Extended Hormone Therapy May Be of Benefit

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SAN ANTONIO — Women who were premenopausal at diagnosis of early-stage breast cancer and subsequently completed 5 years of adjuvant tamoxifen derived additional benefit from extended aromatase inhibitor therapy, according to a new secondary analysis of a landmark clinical trial.

Five years of extended aromatase inhibitor therapy led to significantly improved disease-free survival in the National Cancer Institute of Canada Clinical Trials Group MA 17 trial, even with a median 3-year and maximum 6-year delay between completion of the tamoxifen regimen and the start of letrozole, Dr. Paul E. Goss reported at the San Antonio Breast Cancer Symposium.

Previous results from MA 17 led to regulatory approval of 5 years of letrozole following 5 years of adjuvant tamoxifen in patients with early-stage breast cancer. However, since most trials of early adjuvant aromatase inhibitor therapy required participants to be postmenopausal at diagnosis of their breast cancer, up until now the common clinical practice in low-risk women with premenopausal breast cancer has been to give 5 years of tamoxifen and then stop.

The new MA 17 analysis found that extended aromatase inhibitor therapy is beneficial in women who are premenopausal at diagnosis and become postmenopausal before or during adjuvant tamoxifen therapy. Such patients actually derived greater benefit than did women who were postmenopausal at diagnosis, according to Dr. Goss, director of breast cancer research at Massachusetts General Hospital and professor of medicine at Harvard Medical School, Boston.

Indeed, breast cancer patients who are premenopausal at diagnosis but become postmenopausal before or during tamoxifen therapy should routinely be considered for 5 years of extended aromatase inhibitor therapy, he added.

The MA 17 trial included 889 women who were premenopausal and 4,277 who were postmenopausal at the time of their primary cancer diagnosis. There were nine recurrences in 424 premenopausal-at-diagnosis patients randomized to letrozole after tamoxifen, which translated to an absolute 10.1% advantage in 4-year disease-free survival over the premenopausal-at-diagnosis group assigned to placebo following tamoxifen (Hazard ratio = 0.25, $P = .0001$).

In contrast, there were 83 recurrences among 2,157 postmenopausal women who got extended adjuvant therapy with letrozole, for an absolute 3.3% improvement over placebo in terms of 4-year disease-free survival (HR = 0.69,P = .0008). Recurrence was 61% less likely in letrozole-treated women who were premenopausal at diagnosis of their primary breast cancer than in those who were postmenopausal at that time.

Particularly striking was the advantage conferred by extended aromatase inhibitor therapy in women with node-negative premenopausal breast cancer. Their 4-year disease-free survival was 100% compared to 88.5% in those on placebo, for an absolute 11.5% difference, which Dr. Goss called "remarkable."

The benefit of extended adjuvant therapy was similar in the 290 women with premenopausal breast cancer who didn't start adjuvant letrozole until a median of 3 and maximum of 6 years after they completed their tamoxifen regimen and in those who started letrozole directly after tamoxifen. The 5-year disease-free survival in the delayed-start group with premenopausal breast cancer was an absolute 8.2% better than in 135 others who elected not to go on the aromatase inhibitor.

The same trends seen in disease-free survival were noted in terms of the end point of 4-year distant disease-free survival.

Women with premenopausal breast cancer tolerated letrozole well. They had a 24% incidence of arthralgia compared to 16% with placebo, but only a 10% rate of vaginal bleeding vs. 16% with placebo. Letrozole-treated women with postmenopausal breast cancer had significantly higher rates of hot flashes than with placebo, by a margin of 55% to 50%, as well as arthralgia (25% vs. 21%), myalgia (15% vs. 12%), and hair loss (5% vs. 3%). Dr. Goss is on the speakers bureaus for Novartis, Wyeth, and GlaxoSmithKline. ■