LONG-TERM TAMOXIFEN IN ER+ BREAST CANCER

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TRIAL SUMMARY: Prolonging adjuvant tamoxifen beyond 5 years improves OS


BACKGROUND

For women with estrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis.

The worldwide ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter) aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years. The trial randomized 12,894 women with early breast cancer who had completed 5 years of treatment with tamoxifen to either continue tamoxifen to 10 years or stop at 5 years (open control). Allocation (1:1) was by central computer, using minimization. After entry (between 1996 and 2005), yearly followup forms recorded any recurrence, second cancer, hospital admission, or death. The results reported effects on breast cancer outcomes among the 6846 women with ER-positive disease, and side effects among all women (with positive, negative or unknown ER status).

FINDINGS

Among women with ER-positive disease, allocation to continue tamoxifen reduced the risk of breast cancer recurrence (617 recurrences in 3428 women allocated to continue vs 711 in 3418 controls, p=0.002), reduced breast cancer mortality (331 deaths vs 397 deaths, p=0.01), and reduced overall mortality (639 deaths vs 722 deaths, p=0.01). The reductions in adverse breast cancer outcomes appeared to be less extreme before than after year 10 (recurrence rate ratio [RR] 0.90 [95% CI 0.79–1.02] during years 5–9 and 0.75 [0.62–0.90] in later years; breast cancer mortality RR 0.97 [0.79–1.18] during years 5–9 and 0.71 [0.58–0.88] in later years). The cumulative risk of recurrence during years 5–14 was 21.4% for women allocated to continue vs 25.1% for controls. Treatment allocation seemed to have no effect on breast cancer outcome among 1248 women with ER-negative disease, and an intermediate effect among 4800 women with unknown ER status. Among all 12,894 women, mortality without recurrence from causes other than breast cancer was little affected (691 deaths without recurrence in 6454 women allocated to continue vs 679 deaths in 6440 controls; RR 0.99 [0.89–1.10]; p=0.84).

For the incidence (hospitalization or death) rates of specific diseases, RRs were as follows: pulmonary embolus 1.87 (95% CI 1.13–3.07, p=0.01 [including 0.2% mortality in both treatment groups]), stroke 1.06 (0.83–1.36), ischemic heart disease 0.76 (0.60–0.95, p=0.02), and endometrial cancer 1.74 (1.30–2.34, p=0.0002). The cumulative risk of endometrial cancer during years 5–14 was 3.1% (mortality 0.4%) for women allocated to continue vs 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%). Long-term followup still continues.

COMMENTARY: Adjuvant endocrine therapy in the setting of hormone receptor (HR)-positive, early-stage breast cancer reduces the risk of cancer recurrence and death from breast cancer.1 In the most recent Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis, 5 years of tamoxifen vs no adjuvant tamoxifen reduced the risk of breast cancer recurrence in patients with ER-positive disease (n=10,645) throughout the first 15 years (relative risk [RR] 0.53 during years 0–4 and RR 0.68 during years 5–9). There was no further benefit after 10 years with a RR 0.97 during years 10–14. Mortality was also reduced by approximately one-third during the first 15 years (RR 0.71 during years 0–4, 0.66 during years 5–9 and 0.68 during years 10–14; p<0.0001).

For premenopausal women, 5 years of tamoxifen is the standard treatment whereas for postmenopausal women, aromatase inhibitors (AI) upfront or sequentially after tamoxifen are options for endocrine therapy. As AIs are contraindicated in women with residual ovarian function, premenopausal women do not have the option of these agents. However, breast cancer recurrences continue after 5 years of endocrine therapy with a mean hazard of recurrence of approximately 4% per year between year 5 to 12 post surgery.2 Postmenopausal women completing 5 years of tamoxifen can consider extended adjuvant therapy with an AI, which may reduce breast cancer recurrences3–5 and improve survival in higher-risk women.3 Several trials have reported outcomes in women taking 10 years of tamoxifen vs 5.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B14 trial, 1172 women with ER-positive, node-negative breast cancer who remained disease-free after 5 years of tamoxifen were randomized to receive 5 more years of...
have now been reported. But 2 more recent adjuvant trials of tamoxifen duration women who participated in the duration portion of this trial. benefit to continuing tamoxifen beyond 5 years in the 342 a median followup of 15 years, there was no additional benefit to continued tamoxifen beyond 5 years. With a median followup of 15 years, there was no additional benefit to continuing tamoxifen beyond 5 years in the 342 women who participated in the duration portion of this trial. But 2 more recent adjuvant trials of tamoxifen duration have now been reported.

