone function includes a continual balance between osteoclastic (bone "destructive") and osteoblastic (bone "building") activity. Zoledronic acid works to maintain bone density by inhibiting osteoclastic processes. The drug also is used in the treatment of hypercalcemia of malignancy, multiple myeloma, and osteolytic metastases from solid tumors. Usage is contraindicated in the presence of renal failure (Osborne, 2002), and caution should be used when given with other nephrotoxic medications. Nurses should monitor for and teach patients the signs and symptoms of osteonecrosis of the jaw, a serious complication associated with bisphosphonate therapy when patients are on treatment (Cope, 2005). No major dental work should be done during therapy, and patients should be instructed to consult with their oncologists prior to any dental procedures as well as make their dentists aware of exposure to zoledronic acid.

Nurses also should be aware of the potential for increased and prolonged hypocalcemia when zoledronic acid is given concomitantly with aminoglycosides or loop diuretics.

Cope, D. (2005). Clinical update: A nonhealing fractured mandible. *Clinical Journal of Oncology Nursing, 9*(6), 685–687.

Hershman, D.L., McMahon, D.J., Crew, K.D., Cremers, S., Irani, D., Cucchiara, G., et al. (2008). Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *Journal of Clinical Oncology, 26*(29), 4739–4745.

Osborne, A. (2002). Zoledronic acid. *Clinical Journal of Oncology Nursing, 6*(6), 365–366.

Palonosetron Hydrochloride Available in Capsule Form

Palonosetron hydrochloride (Aloxi™, Eisai & Hilsinn Healthcare) is now available in a 0.5 mg capsule to be used in the prevention of CINV. The capsule should be given one hour prior to chemotherapy administration and may be taken with or without food. Palonosetron hydrochloride, a 5-HT$_3$ inhibitor, was previously approved for IV formulations of 0.25 mg given over 30 seconds for prevention of CINV and 0.075 mg given over 10 seconds for the prevention of nausea and vomiting after surgery.

For more information, visit www.aloxi.com/PrescribingInformation.aspx.

Cetuximab May Have Benefits for Patients With Head and Neck Cancers

Adding the monoclonal antibody cetuximab (Erbitux®, Bristol-Myers Squibb and ImClone) to platinum-based regimens may have use in the first-line setting for treating squamous cell head and neck cancers. In a study funded by Merck of previously untreated patients (N = 442), patients were randomized to receive standard platinum-based regimens with (n = 222) or without (n = 220) cetuximab. The platinum regimens included fluorouracil along with cisplatin or carboplatin in three-week cycles for a maximum of six cycles. Cetuximab was dosed at 400 mg/m^2 for the initial dose followed by weekly doses at 250 mg/m^2 until disease progression or intolerable toxicities presented. Patients in the cetuximab arm demonstrated improved median overall survival (10.1 months versus 7.4 months, $p = 0.04$) and median progression-free survival time (5.6 months versus 3.3 months, $p < 0.001$) (Vermorken et al., 2008).

Vermorken, J.B., Mesia, R., Rivera, F., Remenar, E., Kawecki, A., Rottey, S., et al. (2008). Platinum-based chemotherapy plus cetuximab in head and neck cancer. *New England Journal of Medicine, 359*(11), 1116–1127.

Platelet Stimulator Approved for Certain Populations

The FDA has approved the thrombopoiesis-stimulating agent 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. Risks associated with romiplostim use include fibrous deposits in the bone marrow and blood clots secondary to excessive increases in platelet counts. Upon cessation of romiplostim therapy, a risk exists for platelet nadirs to be even lower than levels observed prior to therapy initiation. In addition, for patients with myelodysplasia, a risk exists of transformation to acute myeloid leukemia (AML). According to an FDA news release, 4 of 44 patients with myelodysplasia receiving romiplostim developed AML. However, the French-American-British classification of the patients prior to

treatment with romiplostim was not available; therefore, drawing conclusions regarding the role, if any, romiplostim had in the transformation from myelodysplasia to AML is difficult.

A Risk Evaluation and Mitigation Strategy (REMS) has been developed by the FDA for romiplostim that requires all patients and prescribers to enroll in a program for tracking the long-term safety of the drug. A primary purpose of the REMS is to ensure that the benefits of romiplostim continue to outweigh the risks.

ITP is a disease process in which the immune system is involved in the destruction of platelets and sometimes appears to produce auto-antibodies that inhibit 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, visit www.fda.gov/bbs/topicsNEWS/2008NEW01876.html.

