Anastrozole had a better risk–benefit profile than tamoxifen as adjuvant treatment for breast cancer in postmenopausal women

Buzdar A, Howell A, Cuzick J, et al. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial.** Lancet Oncol. 2006;7:633-43.

Clinical impact ratings: Oncology ★★★★★☆☆

QUESTION

In postmenopausal women with early breast cancer, what are the relative safety, tolerability, and risk–benefit profiles of anastrozole and tamoxifen as adjuvant treatments?

METHODS

Design: Randomized controlled trial (Arimidex, Tamoxifen, Alone or in Combination [ATAC] trial).

Allocation: {Concealed}†.*

Blinding: Blinded (clinicians, patients, data collectors, and outcome assessors).*

Follow-up period: Median 68 months (range 1 to 93 mo).

Setting: 381 centers in 21 countries.

Patients: 6241 postmenopausal women (mean age 64 y) who had {recently completed surgery with or without chemotherapy for}† early-stage breast cancer.

Intervention: Anastrozole, 1 mg (n = 3125), or tamoxifen, 20 mg (n = 3116), once daily for 5 years.

Outcomes: Adverse events and risk–benefit profiles using 2 global indices: the Global Index of the Women's Health Initiative (WHI) (breast cancer recurrence, death, coronary heart disease, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, or hip fracture) and the Global Index of Disease-Free Survival and Serious Adverse Events (DFS+SAE) (breast cancer recurrence, death, or any serious adverse event).

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Anastrozole caused fewer treatment-related adverse events, adverse events leading to withdrawal, and serious treatment-related adverse events than did tamoxifen (Table). Risks for cerebrovascular events, venous thromboembolic events, and endometrial cancer were lower with anastrozole; risk for fracture was lower with tamoxifen; and risks for cardiovascular events were similar in the 2 groups. The risk–benefit profile favored anastrozole using both global indices (Table).

CONCLUSIONS

Postmenopausal women taking anastrozole as adjuvant treatment for early breast cancer were less likely to have treatment-related adverse events or to withdraw from treatment because of side effects than were those taking tamoxifen. Anastrozole had a better risk–benefit profile than did tamoxifen.

Source of funding: AstraZeneca.

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*See Glossary.

†**Baum M. Buzdar A, Cuzick J, et al.** Lancet. 2002;359:2131-9.

Anastrozole vs tamoxifen as adjuvant treatment in postmenopausal women with early breast cancer at median 68 months‡

Outcomes	Anastrozole	Tamoxifen	RRR (95% CI)	NNT (CI)
Treatment-related adverse events	61%	68%	11% (8 to 14)	14 (11 to 19)
Adverse events leading to withdrawal	11%	14%	22% (11 to 32)	32 (22 to 64)
Serious treatment-related adverse events	5%	9%	47% (36 to 57)	24 (20 to 31)
Global index–WHI	24%	27%	13% (5.1 to 20)	29 (19 to 72)
Global index–DFS+SAE	46%	51%	8.6% (4.2 to 13)	23 (15 to 47)

‡WHI = Women's Health Initiative; DFS+SAE = Disease-Free Survival and Serious Adverse Events. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from relative risks and hazard ratios in article.

COMMENTARY

The use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer has rapidly been adopted by oncologists, driven by evidence from several randomized trials showing a modest but consistent reduction in breast cancer events and a lower incidence of adverse events. The trial by the ATAC Trialists' Group highlights the differences in the side-effect profiles of anastrozole and tamoxifen. The anastrozole group had fewer adverse events leading to stopping therapy and a modestly higher score in global indices of quality of life.

Despite these findings, the timing of aromatase inhibitor therapy remains controversial: Should it be used initially or only after 2 to 3 years of tamoxifen use? Subsequent reports of the ATAC trial have continued to show a reduction in breast cancer events but have not yet shown a statistically significant benefit in overall survival (1). Cost-effectiveness analyses of adjuvant aromatase inhibitors have projected incremental cost-effectiveness or cost-utility ratios that are generally considered favorable, if the observed reductions in systemic breast cancer recurrences translate into improvements in overall survival (2, 3).

This study underemphasizes the primary concern with long-term use of aromatase inhibitors, namely, greater bone loss and, by inference, greater long-term risk for osteoporotic fractures. Current guidelines for clinicians caring for women on aromatase inhibitors stress the need to monitor bone mineral density; use supplemental calcium with vitamin D; and, if necessary, add bisphosphonates. Clinicians will need to switch their attention from the gynecologic toxicities of tamoxifen to bone health (4). For women with known osteoporosis or a previous hysterectomy, tamoxifen probably remains the preferred therapy.

Knowledge of the long-term benefits and risks of aromatase inhibitors is still evolving. The optimal strategy after 5 years of adjuvant aromatase inhibition remains uncertain and is the subject of ongoing randomized trials.

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