

## Letrozole: The treatment profile, the remaining questions

Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. Posted October 9, 2003. Because of its potential therapeutic implications, this report was published early at: [www.nejm.org](http://www.nejm.org). It appears in the November 6 issue.

**OBJECTIVE** To test the effectiveness of 5 years of letrozole therapy in postmenopausal women with estrogen-receptor–positive forms of early breast cancer who have completed 5 years of tamoxifen therapy.

**CONCLUSION** The primary endpoint, disease-free survival, significantly improved with letrozole therapy compared with placebo.

The study was halted and patients were informed of the results even before this initial report was published, less than halfway into the trial period.

Women who match the study group criteria should be considered for letrozole treatment, although the trial's early termination leaves optimal duration of treatment undefined and the question of long-term toxicity unanswered, the investigators stated in their report.

**WHO MAY BE AFFECTED** Postmenopausal women with primary breast cancer.

**BACKGROUND** In women with hormone-dependent breast cancer, tamoxifen therapy prolongs postoperative disease-free and overall survival for 5 years, but has not been found beneficial beyond the 5-year mark. This Canadian-led international clinical trial analyzed the effects of treatment with letrozole in years 5 through 10 after diagnosis. The research question was whether the aromatase inhibitor letrozole, by suppressing estrogen production, would improve the

outcome after the initial 5-year course of tamoxifen. Estrogen is thought to stimulate development and growth of breast cancer.

**METHODS AND RESULTS** This double-blind, placebo-controlled trial enrolled 5,157 postmenopausal women with primary breast cancer who had completed 4.5 to 6 years of adjuvant tamoxifen therapy less than 3 months before study enrollment. Of this group, 2,575 were randomized to receive 2.5 mg oral letrozole daily for 5 years; the remaining 2,582 received placebo. The study included women in the United States, Canada, and Europe. All patients were to undergo clinical evaluation twice in the first year and annually thereafter.

At the first interim analysis, after a median follow-up of 2.4 years, results in the letrozole group were significantly more favorable in these respects:

- **Greater disease-free survival:** 93% versus 87%.
- **Lower primary cancer recurrence rate:** 2.4% versus 4.1%.
- **Lower rate of new contralateral breast cancers:** 0.5% versus 1%.

**EXPERT COMMENTARY** In the United States, more than 200,000 women are diagnosed with invasive breast cancer each year. The vast majority have disease that is confined to the breast or regional lymph nodes, and more than two thirds have disease that is hormone-receptor positive. Many of these patients are being placed on tamoxifen. All told, as many as 1 million women may be taking tamoxifen as adjuvant therapy for resected breast cancer.

Although a 5-year course of tamoxifen substantially lowers the risk of disease recurrence and death in women with invasive

breast cancer, the quest for additional therapies that may extend the disease-free window continues. In recent years, there has been considerable focus on third-generation aromatase inhibitors as possible adjuvant treatment.

**'Postmenopausal women with hormone-receptor-positive tumors who have completed about 5 years of adjuvant tamoxifen therapy should be considered for letrozole treatment.'** (Goss et al, *N Engl J Med*)

**Anastrozole paves the way.** The ATAC trial compared a 5-year course of tamoxifen with a 5-year course of anastrozole in postmenopausal women.<sup>1</sup> Researchers found that anastrozole results in a statistically significant decrease in recurrences compared to tamoxifen; however, there has been no reported difference in survival, and follow-up remains relatively limited.

This study led the US Food and Drug Administration to approve anastrozole in the adjuvant setting, but many physicians continue to recommend tamoxifen for most postmenopausal women and all premenopausal women with receptor-positive breast cancer.<sup>2</sup>

**Letrozole: 4 caveats.** The current study, led by Goss on behalf of the National Cancer Institute of Canada and the North American Intergroup, randomized women who completed a 5-year course of tamoxifen to either letrozole or placebo. With a median follow-up of just under 2.5 years, the data safety monitoring board stopped and unblinded the trial due to a statistically significant difference in recurrences favoring the letrozole arm.

Physicians and patients alike have celebrated these results, heartened that a treatment has been identified for use after 5

years of tamoxifen therapy. However, we must bear several issues in mind:

1. No patient from the trial has completed the full 5-year course.
2. The absolute benefits associated with treatment are modest (just over 2% for recurrences and approximately 1% in distant disease-free survival).
3. The long-term toxicity is uncertain.
4. There is concern that aromatase inhibitors may result in bone loss, and it is not fully established to what extent any bone loss can be ameliorated with bisphosphonates or other therapies.

Further follow-up is needed to establish a clear picture of the risk-benefit relationship, though the unblinding of the trial will complicate future interpretation of the findings.

**Nevertheless, the results are clinically meaningful.** Many women remain at moderate risk of disease recurrence even after a 5-year course of tamoxifen, and letrozole can decrease this risk. In the next few years, multiple trials will provide additional information about aromatase inhibitors as adjuvant therapy. The landscape may well change in the not-so-distant future.

**BOTTOM LINE** Physicians should discuss the pros and cons of letrozole therapy with postmenopausal women completing a 5-year course of tamoxifen. However, both doctor and patient must carefully weigh the treatment's known benefits against potential risks. ■

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2. Winer EP, Hudis C, Burstein HJ et al. American Society of Clinical Oncology Technology Assessment Working Group Update: use of aromatase inhibitors in the adjuvant setting. *J Clin Oncol*. 2003;21:2597-2599.