PHARMACY CORNER

Accelerated Approval Granted for Combination Therapy

The U.S. Food and Drug Administration (FDA) has granted accelerated approval for combination therapy using lapatinib (Tykerb®, GlaxoSmithKline) and letrozole (Femara®, Novartis Pharmaceuticals) to treat postmenopausal women with metastatic breast cancer that is both hormone receptor positive and HER2 positive when hormone therapy is indicated.

Accelerated approval was granted based on the results of a single study, EGF30008, that randomly assigned women with hormone-positive disease who had not been previously treated for metastatic disease (N = 1,286) to receive either letrozole (1,500 mg orally daily) plus placebo or letrozole (1,500 mg orally daily) plus lapatinib (2.5 mg orally daily). In the subgroup of women whose tumors overly expressed the HER2 receptor (n = 219), a significant improvement in progression-free survival (PFS) was seen in the combination treatment arm. PFS in the letrozole plus lapatinib arm was 35.4 weeks, whereas the PFS in the letrozole plus placebo arm was 13 weeks (hazard ratio [HR] = 0.71; p = 0.019).

For additional information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm203522.htm.

Rituximab Now Used to Treat Chronic Lymphocytic Leukemia

The FDA has granted approval for treating chronic lymphocytic leukemia (CLL) with rituximab (Rituxan®, Genentech) when used in combination with fludarabine and cyclophosphamide (FC). Approval was granted based on the findings of improved PFS seen in two randomized, open-label trials comparing rituximab plus FC (R+FC) to FC alone.

In study ML17102 (N = 817), conducted by the German CLL Group, median PFS was 39.8 months in the R+FC group (n = 408) versus 31.5 months in the FC group (n = 409) ($p < 0.01$). Patients in this study had not previously been treated.

The second study, BO17072, was conducted by Roche and Biogen Idec. Patients enrolled (N = 522) had relapsed or refractory CLL following prior treatment with systemic therapy. In this study, median PFS survival was 26.7 months in the R+FC group (n = 276) versus 21.7 months in the FC group (n = 276) ($p = 0.022$).

Treatment regimens for all patients included fludarabine 25 mg/m^2 per day and cyclophosphamide 250 mg/m^2 per day for three days in six 28-day cycles. For patients in the R+FC groups, rituximab was given on the day prior to chemotherapy initiation (i.e., chemotherapy was given on days 2–4). This initial rituximab was dosed at 375 mg/m^2. In subsequent cycles, rituximab was dosed at 500 mg/m^2 and given on the same day as chemotherapy.

For additional information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm201392.htm.

SAFETY CONCERNS

Paroxetine Use May Limit Effectiveness of Tamoxifen

As reported by Kelly et al. (2010), use of paroxetine (Paxil®, GlaxoSmithKline) may reduce or eliminate the effectiveness of tamoxifen (Nolvadex®, AstraZeneca) in preventing breast cancer recurrence based on the results of a population-based retrospective cohort study among women in Ontario, Canada, aged 66 years and older from 1993–2005 and treated concomitantly with paroxetine and tamoxifen (N = 2,430). In addition, the greater amount of time in which these two drug therapies overlapped was positively correlated with an increased risk of death from breast cancer ($p < 0.05$). Simplifying the study results, the researchers estimated that a 41% overlap in treatment time with tamoxifen and paroxetine would result in one additional death for every 19.7 patients treated within five years of tamoxifen cessation (95% confidence interval [CI] 12.5–46.3).

Conversion of tamoxifen into its active components in the body is dependent on metabolism via the cytochrome P450 isoenzyme 2D6 (CYP2D6). Paroxetine was hypothesized to reduce the effectiveness of tamoxifen because it is a potent and irreversible inhibitor of CYP2D6.

This study highlights the need for additional research because depression is seen in almost 25% of patients with breast cancer. The need to manage depression is important, but, as highlighted by this study, the risks versus benefits of any treatment approach should be carefully evaluated. Of note, Kelly et al. (2010) did not see an increased risk of death from breast cancer with the use of other antidepressants.

In addition, the study did not provide data on the effect of paroxetine use with tamoxifen in premenopausal patients. Tamoxifen use has decreased in postmenopausal women because aromatase-inhibitors have become the standard of care in this population.

Kelly, C.M., Juurlink, D.N., Gomes, T., Duong-Hua, M., Pritchard, K.I., Austin, P.C., & Paszat, L.F. (2010). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. *BMJ, 340*, c693. doi: 10.1136/bmj.c693

Program Evaluates Risks With Erythropoiesis-Stimulating Agents

Citing an increased risk for tumor progression and increased mortality with the use of erythropoiesis-stimulating agents (ESAs), the FDA is now requiring that these agents only be administered under a Risk Evaluation and Mitigation Strategy (REMS) program. ESAs include epoetin alfa (Epogen®, Amgen Inc.; Procrit®, Ortho Biotech, Inc.) and darbepoetin alfa (Aranesp®, Amgen Inc.). These drugs have been commonly used to treat anemia in patients with cancer. The arguments for use in the oncology setting had included improvements in quality of life with a reduction in the need for red blood cell transfusions, but concerns regarding safety have persisted with reports of increased incidence of blood clots as well as other conditions.

Healthcare providers wishing to prescribe ESAs to patients with cancer must now enroll in the FDA's ESA APPRISE Oncology program.

For additional information, visit www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm.

