Exemestane is Effective for the Chemoprevention of Breast Cancer

A recent study shows that the aromatase inhibitor exemestane is useful for the chemoprevention of breast cancer in postmenopausal women who are at a moderately increased risk of the disease (N Engl J Med. 2011; 364:2381-2391).

Paul Goss, MD, PhD, professor of medicine at Harvard Medical School and director of breast cancer research at Massachusetts General Hospital in Boston, and colleagues reported results of the randomized, double-blind, phase 3 National Cancer Institute of Canada Clinical Trials Group Mammary Prevention Trial. Results showed that invasive breast cancer incidence was reduced by 65% with exemestane versus placebo.

Dr. Goss says this trial provides postmenopausal women with another option for the chemoprevention of breast cancer. “It seems that exemestane is safer than other chemoprevention options,” he says. “The efficacy is at least as good or better for chemoprevention based on indirect comparisons, and it has previously been established as better in preventing breast cancer recurrence in randomized trials comparing tamoxifen and exemestane in patients with early breast cancer.”

Current Approaches

Two selective estrogen receptor modulators, tamoxifen and raloxifene, are currently approved by the US Food and Drug Administration for the chemoprevention of breast cancer. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial, which included 13,388 women, tamoxifen significantly reduced the incidence of invasive breast cancer by 49% compared with placebo (J Natl Cancer Inst. 1998;90:1371-1388). Women were eligible for the P-1 trial if they had at least one of the following risk factors: age 60 years or older (49% of participants); Gail model 5-year breast cancer risk score greater than 1.66% (40% of participants); and prior breast biopsy showing atypical ductal or lobular hyperplasia or LCIS, or prior DCIS treated with mastectomy (11% of participants). Women with prior invasive breast cancer or DCIS who were treated with lumpectomy were excluded. Mammograms were done within 12 months of randomization and every 12 months from the time of the initial mammogram during and after the treatment. The exemestane and placebo groups were well balanced for race, body mass index (BMI), and breast cancer risk factors.

At a median follow-up of 35 months, 11 invasive breast cancers were diagnosed in the exemestane group versus 32 in the women treated with placebo, giving a significant reduction. Subsequently, the NSABP P-2 study, which included 19,747 women, reported similar efficacy in breast cancer prevention using tamoxifen or raloxifene (JAMA. 2006;295:2727-2741). The P-2 trial included only postmenopausal women with a Gail model 5-year breast cancer risk score of 1.66% or greater. Both trials excluded women with a history of invasive breast cancer or ductal carcinoma in situ (DCIS).

In an update of the NSABP P-2 trial, raloxifene was found to have 76% of the effectiveness of tamoxifen for the prevention of invasive breast cancer, but caused significantly less uterine cancer and fewer thrombembolic events (Cancer Prev Res (Phila). 2010;3:696-706). Despite the proven efficacy, the uptake of tamoxifen or raloxifene for breast cancer prevention has been low, possibly because of associated toxicities.

Study Findings

The current trial randomized 4560 women to receive either exemestane or placebo. In addition to being postmenopausal, participants also had to have one of the following characteristics: age 60 years or older (49% of participants); Gail model 5-year breast cancer risk score greater than 1.66% (40% of participants); and prior breast biopsy showing atypical ductal or lobular hyperplasia or LCIS, or prior DCIS treated with mastectomy (11% of participants). Women with prior invasive breast cancer or DCIS who were treated with lumpectomy were excluded. Mammograms were done within 12 months of randomization and every 12 months from the time of the initial mammogram during and after the treatment. The exemestane and placebo groups were well balanced for race, body mass index (BMI), and breast cancer risk factors.

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65% relative reduction in the annual incidence of breast cancer (annual incidence of 0.19% with exemestane vs 0.55% with placebo). Exemestane appeared to be superior to placebo in all prespecified subgroups: concurrent use of low-dose aspirin; Gail model 5-year breast cancer risk score; age; BMI; prior atypical ductal hyperplasia, atypical lobular hyperplasia, or LCIS; and DCIS treated with mastectomy. The incidence of invasive breast cancer plus DCIS was lower in the exemestane group (20 vs 44 in the placebo group, for a hazard ratio [HR] of 0.47). In addition, the combined incidence of LCIS, atypical ductal hyperplasia, and atypical lobular hyperplasia was 4 in the exemestane group versus 11 in the placebo group, for an HR of 0.36. To prevent one case of invasive breast cancer, 94 women would need to be treated with exemestane for 3 years. The authors projected that this number would be 26 with 5 years of exemestane; however, few women had completed 5 years of therapy at the time of the final analysis.

Arthritis and hot flashes were significantly more frequent in the exemestane group, but differences in the incidence of grade 2 or higher toxicity were not large (6.5% vs 4% for arthritis and 18.3% vs 11.9% for hot flashes). There were no significant differences for exemestane versus placebo with regard to prespecified secondary endpoints of toxicity, including new cases of osteoporosis, fracture rates, occurrence of cancers other than breast, quality-of-life measures, or cardiovascular events. No serious adverse events or end-organ toxicities, including fractures, were found to be caused by exemestane.

Dr. Goss says his group next plans to study how mammographic findings, concurrent bisphosphonate use, and ethnicity may help to identify subgroups of women who may benefit more from such outcomes. “We also have serum and tumor tissue on most women and we plan tumor signature and host pharmacogenomic studies,” he says.

Study Limitations and Implications

The authors note that the median follow-up of 3 years is relatively short and the total number of breast cancer events was small. The preventive effect, however, appears strong and the safety profile was quite good. The protocol-specified number of events was reached and women on placebo, after unblinding, will now be offered the option to receive exemestane. Dr. Goss says the bottom line for clinicians is that women meeting the criteria for entry in this study should consider a trial of exemestane for an initial period of about 3 months. If they are tolerating it well, they should then consider taking 3 to 5 years of therapy with bone mineral assessment at baseline and appropriate treatment and follow-up of bone density as needed.

Otis Brawley, MD, chief medical and scientific officer of the American Cancer Society, says that for now he prefers tamoxifen and raloxifene for breast cancer prevention. “My concern is that the trial was relatively short and the side effects of aromatase inhibitors, especially osteoporosis, are significant,” he says. He adds, however, that the study shows that women concerned about breast cancer can reduce their risk with these drugs and an overall education curriculum for clinicians needs to stress prevention.