Is Anastrozole Better than Tamoxifen as Adjuvant Therapy for Early Breast Cancer in Postmenopausal Women?

Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. The ATAC (Arimidex, tamoxifen alone or in combination) Trialists' Group. Lancet 2002;359:2131–9.

Study Overview

Objective. To compare the safety and efficacy of the selective aromatase inhibitor anastrozole (Arimidex) with that of tamoxifen and the combination of anastrozole plus tamoxifen as adjuvant therapy for postmenopausal early breast cancer.

Design. Multicenter, double-blind, randomized controlled trial. Analyses were by intention-to-treat.

Setting and participants. Participants included 9366 postmenopausal women from 21 countries with invasive early breast cancer who were eligible for adjuvant hormonal therapy after completing primary therapy of surgery and chemotherapy (if given). Participants were block randomized to receive tamoxifen ($n = 3116$), anastrozole ($n = 3125$), or both ($n = 3125$). Patient characteristics and clinical course were assessed at entry and at 3 months, 6 months, and every 6 months afterwards. The study was designed to follow patients for 10 years.

Main outcome measures. Primary outcomes were disease-free survival and occurrence of adverse events. Rates of contralateral breast cancer also were measured.

Main results. The mean follow-up period was 3.3 years. Disease-free survival at 3 years of follow-up was 89.4% for patients receiving anastrozole versus 87.4% for those taking tamoxifen (hazard ratio [HR], 0.83 [95% confidence interval {CI}, 0.71–0.96]; $P = 0.013$). 3-year disease-free survival was not statistically different between patients taking tamoxifen and those using combination therapy (87.2%; HR, 1.02 [95% CI, 0.89–1.18]; $P = 0.8$). The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone receptor–positive patients but not the receptor-negative patients. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio, 0.42 [95% CI, 0.22–0.79]; $P = 0.007$). Incidence of vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flashes was lower in the anastrozole group compared with the tamoxifen group, whereas incidence of musculoskeletal disorders and fractures was higher in the anastrozole group.

Conclusion. At 3 years of follow-up, anastrozole compares favorably with tamoxifen as an adjuvant treatment for early postmenopausal breast cancer. Long-term follow-up data are forthcoming.

Commentary

A large body of evidence has established the efficacy of tamoxifen as an adjuvant treatment for early breast cancers that are hormone-sensitive. Based on data derived from 10-years follow-up of more than 30,000 women, we now know that tamoxifen reduces cancer recurrence at the first, second, and fifth year of follow-up by 21%, 29%, and 47%, respectively [1]. Despite these proven benefits, tamoxifen's side-effect profile includes endometrial cancer and thromboembolic disease. Motivated by recent data showing a modest benefit of anastrozole over tamoxifen in advanced breast cancer and the absence of endometrial cancer and thromboembolic disease as its side effect, the ATAC (Arimidex tamoxifen alone or in combination) trial has been undertaken to demonstrate the equivalence of anastrozole to tamoxifen and the possible benefit of combination therapy with anastrozole and tamoxifen in treating early breast cancer.

This article represents an early report on the ongoing 10-year ATAC trial. After 3 years of follow-up, anastrozole seems to confer minor benefit in preventing cancer recurrence over tamoxifen while offering a reduction in endometrial cancers and thromboembolic events. Anastrozole also seems to offer significant benefits over tamoxifen by cutting the contralateral breast cancer rate by more than half.

Given these statistically significant results demonstrating benefit of anastrozole over tamoxifen and a favorable side-effect profile, should clinicians now abandon tamoxifen in favor of anastrozole as the agent of choice for the adjuvant treatment of early breast cancer? The answer, unfortunately, is no—or at least not yet. The reasons lie in the relatively high risk of cancer recurrence beyond the initial 2 to 3 years

of cancer-free survival. As was discussed in a commentary in the same issue [2], over half of the expected recurrences in estrogen receptor–positive and node-positive breast cancers occur after the first 3 years of follow-up. Tamoxifen has been shown to offer incremental and clinically significant protection against cancer recurrence during years 3, 4, and 5 of adjuvant therapy—such a claim cannot be made for anastrozole until we have additional follow-up data from the ATAC trial.

Furthermore, we do not yet know whether anastrozole is capable of preventing recurrence after therapy is stopped; the agent may be delaying the presentation of recurrence rather than truly preventing it. Previous research has shown that tamoxifen continues to offer a protective effect against cancer recurrence for the 5 years after the cessation of the standard 5-year therapy. Once again, anastrozole cannot claim to offer this benefit until the 10-year ATAC trial has been completed.

Finally, anastrozole is not without risk. Even after 3 years of follow-up, a signifcant increase in bone fractures and other musculoskeletal complaints was found in the anastrozole group compared with the tamoxifen group. Given the marginal (albeit statistically significant) benefit demonstrated so far in the ATAC trial, anastrozole should not be favored over tamoxifen until further follow-up efficacy and safety data become available.

Applications for Clinical Practice

While short-term follow-up data show that anastrozole is well tolerated and may be marginally superior to tamoxifen in preventing breast cancer recurrence, its efficacy in preventing long-term cancer recurrence and mortality remains to be defined. Until then, tamoxifen should remain the standard of care in the adjuvant treatment of early breast cancer.

–Review by Eric G. Poon, MD

References

1. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451–67.
2. Ravdin P. Aromatase inhibitors for the endocrine adjuvant treatment of breast cancer. Lancet 2002;359:2126–7.