Does extending aromatase-inhibitor use from 5 to 10 years benefit menopausal women with hormone-positive breast cancer?

In terms of improving the 5-year disease-free survival (DFS) rate, yes, according to results of a randomized study that compared extended letrozole treatment with placebo, in which the DFS rates were 95% and 91%, respectively. **No benefit was seen in the rate of overall survival, however:** 93% in the letrozole group versus 94% in the placebo group. Although no significant differences in quality of life measures were found in women extending aromatase inhibitor treatment from 5 to 10 years, bone-related toxic effects occurred more frequently among patients receiving letrozole versus placebo.

FAST TRACK

Adverse effects, quality of life measures, drug cost, and individual risk of disease recurrence must be considered when counseling patients on continuing hormonal adjuvant therapy

Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years [published online ahead of print June 5, 2016]. N Engl J Med. doi:10.1056/NEJMoa1604700.

EXPERT COMMENTARY

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Since the current treatment choice for hormone-receptor–positive early breast cancer in postmenopausal women is 5 years of aromatase inhibitor (AI) therapy, or AI therapy following initial tamoxifen treatment, could 10 years of an AI be beneficial to cancer recurrence? Goss and colleagues analyzed this question in the MA.17R trial, a North American Breast Cancer Group trial coordinated by the Canadian Cancer Trials Group. (Results of the prior MA.17 trial were published in 2003.[1])

The randomized, double-blind, placebo-controlled trial evaluated the effect of 5 years of extended AI (letrozole 2.5 mg) treatment compared with placebo in menopausal women with hormone-receptor–positive breast cancer who had previously received 5 years of hormonal adjuvant therapy with tamoxifen alone or plus AIs. Of note, this study was funded in part by Novartis, the pharmaceutical manufacturer of letrozole, though the company had no role in either study design or writing of the manuscript. Seven of the 20 authors disclosed some sort of relationship with industry (some with the manufacturer of letrozole), including

The author reports no financial relationships relevant to this article.

CONTINUED ON PAGE 51

CONTINUED FROM PAGE 52

membership on advisory boards, board of directors, steering committees, or data and safety monitoring committees or receiving lecturer or consulting fees or grant support.

The trial's primary end point was DFS. Secondary end points included overall survival, the incidence of contralateral breast cancer, quality of life (QOL), and long-term safety.

Details of the study

Women were eligible to participate in the study if they were disease free after having completed 4.5 to 6 years of therapy with any AI and if their primary tumor was hormone-receptor positive. A total of 1,918 women were included in the trial and were randomly assigned to receive either letrozole treatment (n = 959) or placebo (n = 959).

Clinical evaluation was performed annually and included assessments of new bone fracture and new-onset osteoporosis, blood tests, mammography, and assessment of toxic effects. QOL measures were assessed with a validated health survey and a menopause-specific questionnaire. The Common Toxicity Criteria, version 2.0, was used to assess adverse events.

Impact on disease free, overall survival

The rate of 5-year DFS was statistically improved in the letrozole group compared with the placebo group, 95% (95% confidence interval [CI], 93–96) versus 91% (95% CI, 89–93), respectively, a 4% improvement in DFS. However, there was no impact on disease-specific mortality and no benefit in overall survival (93% [95% CI, 92–95] with letrozole and 94% [95% CI, 92–95] with placebo), as competing causes of death become increasingly important in this older population. Among women who died during the study follow-up, more than half died of causes not related to breast cancer.

QOL measures. More than 85% of participants completed the QOL assessments at each time point. There was no difference in the various QOL measures between the letrozole and the placebo group.

Adverse effects. Expected adverse effects due to AIs were significantly higher in the letrozole group. For example, new-onset osteoporosis occurred in 109 (11%) of letrozole-treated women and in 54 (6%) of the placebo group ($P<.001$), and bone fracture occurred in 133 (14%) of the letrozole group and 88 (9%) of the placebo group ($P = .001$).

Of note, however, fewer toxicities/adverse effects were seen in the AI group in this study than in previously published reports. The authors suggested that these adverse effect data may be lower than expected because the majority of women eligible for this study likely had prior exposure to AIs, and those with significant adverse effects with aromatase inhibitor therapy may have self-selected out of this trial.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

While the study authors selected DFS as the primary outcome, the lack of overall survival, adverse effect profile, and the drug cost (average wholesale price, ~$33,050 for 5 years[2]) make the choice to routinely continue AIs in menopausal women with hormone-receptor–positive breast cancer less clear, and counseling on both the benefits and limitations of continuing hormonal adjuvant therapy will be important for these women.

Continued follow-up of the study participants over time would be useful to determine if, after 10 to 15 years, the benefit of extending AI therapy for an additional 5 years would provide an overall benefit in longevity, as competing causes of death (bone fracture, cardiovascular risk) actually may increase over time in the extended-treatment group compared with the placebo group.

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FAST TRACK

There was no difference in QOL measures between the letrozole group and the placebo group

References

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