Risk Greater With Progestin Use

Hormone Therapy *from page 1*

known menopausal status, or who had an unknown history of hormone therapy.

Of the remaining 56,867 perimenopausal and postmenopausal teachers, 2,857 women (5%) were diagnosed with pathologically confirmed invasive breast cancer through December 2006, after a mean follow-up of 9.8 years. The average age at diagnosis was 67.1 years.

In a multivariate analysis, the investigators adjusted for race/ethnicity, first-degree family history of breast cancer, BMI, smoking history, alcohol consumption during the year prior to baseline, mammographic screening over the prior 2 years, parity and age at first full-term pregnancy, age at menarche, age at menopause, and history of breast biopsy.

Compared with women who never used any hormone therapy, those who did use it had a statistically significant 40% increase in the risk of breast cancer.

The increase in risk was 19% for women who reported at least 15 years of estrogen-alone therapy, and 83% in women who reported at least 15 years of taking combined estrogen-progestin therapy.

Current use of hormonal therapy was associated with higher risk than past use. The greatest increase in risk—69%—was among women who were using estrogen-progestin therapy currently and had never used any other formulation. The investigators noted that duration of use tended to be shorter among former users.

The longer the women used hormone therapy, the greater the risk. The increase associated with duration of use was statistically significant for all forms of hormone therapy. For example, women using estrogen-progestin therapy for less than 2 years at baseline had a 12% increase in the risk of breast cancer compared with women who never used hormone therapy. The increase in risk was 42% for those using estrogen-progestin therapy for 3-5 years, 50% at 6-9 years, 67% at 10-14 years, 79% at 15-19 years, and 92% at 20 years or more.

Among current users of hormonal therapy, the association with breast cancer risk was statistically significant only for tumors that were both estrogen receptor–positive and progesterone receptor–positive, with increased risks of 33% in women who had 15 or more years of estrogen therapy and 84% in those who had been on estrogen and progestin for 15 years or more.

The risks were even higher for women whose tumors were also HER2 positive, but the investigators suggested this might be a statistical fluke because of the small numbers involved. No association was seen between long duration of hormone use and triple-negative tumors.

BMI seemed to modify the risk associated with hormonal therapy, the investigators reported.

Among women with a BMI of 25 or less, the relative risk of breast cancer was 2.1 in current long-term users of estrogen and progestin, compared with women who had never used hormone therapy (P less than .0001). In women with a BMI of 25-30, the relative risk was 1.9 in current long-term users of estrogen and progestin (P less than .0001). However, the effect was not statistically significant in women with a body mass index higher than 30 (RR 1.2, $P = .11$). ■

VITALS

Major Finding: Compared with women who have never used hormone replacement therapy, those who used estrogen therapy for 15 years or more had a 19% greater risk of breast cancer, and those who used combined estrogen-progestin therapy had an 83% greater risk.

Data Source: Prospective observational study of 56,867 perimenopausal and postmenopausal women participating in the California Teachers Study.

Disclosures: The National Cancer Institute and the California Breast Cancer Research Fund sponsored the study. A coauthor disclosed serving as an expert witness for plaintiffs pursuing Prempro litigation.

Aromatase Inhibitor Recommended for Subset of Breast Ca

PBY MARY ANN MOON

FROM THE JOURNAL OF CLINICAL ONCOLOGY

An aromatase inhibitor should be considered as adjuvant therapy for all postmenopausal women with hormone receptor–positive breast cancer, according to an updated American Society of Clinical Oncology clinical practice guideline.

The optimal timing and duration of aromatase inhibitor (AI) treatment are not yet resolved, but it appears to reduce the risk of recurrence when taken at some time during adjuvant therapy—either alone as monotherapy, as sequential therapy before tamoxifen therapy commences or after 2-3 years of tamoxifen treatment, or as extended therapy after 5 years of tamoxifen is completed, said Dr. Harold J. Burstein of the Dana-Farber Cancer Institute, Boston, and his associates on ASCO's Endocrine Therapy for Breast Cancer Update Committee.

The last update on the adjuvant use of AIs for hormone receptor–positive breast cancer was published in 2004. "Our panel carefully reviewed the explosion of research that has emerged in the past 5 years on anti-estrogen drugs, and filled in gaps in our understanding of how best to use these newer treatments, and what the trade-offs and side effects of therapy would be," Dr. Burstein noted in a press statement accompanying the new guideline.