NOTEWORTHY

Study Links Soft Drinks to Pancreatic Cancer

The wisdom of "upsizing" one's soft drink is called into question by data from the Singapore Chinese Health Study. As reported by Mueller et al. (2010), regular consumption of sugarized carbonated beverages appears to increase the risk for pancreatic cancer. The Singapore Chinese Health Study, which has followed 60,524 participants over 14 years, noted an incidence of 140 cases of pancreatic cancer. In examining lifestyle factors, regular consumption of soft drinks (two or more per week) was identified as significantly associated with pancreatic cancer risk (HR = 1.87; 95% CI 1.1–3.15). Researchers also had theorized that consumption of juices would be identified as a risk factor associated with pancreatic cancer, but this was not found to be true in the cohort.

Mueller, N.T., Odegaard, A., Anderson, K., Yuan, J.M., Gross, M., Koh, W.P., & Pereira, M.A. (2010). Soft drink and juice consumption and risk of pancreatic cancer: The Singapore Chinese Health Study. *Cancer Epidemiology, Biomarkers, and Prevention, 19,* 447–455. doi: 10.1158/1055-9965.EPI-09-0862

Smoking Cessation May Reduce Mortality Rate After Diagnosis

Smoking cessation can seem like a hard sell to the smoker already diagnosed with lung cancer. Overcoming the belief that the "damage has already been done" with no benefit to be seen from quitting is a significant hurdle. As nurses, education should be provided to patients regarding the benefits of cessation from a symptom management standpoint.

Additionally, according to Parsons, Daley, Begh, and Aveyard (2010), a prognostic benefit may be found in smoking cessation at least for patients diagnosed with early-stage lung cancer. The authors noted that a significantly increased mortality rate was seen in patients with early-stage non-small cell lung cancer who continued smoking after diagnosis (HR = 2.94; 95% CI 1.15–7.54).

Parsons, A., Daley, A., Begh, R., & Aveyard, P. (2010). Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: Systematic review of observational studies with meta-analysis. *BMJ, 340,* b5569. doi: 10.1136/bmj.b5569

Symptom Screening Not Helpful for Ovarian Cancer Detection

Early detection of ovarian cancer, as with most cancers, is an important factor in successful treatment. Unfortunately, reliable methods to screen for early ovarian cancer are lacking, and use of reported symptoms often is unhelpful as a screening method. As reported by Rossing, Wicklund, Cushing-Haugen, and Weiss (2010), use of symptoms as a method to determine the need for additional evaluation of ovarian cancer is likely to detect disease in only 1 of 100 women. Better screening methods are still needed. At issue with the use of symptoms as a screening tool is that the symptoms often are vague, subjective, and frequently associated with other conditions.

Rossing, M.A., Wicklund, K.G., Cushing-Haugen, K.L., & Weiss, N.S. (2010). Predictive value of symptoms for early detection of ovarian cancer. *Journal of the National Cancer Institute, 102,* 222–229. doi: 10.1093/jnci/djp500

Contralateral Mastectomy Seen as Minor Benefit to Survival

To reduce the recurrence risk of breast cancer, some women choose to have bilateral mastectomies, even when the cancer only is seen in one breast. The rationale is that once breast cancer occurs, the chances of cancer occurring in the contralateral breast increases. However, a mastectomy is not a minor procedure, and it would be useful to have evidence indicating that this approach to prevention is effective.

Bedrosian, Hu, and Chang (2010) examined this question of benefit and reported a "small improvement" in five-year survival among women with breast cancer who had subsequently undergone contralateral prophylactic mastectomy (CPM). An observational study, data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. In the period from 1988–2003, 107,106 women were identified who underwent mastectomy as treatment, and a subset of 8,902 women who underwent CPM were identified. The survival benefit was associated with CPM (HR of death = 0.63; 95% CI 0.57–0.69; $p < 0.001$). However, it should be noted that this benefit was largely seen in younger women who had presented with early-stage estrogen receptor–negative tumors. Presumably, this benefit is related to the higher baseline risk in contralateral tumors in this group.

Bedrosian, I., Hu, C., & Chang, G.J. (2010). Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *Journal of the National Cancer Institute, 102,* 401–409. doi: 10.1093/jnci/djq018

Monoclonal Antibodies May Treat *Clostridium Difficile*

Although not currently an approved approach to treatment, monoclonal antibody therapies may play a role in the future treatment of *Clostridium difficile* intestinal infections.

Patients with *C. difficile* typically exhibit severe diarrhea that places them at increased risk for dehydration and dangerous electrolyte imbalances. Patients who are immunocompromised, such as those seen in the oncology setting, are at increased risk for contracting *C. difficile*. Strains of *C. difficile* that are resistant to traditional treatment approaches with metronidazole and oral vancomycin have emerged. The incidence, severity, and recurrence following treatment have all been on the rise.

As reported by Lowy et al. (2010), a randomized study of patients with *C. difficile* (N = 200) showed that the addition of fully human monoclonal antibodies against *C. difficile* toxins A and B to standard therapy resulted in dramatic reductions in recurrence rate versus standard therapy plus placebo. After 84 days, the recurrence rate in the treatment arm was 7% versus 25% in the placebo group (95% CI 7–29; $p < 0.001$).

Lowy, I., Molrine, D.C., Leav, B.A., Blair, B.M., Baxter, R., & Gerding, D.N. (2010). Treatment with monoclonal antibodies against clostridium difficile infections. *New England Journal of Medicine, 362,* 197–205. doi: 10.1056/NEJMoa0907635

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