Report from the San Antonio Breast Cancer Symposium

Breast cancer

EXTENDED ADJUVANT THERAPY

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TRIAL SUMMARY: No significant difference in OS with more letrozole

Mamounas EP, Bandos H, Lembersky BC, et al. A randomized, double-blinded, placebo-controlled clinical trial to evaluate extended adjuvant endocrine therapy (5 years letrozole) in postmenopausal women with hormone receptor-positive breast cancer who have completed previous adjuvant endocrine therapy: Initial results of NRG oncology/NSABP B-42. San Antonio Breast Cancer Symposium, December 6-10, 2016. Abstract S1-05.

The NSABP B-42 trial aimed to determine whether 5 years of letrozole (L) vs placebo (P) improves disease-free survival (DFS) in patients who have completed 5 years of hormonal therapy with either aromatase inhibitor (AI) or tamoxifen (Tam) followed by an AI. Postmenopausal patients with stage I-III, estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+) carcinoma of the breast were included. Patients must have had a lumpectomy with axillary nodal staging followed by radiation or a total mastectomy and received adjuvant or neoadjuvant chemotherapy at the time of diagnosis for between 63 and 75 months. Hormonal therapy must have been an AI or a combination of up to 3 years of Tam followed by an AI. Osteoporotic fractures and other malignancies were among exclusionary criteria.

Stratification was by pathologic nodal status, prior adjuvant Tam or not, and baseline dexa-T scores (>2.0, ≤ 2.0 SD). Primary endpoint was DFS, including local, regional, distant recurrence (DR), second primary cancers and deaths from any cause as first event. Secondary endpoints included overall survival (OS), breast cancer-free interval (BCFI including recurrence or contralateral breast cancer as first event), osteoporotic fractures (OF), and arterial thrombotic (AT) events.

Results: From September 2006 to January 2010, 3966 patients were randomly assigned to 2.5 mg of L or P daily for 5 years. Among patients, 34% were <60 years, 57% were node-negative, 39% received prior TAM, and 14% were HER2+). Median followup for 3923 patients included in the analyses was 6.9 years.

As of August 2016, 631 DFS events occurred (L=292, P=339); L did not result in statistically significant increase in DFS vs P (HR, 0.85; 95% CI, 0.73–0.999; p=0.048), even after adjusting for age or surgery type; 7-yr DFS was 84.7% for L vs 81.3% for P. There were no significant interactions between treatment and stratification variables; 310 deaths occurred (L=164, P=146); there was no statistically significant difference in OS with L vs P (HR, 1.15; 95% CI, 0.92–1.44; p=0.22); 7-yr OS was 91.8% for L and 92.3% for P.

Letrozole did provide significant improvement in the cumulative incidence of breast cancer-free interval (6.7% at 7 years for L vs 10% for P) and 28% reduction in distant recurrence. However, at 7 years there were more osteoporotic fractures with L (91 vs 78 for P), as well as a nonsignificant increase in arterial thrombotic events (4.0% with L vs 3.4% for P).

IN BRIEF

Already known

- About half of breast cancer recurrences in patients with hormone receptor-positive (HR+) breast cancer occur more than 5 years after diagnosis.
- The MA17.R trial found a disease-free survival (DFS) benefit with extending aromatase inhibitor (AI) therapy to 10 years.

What this study showed

- No significant difference in DFS was found between women who received an additional 5 years of letrozole after completing 5 years of AI vs placebo. Prolonged AI increased the occurrence of osetoporotic fracture.

Next steps

- Carefully assess patients before considering extending AI therapy beyond 5 years after diagnosis, notably for fracture risk.

COMMENTARY: In 2012, more than 6 million women around the world survived at least 5 years after breast cancer diagnosis; the vast majority of these women have ER+ breast cancer. Prior studies have shown that about half of the recurrences and about two-thirds of the deaths among patients with HR+ breast cancer occur more that 5 years after diagnosis. Postmenopausal women with HR+ breast cancer are currently treated with 5 years of hormone therapy. Many large clinical trials have studied whether extending adjuvant hormonal therapy for longer than 5 years can lower the rates of breast cancer recurrence and death

Data from 2 related abstracts from the MA17.R trial[1]

this population of patients who completed previous adjuvant endocrine therapy did not show a statistically significant improvement in DFS or OS, even after adjusting for age and surgery. The additional 5 years did improve some outcomes related to recurrence.

Overall, these trials suggest that careful assessment of potential risks and benefits is required before recommending extended letrozole therapy to a postmenopausal patient with early-stage breast cancer. Such an assessment needs to include patient and tumour characteristics, existing comorbidities, information on bone mineral density, and how well the patients tolerated the first 5 years of endocrine therapy.

References

1. Goss, P. E., et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *NEJM* 2016 375(3):209-19.