New Indications Presented for Pemetrexed

Pemetrexed (Alimta™, Eli Lilly & Co.) has received first-line setting approval in treating nonsquamous non-small cell lung cancer (NS-NSCLC) when combined with cisplatin. Approval was based on a multicenter, randomized, open-label study of 1,725 patients with stage IIIb/IV NSCLC comparing pemetrexed plus cisplatin to gemcitabine plus cisplatin. Similar results were seen in both treatment arms except for patients with squamous cell histology. In this group, a decrease in overall survival was seen in the pemetrexed plus cisplatin arm; therefore, pemetrexed is not an indicated option for patients with squamous cell lung cancer. Previously, this detrimental effect on overall survival was seen in comparisons of pemetrexed versus docetaxel as single agents in patients with previously treated stage III/IV NSCLC. The most common side effects seen with pemetrexed plus cisplatin were nausea (56%), fatigue (43%), vomiting (40%), anemia (33%), neutropenia (29%), anorexia (27%), and constipation (21%).

For more information, visit www.ons.org/news.shtml.

SAFETY CONCERNS

Rituximab Label Reflects Updated Warnings

Package label warnings for rituximab (Rituxan™, Genentech) have been updated to reflect the first reported case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient being treated for rheumatoid arthritis. Many confounding factors existed in the case of PML, including a long history of immunosuppressant therapy; therefore, the contributory nature of rituximab is difficult to determine. However, PML has previously been observed in patients with hematologic malignancies and autoimmune diseases treated with rituximab. PML should be considered when patients treated with rituximab exhibit neurologic changes. Other serious adverse reactions noted with rituximab include fatal infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hepatitis B reactivation, arrhythmias, and angina.

For additional information, visit www.fda.gov/medwatch/safety/2008/safety08.htm#Rituxan.

Vytorin™ May be Linked to Increased Cancer Incidence

The FDA is evaluating a possible link between the use of the combination statin drug ezetimibe-simvastatin (Vytorin™, Merck and Schering-Plough Pharmaceuticals) and cancer incidence. A greater percentage of patients treated with the drug in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial were diagnosed with and died from cancer during the five-year trial compared to patients treated with placebo. The FDA alert regarding an ongoing safety review did not specify how great the percentage was.

Some researchers, however, question the quality of evidence linking statin use and cancer incidence. A systematic review and meta-analysis of 42 studies found no conclusive link between cancer risk and statin usage (Kuoppala, Lamminpaa, & Pukkala, 2008).

In the SEAS Trial, the combination of ezetimibe (Zetia™, Merck and Schering-Plough Pharmaceuticals) and simvastatin (Zocor™, Merck), as the lipid-lowering treatment Vytorin, was hoped to reduce the incidence of major cardiac events in patients with aortic stenosis. However, no benefit was found in reducing the risk for mitral valve replacements, congestive heart failure, or ischemic cardiovascular events.

For additional information, visit www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin_SEAS.htm

Kuoppala, J., Lamminpaa, A., & Pukkala, E. (2008). Statins and cancer: A systematic review and meta-analysis. *European Journal of Cancer, 44*(15), 2122–2132.

Vinca Alkaloid Mishap Leads to Fatality

A fatal error occurred when vindesine, mistaken for methylprednisolone, was administered intrathecally to a 25-year-old woman with non-Hodgkin lymphoma. Although measures to prevent fatal errors involving erroneous intrathecal vincristine have frequently been discussed in the literature, nurses should be aware that all of the vinca alkaloids are similarly fatal when administered via this route (2008 Institute for Safe Medication Practices [ISMP], 2008).

ISMP recommends never having vinca alkaloids in the same room in which intrathecal medications are to be given. Another key recommendation is that vinka alkaloids always be prepared in infusion bags, not syringes, as the larger volume would prevent confusion with intrathecal medications prepared in syringes (2008 ISMP, 2008).

Vinca alkaloids, originally derived from the flower of the periwinkle plant, include vincristine, vinblastine, vinorelbine, and vindesine. In the United States, vindesine is an investigational agent. All of the vinca drugs work by binding to tubulin within the cell nucleus and, therefore, interfering with the formation of the mitotic spindle, key to the process of cell division. As affected tumor cells attempt to divide, apoptosis results.

2008 Institute for Safe Medication Practices. (2008). Safety briefs. *ISMP Medication Safety Alert, 13*(16), 1.

Warnings Issued for Erlotinib Use

Cases of hepatic failure and hepatorenal syndrome, including cases leading to fatality, have been noted with the use of erlotinib (Tarceva™, OSI Pharmaceuticals and Genentech, Inc.). Manufacturer recommendations include stronger warnings to closely monitor hepatic

function in patients with preexisting hepatic impairment. Discontinuation of the drug should be considered when severe changes in hepatic function occur in patients with normal hepatic function before treatment.