The Adjuvant Tamoxifen — To offer more? (ATTom) study randomized 6,934 women with ER-positive or ER-unknown early breast cancer to 5 additional years of tamoxifen or none after completing at least 4 years of tamoxifen therapy. After a median followup of 4.2 years, there were fewer recurrences (415 vs 442) with a RR of 0.94 (95% CI 0.81–1.09, p=0.4) in women taking 10 years of tamoxifen vs 5 years, a difference that fell short of statistical significance. Of note, in this trial, 39% of cancers were ER-positive and 61% were ER-unknown. Now, the updated results of the Adjuvant Tamoxifen Long Against Short (ATLAS) trial have been reported. In this trial, 12,894 women with early breast cancer who had completed 5 years of adjuvant tamoxifen therapy were randomized to continue tamoxifen for another 5 years or stop at 5 years.

The investigators report outcomes in 6,846 women with ER-positive cancer and report side effects among all women in the trial. Approximately half of the study population were less than 55 years in age. Women who took 10 years of tamoxifen had less breast cancer recurrences vs those taking 5 years of therapy (617 vs 711, RR 0.84, 95% CI 0.76–0.94, p=0.002), reduced breast cancer mortality (331 vs 397, p=0.01) and reduced overall mortality. The breast cancer mortality during years 5–14 was 12.2% for women on continued tamoxifen vs 15.0% for controls with an absolute mortality reduction of 2.8%. Of note, these effects on recurrence and survival were seen only during the second decade after diagnosis, which may reflect the carryover effect of 5 prior years of tamoxifen therapy in both study arms. Women aged <55 had a similar benefit to those 55 years and older.

Longer tamoxifen therapy was associated with increased risk of pulmonary embolus (RR 1.87; 95% CI 1.13–3.07, p=0.01) but similar mortality rate (0.2%) in both treatment groups.

Ten years of tamoxifen was also associated with a non-statistically significant increased risk of stroke (RR 1.06; 95% CI 0.83–1.36, p=0.63), and endometrial cancer (3.1% vs 1.6%; RR 1.74; 95% CI 1.30–2.34, p=0.0002) with an absolute mortality increase of 0.2%. However, longer tamoxifen use was associated with less ischemic heart disease (RR 0.76; 95% CI 0.60–0.95; p=0.02).

Therefore, 10 years of adjuvant tamoxifen was superior to 5 years in reducing breast cancer recurrence and improving survival in women with ER-positive early breast cancer, and the main benefits occurred 10 years after initial surgery. The ATLAS study is the first trial of extended adjuvant tamoxifen showing additional benefit in this population and this strategy could be considered in women completing 5 years of tamoxifen who remain at risk of late cancer recurrences. Any benefits in breast cancer outcomes, however, need to be balanced against a slightly increased risk of PE, stroke and endometrial cancer, taking into account a slightly lowered risk of ischemic heart disease. Premenopausal women who do not have the option of aromatase inhibitors are among the most promising candidates in whom to consider 10 years of tamoxifen therapy. Notably, in premenopausal women, there is little risk of endometrial cancer and vascular effects should also be lower.

In postmenopausal women, extended adjuvant endocrine therapy with an AI after 5 years of tamoxifen remains the standard, and how this strategy compares to 10 years of adjuvant tamoxifen is unknown. Postmenopausal women who do not tolerate an AI or decline AI treatment might now instead consider extended endocrine therapy with tamoxifen. The ATLAS study’s results suggest that women deemed at higher risk of late cancer recurrence could indeed consider

**IN BRIEF**

**Already known**

- 5 years of adjuvant tamoxifen therapy in ER+ early breast cancer reduces cancer recurrence and improves survival.
- Up to another 5 years of extended adjuvant endocrine therapy with an AI in postmenopausal women can reduce cancer recurrence further and potentially improve survival in higher-risk patients.
- AIs are contraindicated in premenopausal women but these women remain at risk for cancer recurrence after 5 years of tamoxifen therapy.

**What this study showed**

- 10 years of adjuvant tamoxifen compared to 5 years reduced cancer recurrence and improved survival in ER+ breast cancer, especially after year 10.
- This strategy was associated with a small but higher risk of PE and endometrial cancer but lower incidence of ischemic heart disease.

**Next steps**

- Await the EBCTCG meta-analysis of trials of 10 years of tamoxifen vs 5 years and the updated results from the ATTom study.
longer tamoxifen therapy after completing 5 years of tamoxifen. Updated results from the ATTom trial are anticipated in the next year, however, as well as a meta-analysis of trials of extended adjuvant tamoxifen therapy by the Early Breast Cancer Trialists Collaborative Group. These may bring further clarity on the optimal duration of tamoxifen therapy.

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**References**