The review by the expert panel focused on 12 prospective randomized clinical trials gleaned from 484 articles or abstracts from the medical literature, presentations, or posters.

The data are somewhat limited. Most of the studies had relatively short follow-up times, and the longest median follow-up was a period of only 8 years. Because of that and patients' generally favorable prognoses, few breast cancer events occurred during follow-up.

In addition, the assessment of important subgroups of patients was limited by relatively small sample sizes, and the small samples also limited analysis of quality-of-life data, according to Dr. Burstein and his colleagues (J. Clin. Oncol. 2010 [doi:10.1200/JCO.2009.26.3756]).

Among the committee's major findings:

► Adding an AI to adjuvant therapy improves disease-free survival and reduces the risk of distant metastasis, locoregional recurrence, and contralateral breast cancer. The reduction is modest—typically less than 5% over several years—but these outcomes are clinically important to patients. Only a few trials demonstrated a statistically significant increase in overall survival.

► AI therapy should not extend beyond a period of 5 years, as either initial or extended adjuvant treatment, because results on longer-term treatment are not yet available.

► The optimal length of time before switching from tamoxifen to an AI is unknown. For sequential treatment, patients should receive an AI after 2-3 years of tamoxifen, for a total of 5 years of adjuvant endocrine therapy. Alternatively, patients who begin an AI but discontinue it before 5 years have elapsed can consider taking tamoxifen until a total of 5 years of endocrine therapy accrue. For extended therapy, patients can be offered an AI after they have taken 5 years of tamoxifen. The data on extended therapy, however, are not as extensive as with sequential therapy.

Adding an aromatase inhibitor to adjuvant therapy improves disease-free survival and reduces the risk of distant metastasis, locoregional recurrence, and contralateral breast cancer.

► As of now, no clinically important differences in effectiveness have been reported among the three commercially available aromatase inhibitors (anastrozole, letrozole, and exemestane).

► Research to date has not revealed a specific marker that identifies patients most likely to benefit from AI therapy, nor a clinical subset of patients most likely to benefit.

► AIs generally are well tolerated by patients. The drugs have been linked to increased risk of hypercholesterolemia and hypertension, and possibly of cardiovascular disease, but longer follow-up is needed to determine potential cardiovascular toxicity.

AIs also frequently cause a mild to moderate musculoskeletal/arthralgia syndrome. They have been associated with a greater loss of bone mineral density and a 2%-4% increased risk of fracture, compared with tamoxifen, but the long-term impact of treatment on bone is not yet known.

AIs appear to have fewer gynecologic adverse effects than tamoxifen. An increased risk of uterine cancer, benign endometrial pathology, hysterectomy, and vaginal discharge has not yet been noted with AIs, as it has with tamoxifen. AIs may produce fewer hot flashes and less vaginal dryness than tamoxifen.

The committee stressed that the late effects of AI therapy, as well as the possible adverse effects of extended AI therapy, have not yet been fully characterized. The committee also noted that there is no evidence yet for or against the usefulness of AI therapy in men with breast cancer.

To facilitate treatment adherence, the updated guideline emphasized that clinicians should alert their patients to common adverse effects and potential toxicities of AIs. Research shows that up to 40% of patients discontinue tamoxifen within 3 years and half do so within 5 years, and the findings with AIs are similar. The clear majority of patients who stop treatment prematurely do so because of adverse effects.

In particular, the musculoskeletal effects of AIs prompted discontinuation in more than 10% of women in one study. "Information support for patients about anticipated adverse effects and management of those adverse effects may increase persistence," according to the guideline.

Monetary constraints are another cause of nonadherence with AI therapy. In one study of patients taking tamoxifen, 60% of those who discontinued treatment early said that the cost of the drug was a key factor. "It is likely that the out-of-pocket costs of AIs pose an even greater barrier to patients," the committee said.

The complete clinical practice guideline is available online at www.asco.org/guidelines/endocrinebreast. A corresponding patient guide is available on ASCO's patient Web site, www.cancer.net. ■

Disclosures: *Some of the update committee members reported ties to Pfizer, Novartis, and AstraZeneca.*