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

NOTEWORTHY

Incense Use Linked to Squamous Cell Carcinoma

In a prospective cohort study of 61,320 Singapore Chinese, a correlation was noted between heavy incense use and the development of respiratory squamous cell carcinomas. The cohort was enrolled from 1993–1998 and followed through 2005 for the occurrence of cancer. Incense usage was noted to correlate with an increase in upper respiratory tract carcinomas, but not lung cancer. Duration and intensity of incense use were positively associated with squamous cell carcinomas, but not nonsquamous cell carcinomas. According to Friborg et al. (2008), the relative risk for squamous cell carcinoma in long-term users of incense was 1.8 (95% confidence interval, p = 0.004).

Friborg, J.T., Yuan, J.M., Want, R., Koh, W.P., Lee, H.P., & Yu, M.C. (2008). Incense use and respiratory tract carcinomas: A prospective cohort study. *Cancer, 113*(7), 1676–1684.

National Comprehensive Cancer Network Developing Chemotherapy Order Templates

The National Comprehensive Cancer Network (NCCN) continues to develop its Web site devoted to chemotherapy order templates. The goal of this Web site is to encourage standardized approaches to care, reduce medication errors, and assist in the anticipation and management of adverse events associated with chemotherapy and biologic therapy treatment regimens. The newest order templates include breast, ovarian, and testicular cancer. Other order templates available include bladder, kidney, and prostate cancer, as well as chronic myelogenous leukemia. As many cancers are still not covered, the NCCN site is still not a comprehensive resource when searching for order templates, but the plan is to cover many other treatment regimens and diseases in the future.

For more information, visit the NCCN Web site at www.nccn.org.

Additional Approvals Given for Vulvar and Vaginal Cancer Vaccine

Quadrivalent human papillomavirus (HPV) vaccine (Gardasil™, Merck) is now approved for the prevention of vaginal and vulvar cancers caused by HPV types 16 and 18 in women aged 9–26 years. The approval was based on two-year follow-up data of 15,000 study participants in which about half received the vaccine. None of the participants receiving Gardasil developed precancerous vulvar or vaginal lesions caused by HPV 16 or 18. Of the participants in the control arm of the study, 10 developed vulvar lesions and 9 developed vaginal lesions. Gardasil has already received approval as prevention for cervical cancer, genital warts, cervical adenocarcinoma in situ, and cervical, vulvar, and vaginal intraepithelial neoplasias caused by HPV types 6, 11, 16, and 18.

For more information, visit www.fda.gov/bbs/topics/NEWS/2008/NEW01885.html.

Chemopreventive Effect of Cardiac Medications Studied

Christina, Lapane, Hume, Eaton, and Weinstock (2008) evaluated the potential effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) on the occurrence of keratinocyte carcinomas in a cohort of high-risk patients. Noting that angiotensin is a potent angiogenic agent, researchers theorized that ACE inhibitors and ARBs might have a chemoprotective effect in a cohort of 1,051 high-risk participants followed from November 1998 to January 2003. The combined absolute incidence rates of basal and squamous cell carcinomas were 36.6% fewer in those who used ACE inhibitors and ARBs. No differences were noted in cancer-related mortality. However, because the participants were all high-risk participants in the randomized Department of Veteran Affairs Topical Tretnoin Chemoprevention (VATTC) Trial, generalizing the findings to populations at normal risk for keratinocyte carcinomas is not possible (Christina et al.).

Christina, J.B., Lapane, K.L., Hume, A.L., Eaton, C.B., & Weinstock, M.A. (2008). Association of ACE inhibitors and angiotensin receptor blockers with keratinocyte cancer prevention in the randomized VATTC trial. *Journal of the National Cancer Institute, 100*(17), 1223–1232.

PRODUCTS

Radiopharmaceutical Receives Approval

The diagnostic radiopharmaceutical iobenguane I 123 injection (AndreView™, GM Healthcare) has received FDA approval as an adjunct to other tests in detecting pheochromocytomas and neuroblastomas. Iobenguane accumulates in tumors derived from the neural crest, which contributes to better visualization of these types of tumors when iobenguane I 123 is used.

For additional information, visit www.fda.gov/cder/foi/label/2008/22290lbl.pdf.

Ultrasound May Deliver Chemotherapy Dose

Royal Philips Electronics of the Netherlands is developing ultrasound technology that may one day allow additional options for delivering localized chemotherapy. Currently, ultrasound imaging can be enhanced with the usage of IV-administered gas-filled microbubbles (fewer than 5 mc in diameter) acting as contrast. By giving microbubbles that also encapsulate chemotherapy and then administering a bubble-rupturing ultrasound pulse at the site of the tumor, the hope is to provide an avenue of focused chemotherapy delivery.

The benefit hypothesized is one of increased drug effectiveness at the tumor site with reductions in systemic toxicities.

For more information, including images and video, visit www.philips.com/media.

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Digital Object Identifier: 10.1188/09.ONF.114-116