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.