Exemestane Beneficial After Adjuvant Tamoxifen

BY BRUCE JANCIN
Denver Bureau

San Antonio — Breast cancer patients randomized to exemestane following 5 years of adjuvant tamoxifen were 56% less likely to experience a relapse than were those assigned instead to placebo in the National Surgical Adjuvant Breast and Bowel Project B-33 trial, Dr. Terry P. Mamounas said at a breast cancer symposium that was sponsored by the Cancer Therapy and Research Center.

This result underestimates the benefits of a course of exemestane (Aromasin) following tamoxifen, since 44% of participants randomized to placebo in the prematurely halted B-33 trial crossed over to exemestane and were on the aromatase inhibitor (AI) for much of the median 30-month follow-up, even though for the intent-to-treat analysis they were counted in the placebo arm, noted Dr. Mamounas, medical director of the Aultman Cancer Center in Canton, Ohio.

The NSABP B-33 trial thus shows that exemestane, like the other two approved AIs, is effective when employed in what has come to be called the extended adjuvant hormonal therapy strategy. This was previously shown to be the case for 5 years of letrozole (Femara) following 5 years of tamoxifen in the National Cancer Institute of Canada MA.17 trial, and for 5 years of anastrozole (Arimidex) after 5 years of tamoxifen in the Austrian Breast and Colorectal Cancer Study Group Trial 6.

Five years of tamoxifen—long the standard for adjuvant hormonal therapy in breast cancer—has given way to three alternative AI-based strategies, each shown in large randomized trials to be more effective than the former standard, although the alternatives haven't been tested head-to-head.

One strategy involves substituting 5 years of an AI for 5 years of tamoxifen. Another entails sequential therapy with 2-3 years of tamoxifen followed by an AI for the balance of a 5-year course of treatment.

The extended adjuvant therapy strategy is attractive for several reasons. More than half of breast cancer recurrences and more than two-thirds of deaths occur after 5 years on tamoxifen have ended. Most of these recurrent tumors remain hormone sensitive. And as shown in the NSABP B-14 trial, extending tamoxifen beyond 5 years gives no additional benefit, he said.

The double-blind B-33 trial was halted after enrollment of 1,598 of a planned 3,000 postmenopausal women who had completed 5 years of tamoxifen for hormone receptor–positive early-stage breast cancer. B-33 was stopped because of the announcement in October 2003 that the Canadian MA.17 trial had shown a dramatic advantage for letrozole over placebo for extended adjuvant therapy. The B-33 investigators decided for ethical reasons to unblind their study and offer exemestane free to the placebo group.

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DR. MAMOUNAS

In Dr. Mamounas' intent-to-treat analysis at a median follow-up of 30 months, there were 17 recurrences in 783 patients in the group originally assigned to exemestane, representing a 56% relative risk reduction, compared with the placebo arm. The 4-year estimated disease-free survival rate was 91% in the exemestane group and 89% in the placebo arm, which was of borderline significance.

Of the patients randomized to exemestane, 10% experienced grade 3 or 4 toxicities. The most common were arthralgia, fatigue, and bone pain. As of May 2006, 46 patients in the exemestane group had fractures, as did 40 in the placebo group. According to Dr. Mamounas, the toxicities associated with exemestane are "acceptable for the adjuvant setting."

The increase in relapse- and disease-free survival observed with exemestane in the B-33 trial were of similar magnitude to the benefits seen with the other AIs in earlier clinical trials of extended adjuvant hormonal therapy, he added.

Dr. Mamounas is on the speakers bureaus and is a consultant for Pfizer Inc., which markets exemestane, Novartis, which makes letrozole, and AstraZeneca, which markets anastrozole. ■