Disease-free survival was greater with letrozole than tamoxifen in postmenopausal women with early breast cancer

Thürlimann B, Keshaviah A, Coates AS, et al. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** N Engl J Med. 2005;353:2747-57.

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

QUESTION

In postmenopausal women, is letrozole more effective than tamoxifen as adjuvant treatment for early hormone-receptor–positive (HR+) breast cancer?

METHODS

Design: Randomized controlled trial (Breast International Group [BIG] 1-98 study).
Allocation: Concealed.*
Blinding: Blinded {patients, clinicians, outcome assessors, data analysts, and data safety and monitoring committee}†.*
Follow-up period: Median 26 months.
Setting: Several hundred centers worldwide.
Patients: 8028 postmenopausal women 38 to 90 years of age (median age 61 y) with invasive breast cancer positive for estrogen and/or progesterone receptors; primary surgery resulting in clear margins; and adequate hematologic, renal, and hepatic function. Exclusion criteria included evidence of metastatic disease and other cancer in the previous 5 years.
Intervention: Letrozole, 2.5 mg daily (n = 4015), or tamoxifen, 20 mg daily (n = 4013), for 2 or 5 years. (Patients allocated to 2-y treatment received the alternate drug for the next 3 y but were censored 30 d after switching for this analysis).
Outcomes: Disease-free survival (ended by any recurrence, new cancer in the contralateral breast or elsewhere in the body, or death), systemic disease-free survival (as above but excluding breast events), overall survival, and adverse events.
Patient follow-up: 99.8% (intention-to-treat analysis).

MAIN RESULTS

Letrozole resulted in greater disease-free survival and systemic disease-free survival than tamoxifen, but groups did not differ for overall survival (Table). Estimated 5-year disease-free survival rates were 84% with letrozole and 81% with tamoxifen. Women taking letrozole were more likely to have hypercholesterolemia, cardiac events, fractures, and arthralgia but less likely to have thromboembolic events, vaginal bleeding, and vasomotor symptoms.

CONCLUSION

In postmenopausal women with early hormone-receptor–positive breast cancer, adjuvant therapy with letrozole resulted in greater disease-free survival than tamoxifen.

Source of funding: Novartis.

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*See Glossary.

†Information provided by author.

Letrozole vs tamoxifen for early breast cancer in postmenopausal women after a median follow-up of 26 months‡

Outcomes	Letrozole	Tamoxifen	RRR (95% CI)	NNT (CI)
Disease-free survival event	8.8%	11%	18% (6.6 to 29)	52 (33 to 141)
Systemic disease-free survival event	8.1%	9.6%	16% (2.9 to 27)	64 (39 to 365)
Death from any cause	4.1%	4.8%	14% (–5.8 to 29)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from hazard ratios in article.

COMMENTARY

The first report of the BIG 1-98 trial adds to the growing literature supporting the use of aromatase inhibitors (AIs) as first-line adjuvant therapy for postmenopausal women with HR+ breast cancer. 6 other trials in similar populations have reported comparable results: Women who received AIs, either as monotherapy or in sequence with tamoxifen, had greater disease-free survival than women who received tamoxifen alone (1-5).

Adjuvant AI therapy is clearly here to stay for postmenopausal women with early-stage HR+ breast cancer. A number of questions remain, however. First, will AIs help women live longer? Most trials have shown trends toward longer overall survival, and some have shown significant benefit in a subgroup, but none has yet shown a statistically significant overall survival benefit. Given the excellent prognosis of early-stage HR+ breast cancer and the fact that many women crossed over to an AI or received an AI off-study once favorable data emerged, it is possible that an overall survival advantage will never be shown. A meta-analysis would be helpful to address this issue. Second, should these patients receive AI monotherapy or sequential therapy with tamoxifen and an AI, and if the latter, in what order? Further follow-up of BIG 1-98 will provide these answers.

Finally, do we need to temper our enthusiasm for AIs in light of evidence that certain serious side effects—fractures and perhaps hypercholesterolemia and cardiovascular events—occur more often with AIs than with tamoxifen? Just as it took more than 2 decades for the association between tamoxifen and endometrial cancer to become apparent, longer follow-up of the thousands of patients who have now received AIs is essential to confirm that they are truly the treatment of choice for postmenopausal women with HR+ breast cancer.

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