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Authors
Chlebowski, Rowan T
Budoff, Matthew J

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EDITORIAL

Changing Adjuvant Breast-Cancer Therapy with a Signal for Prevention

Rowan T. Chlebowski, M.D., Ph.D., and Matthew J. Budoff, M.D.

Five randomized, full-scale studies have reported that 10 years of adjuvant endocrine therapy is beneficial for postmenopausal women with hormone-receptor–positive breast cancer. However, no prior study has involved more than 5 years of aromatase-inhibitor use or assessed a duration of adjuvant endocrine therapy of more than 10 years.[1] Goss and colleagues[2] now provide results from the MA.17R trial supporting the use of an aromatase inhibitor for 10 years and the use of adjuvant endocrine therapy for even longer total durations. The beneficial effects of increasing disease-free survival, with a favorable toxicity profile for continuing the aromatase inhibitor letrozole for 5 additional years, are reassuring, and the findings have direct application for clinical practice.

The greatest effect reported in the MA.17R trial for the aromatase inhibitor — a reduction in the risk of new contralateral breast cancers — suggests similarities and invites comparisons with the findings of trials involving chemoprevention of breast cancer. In this regard, Santen and colleagues[3] used a clinically based model that incorporated the doubling time for breast cancer, a detection threshold, and the prevalence of subclinical breast cancer in postmenopausal women to suggest that trials of breast-cancer prevention that report results after approximately 5 years of follow-up provide findings on nearly 95% of already-established, preclinical cancers.

In the MA.17R trial, in which placebo was the comparator, the influence of letrozole on hot flashes, arthralgia, myalgia, and quality of life was remarkably modest as compared with the results of most trials of adjuvant breast cancer in which tamoxifen was the comparator.[1] However, the findings closely parallel those reported in trials of the prevention of primary breast cancer in which the incidence of breast cancer in patients receiving an aromatase inhibitor was significantly lower than that in patients receiving placebo.[4,5] As suggested by Goss and colleagues, the favorable side-effect profile in the MA.17R trial may be due to the self-selection of women who had limited side effects during previous treatment with letrozole. Perhaps a similar process was seen in the prevention studies in which many participants had limited side effects with prescription or nonprescription medication use and thus might expect few additional problems when adding a study medication.[6] In any event, the apparent difference in side effects in the MA.17R trial and the aromatase-inhibitor chemoprevention trials as compared with most other trials of adjuvant therapy points to the importance of placebo controls in the generation of reliable information on side effects.

Fractures and cardiovascular risk have long been concerns when aromatase inhibitors are used.[1] In the MA.17R trial, there were significantly more fractures with letrozole, with an absolute difference of 4 percentage points. Somewhat in contrast, in the two chemoprevention trials evaluating aromatase inhibitors, neither of which mandated the monitoring of bone mineral density or the use of bisphosphonates, no significant increase in the risk of fracture was seen.[4,5] In these chemoprevention trials, bisphosphonates were used by 16 to 24% of participants. Although the duration of use of the aromatase inhibitor was longer in the MA.17R trial, perhaps

the implementation of bone-health maintenance strategies could abrogate the risk of fracture, even in patients receiving long-term treatment with an aromatase inhibitor. Finally, the absence of a signal of cardiovascular risk in the MA.17R trial is reassuring and is supported by a finding from a recent observational study in which no increase in stroke or myocardial infarction was observed with the use of an aromatase inhibitor.[7]

The reduction in contralateral breast cancers and the favorable safety profile seen with letrozole in the MA.17R trial provide support for the use of aromatase inhibitors for chemoprevention in clinical practice. With regard to primary prevention, the approach of oncologists to the treatment of cancer and of cardiologists to the treatment of cardiovascular disease is noteworthy given that these diseases share major risk factors and are leading causes of death in postmenopausal women. The use of mammography for the early detection of breast cancer is standard and widely implemented in clinical practice, but the use of chemoprevention for breast cancer receives scant attention from the oncology community.[6,8] In contrast, cardiologists have focused on long-term prevention (by means of statins, blood-pressure control, aspirin, and recommendations for diet and exercise) for an increasing proportion of the adult population.[9] However, there is less focus on the early detection of cardiovascular disease, despite the availability of validated approaches with coronary-artery calcium scans, the use of which has widespread recommendation in guidelines from the American College of Cardiology and the American Heart Association.[9,10] Perhaps each discipline could learn important lessons from the other.

The absence of a report on overall survival benefit in the MA.17R trial at this time should not be surprising. The participants, who in most cases underwent randomization approximately 10 years after the time of diagnosis, have passed the peak risk of recurrence and a considerable proportion of their remaining risk as well. In any event, avoiding a new diagnosis of invasive breast cancer is a benefit in itself. However, the absence of a survival effect will be considered as oncologists and patients with breast cancer weigh the risks and benefits of the use of long-term adjuvant endocrine therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA.

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1. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 2014;32:2255-69.
2. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. DOI: 10.1056/NEJMoa1604700.
3. Santen RJ, Song Y, Yue W, Wang JP, Heitjan DF. Effects of menopausal hormonal therapy on occult breast tumors. J Steroid Biochem Mol Biol 2013;137:150-6.
4. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011;364:2381-91.
5. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 2014;383:1041-8.
6. Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. Cancer Prev Res (Phila) 2014;7:378-87.
7. Haque R, Shi J, Schottinger JE, et al. Cardiovascular disease after aromatase inhibitor use. JAMA Oncol 2016 April 21 (Epub ahead of print).
8. Smith SG, Sestak I, Forster A, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. Ann Oncol 2016;27:575-90.
9. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889-934.
10. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56(25):e50-103.

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