

EDITORIAL



Beyond Tamoxifen — Extending Endocrine Treatment for Early-Stage Breast Cancer

Harold J. Burstein, M.D., Ph.D.

Five years of tamoxifen therapy is the standard adjuvant endocrine therapy for early-stage, hormone-receptor–positive breast cancer.^{1–3} Randomized trials have demonstrated the superiority of five years of treatment over shorter durations for the prevention of a recurrence,^{4,5} as well as a carryover effect that lowers the risk of recurrence for a decade after the completion of five years of tamoxifen therapy and reduces the incidence of contralateral breast cancer. By contrast, several randomized trials have shown that continuing tamoxifen therapy for longer than five years does not improve recurrence-free or overall survival^{6–9} and have raised the disturbing possibility that such a strategy might be deleterious.

Even after five years of tamoxifen therapy, women are at risk for a recurrence in the ipsilateral breast, new tumors in the contralateral breast, and distant metastases. These new events occur at an aggregate rate of 2 to 3 percent per year. Since most of these recurrent or new tumors express hormone receptors, they may be sensitive to further endocrine manipulations. It is against this background that the results of the letrozole trial, led by the National Cancer Institute of Canada on behalf of several cooperative groups and the pharmaceutical company Novartis and reported by Goss et al.¹⁰ in this issue of the *Journal*, are greeted with interest. Letrozole, like other aromatase inhibitors, inhibits the peripheral conversion of androgens into estrogens and reduces the circulating levels of estrogens by more than 95 percent in postmenopausal women.¹¹ It has clinically significant activity in postmenopausal women with advanced breast cancer. The study by Goss et al. investigated whether extended adjuvant therapy with letrozole after five years of tamoxifen therapy

confers a clinical advantage in patients with breast cancer. The question is of particular importance because postmenopausal women with hormone-receptor–positive breast cancer constitute by far the largest demographic group in which breast cancer is diagnosed, and each year hundreds of thousands of women worldwide finish five years of adjuvant tamoxifen therapy.

This placebo-controlled trial recruited more than 5000 women and was designed to mirror routine management in its selection of patients. The primary end point was disease-free survival. A planned interim analysis that was conducted after a median of only 2.4 years of follow-up indicated that the rate of disease-free survival was significantly higher in the letrozole group than in the placebo group (hazard ratio for a recurrence or new contralateral breast cancer in the letrozole group as compared with the placebo group, 0.57; $P < 0.001$). This translates into an absolute difference of 2.2 percent in the rate of breast-cancer events, including distant metastases, ipsilateral recurrences, and new contralateral breast cancers, with an actuarial projection of an absolute difference of 6 percent in the rate of events over four years of follow-up. There was no significant difference in overall survival. The unexpected and robust difference in the rate of events led to the early termination of the study.

Does this result mean that all women who are completing five years of tamoxifen therapy should move on to letrozole therapy? At first glance, one is inclined to say yes. In the short term, the switch to letrozole appears to reduce the risk of tumor recurrence by nearly half. And because women are understandably motivated to prevent recurrences of can-

cer, the absolute difference of 2.2 percent is likely to encourage many to consider letrozole therapy, even in the absence of an overall survival advantage.

There are, however, important caveats. First, the follow-up period in this trial was exceptionally short. None of the women have as yet received the planned five years of therapy with letrozole, and less than 1 percent of the women have received four years of treatment. Because of the early termination of the trial, one can say only that letrozole treatment for a period of two to three years has been evaluated and that the optimal duration of such therapy has not been established.

The second major consideration is the price that is paid for the consequences of profound estrogen deprivation in postmenopausal women. Previous studies have shown that aromatase inhibitors are associated with osteoporosis and osteoporotic fractures, hot flashes and night sweats, musculoskeletal and arthritic discomfort, and impaired sexual function.¹¹ The limited data on toxic effects included in the report by Goss et al. are consistent with these findings. Although letrozole therapy was generally well tolerated and convenient, individual patients may have more pronounced symptoms and be forced to weigh carefully the benefits and side effects of treatment. The long-term safety of aromatase inhibitors is uncertain, and the supplemental data on bone density, cardiovascular health, and quality of life collected as part of this trial have yet to be reported.

Third, it must be acknowledged that the absolute benefits of letrozole therapy are limited. To date, letrozole has reduced the aggregate number of recurrences or new breast cancers from 5.1 percent to 2.9 percent — a reduction of approximately 1 event per 100 women treated per year. Among women who are free of recurrence after five years of tamoxifen therapy, those whose initial tumors carried a good prognosis are at lower risk for late distant metastases than are women whose primary tumors were larger or affected regional lymph nodes. Because of their greater residual jeopardy for recurrence, women who had higher-risk primary breast cancers might receive more benefit from ongoing treatment with letrozole. In addition, a substantial proportion of the apparent benefit of letrozole appears to lie in the prevention of contralateral breast cancers and recurrences in the ipsilateral breast. Locoregional recurrences or contralateral breast cancers accounted for one third of the disease-related

events that occurred, and the reduction in the rates of these events in the letrozole group constituted nearly half of the total reduction in events. These kinds of recurrence are surely meaningful, but such results suggest that the benefits of letrozole might have been less pronounced in women who had undergone ipsilateral or bilateral mastectomy or who were at lower risk for regional recurrence by virtue of improved techniques for surgical or radiation therapy.

These new data should not be interpreted as a recommendation for the use of aromatase inhibitors as primary adjuvant therapy in all cases of postmenopausal, hormone-receptor-positive breast cancer; the trial did not address the question of primary adjuvant therapy.³ In fact, the current results argue that the sequencing and timing of endocrine therapy for early-stage breast cancer may be far more complicated and malleable than previously recognized. Several ongoing international trials are studying the optimal duration and sequencing of tamoxifen and aromatase inhibitors. Results from these trials are expected in the next two to three years. In the meantime, a woman who is considering letrozole therapy after five years of tamoxifen therapy in order to reduce further the risk of a recurrence of breast cancer should be carefully educated about the realistic benefits and the likely side effects of therapy so that she can make a well-informed decision.

From the Division of Medical Oncology, Dana-Farber Cancer Institute, and the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.

This article was published at www.nejm.org on October 9, 2003.

1. National Institutes of Cancer Consensus Development Panel. National Institutes of Health Consensus Development Conference statement: adjuvant therapy for breast cancer, November 1–3, 2000. In: *Journal of the National Cancer Institute monographs*. No. 30. Bethesda, Md.: National Cancer Institute, 2001:5-15.
2. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 2003; 21:3357-65.
3. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: status report 2002. *J Clin Oncol* 2002;20:3317-27.
4. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-67.
5. Bryant J, Fisher B, Dignam J. Duration of adjuvant tamoxifen therapy. In: *Journal of the National Cancer Institute monographs*. No. 30. Bethesda, Md.: National Cancer Institute, 2001:56-61.
6. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: up-

EDITORIAL

dated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst* 2001;93:684-90.

7. Stewart HJ, Prescott RJ, Forrest APM. Scottish Adjuvant Tamoxifen Trial: a randomized study updated to 15 years. *J Natl Cancer Inst* 2001;93:456-62.

8. Tormey DC, Gray R, Falkson HC. Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. *J Natl Cancer Inst* 1996;88:1828-33.

9. Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med* 1998;339:1609-18.

10. Goss PE, Ingle JN, Martino S, et al. A randomized double-blind clinical trial evaluating letrozole adjuvant therapy in postmenopausal women with early stage breast cancer completing five years of tamoxifen. *N Engl J Med* 2003;349.

11. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431-42.

Copyright © 2003 Massachusetts Medical Society.