

Aromatase inhibitors as adjuvant therapy for breast cancer

What have we learned from ATAC and other recent trials?

Administration of tamoxifen for 5 years has been considered standard adjuvant therapy for women with primary estrogen receptor-positive breast cancer. Recent trials of aromatase inhibitors—hormonal agents that dramatically reduce circulating estrogen levels in postmenopausal women—have indicated that superior results can be achieved by using anastrozole (Arimidex) instead of tamoxifen or by substituting anastrozole or exemestane (Aromasin) for tamoxifen during ongoing tamoxifen therapy. Other data indicate that use of letrozole (Femara) after completion of 5 years of tamoxifen therapy is associated with prolonged disease-free survival.

ATAC trial

The multicenter, multinational Arimidex or Tamoxifen Alone or in Combination (ATAC) trial randomized 9,366 postmenopausal women with early invasive breast cancer to 5 years of treatment with anastrozole or tamoxifen alone or in combination; 84% of these patients were estrogen receptor-positive. The main analysis of the study's outcome, initially reported in 2001, showed that after a median follow-up of 33 months, anastrozole alone was superior to tamoxifen alone with regard to disease-free survival (hazard ratio, 0.83) and time to recurrence (hazard ratio, 0.79); no difference in disease-free survival was seen between tamoxifen and the combination treatment.

After the trial's outcome was reported, the American Society of Clinical Oncology (ASCO) recom-

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mended in May 2002 that tamoxifen continue to be considered standard therapy, given the compelling, extensive, and long-term data on tamoxifen treatment.¹ However, because of the ATAC trial findings and other study results suggesting better outcomes in women who had received aromatase inhibitors than in those who had been treated with tamoxifen, ASCO also recommended that the choice of adjuvant therapy be dependent on a discussion of all available data between physician and patient.¹

Recently, an updated efficacy analysis of the ATAC trial data has shown that the benefits of anastrozole treatment compared with tamoxifen increase over time.² At the time of this analysis, patients had a median follow-up of 47 months; of those patients receiving either agent alone, 84% completed 3 years of follow-up and 47% completed 4 years of follow-up. Anastrozole treatment (n = 3,125) was associated with a significant improvement in time to recurrence in the intent-to-treat population compared with tamoxifen (n = 3,116); the hazard ratio for time to recurrence associated with anastrozole versus tamoxifen was 0.83 (95% CI, 0.71–0.96; *P* = 0.015). Among those patients with known estrogen receptor-positive status, the hazard ratio for time to recurrence associated with anastrozole versus tamoxifen was 0.78 (95% CI, 0.65–0.93; *P* = 0.007).

As shown in Table 1, the absolute difference in breast cancer event rates between the two groups increased over time both in the intent-to-treat population and in the population with known estrogen receptor-positive status. Compared with tamoxifen, treatment with anastrozole was

TABLE 1

ATAC trial: breast cancer event rates in intent-to-treat population and in estrogen receptor-positive patients by year of follow-up

Year	Intent-to-treat population			Estrogen receptor-positive population		
	Anastrozole	Tamoxifen	Difference	Anastrozole	Tamoxifen	Difference
1	2.5%	2.3%	-0.2%	1.5%	1.5%	0%
2	5.1%	6.4%	1.3%	3.5%	5.2%	1.7%
3	7.7%	9.4%	1.7%	5.9%	7.7%	1.8%
4	9.8%	12.1%	2.3%	7.8%	10.4%	2.6%

From Klijn.²

TABLE 2

Intergroup Exemestane Study: analysis of outcomes in breast cancer survivors taking exemestane vs tamoxifen

Outcome	Hazard ratio (95% CI)	P value
First event-free survival	0.68 (0.56–0.82)	0.00005
Breast cancer-free survival, censoring deaths in patients without recurrence or contralateral breast cancer	0.63 (0.51–0.77)	0.00001
Distant disease-free survival	0.66 (0.52–0.83)	0.0004
Risk of contralateral breast cancer	0.44 (0.20–0.98)	0.04
Overall survival	0.88 (0.67–1.16)	0.37

CI = confidence interval. From Coombes et al.⁴

also associated with a reduced number of recurrences at all breast cancer sites, including those associated with poorer prognoses—eg, ipsilateral breast (26 for anastrozole vs 38 for tamoxifen), chest wall (37 vs 40), axillary lymph nodes (13 vs 23), and supraclavicular/internal mammary (20 vs 30). The latest findings in the ATAC trial thus continue to favor the use of anastrozole over tamoxifen as adjuvant therapy in postmenopausal women with estrogen receptor-positive disease.

Additional studies

An Italian study, presented at the San Antonio Breast Cancer Symposium in 2003, also has shown that switching patients from tamoxifen to anastrozole is associated with marked benefits.³ In this trial, 426 postmenopausal women with node-positive, estrogen receptor-positive disease who had received tamoxifen for at least 2 years were randomized to continue with tamoxifen treatment (n = 218) or switch to anastrozole (n = 208)

for up to 5 years. After a median follow-up of 24 months, there were 26 events in the tamoxifen group (19 recurrences, 5 second primary tumors, 2 deaths in the absence of disease progression) and 10 in the anastrozole group (8 recurrences, 2 second primary tumors). With adjustment for age, nodal involvement, tumor grade, and treatment of primary tumors, the hazard ratio for relapse in women switched to anastrozole, compared with continuing on tamoxifen treatment, was 0.36 (95% CI, 0.17–0.75; *P* = 0.006).

The recently reported Intergroup Exemestane Study has similarly shown that switching from tamoxifen to exemestane as adjuvant therapy is associated with clinical benefits.⁴ In this trial, 4,742 postmenopausal patients who had tumors that were estrogen receptor-positive or of unknown receptor status and who had no recurrence of their cancer after 2–3 years of tamoxifen treatment were randomized to continue tamoxifen (n = 2,380) or switch to exemestane

(n = 2,362) for the remainder of the 5-year treatment course. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) had occurred, including 183 in the exemestane-treated group and 266 in the tamoxifen-treated group. The unadjusted hazard ratio for events in the exemestane treatment group, compared with the tamoxifen group, was 0.68 (Table 2). The 32% reduction in risk by switching to the aromatase inhibitor corresponded to an absolute benefit in disease-free survival of 4.7% (95% CI, 2.6%–6.8%) at 3 years after randomization (91.5% for exemestane vs 86.8% for tamoxifen).

Exemestane treatment was also associated with significant improvements in disease-free survival, including fewer local and distant recurrences, as well as new tumors in the contralateral breast, compared with similar indices of disease-free survival in patients who were continued on tamoxifen. There was no difference, however, between the two treatment groups with regard to overall survival at the time of analysis.

Aromatase inhibitors after completion of tamoxifen

Another large-scale study has demonstrated that letrozole therapy after 5 years of tamoxifen therapy significantly improves disease-free survival.⁵ In a double-blind, multinational trial, 5,187 postmenopausal women who had received approximately 5 years of tamoxifen treatment for early-stage breast cancer were randomized to receive placebo or letrozole for 5 years. At the time of the first scheduled interim analysis (pre-specified at 171 events), patients had a median follow-up of 2.4 years. A total of 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast had occurred, consisting of 75 in the letrozole group and 132 in the placebo

TABLE 3

Disease-free and overall survival by year in patients receiving letrozole or placebo after 5 years of tamoxifen therapy

	Letrozole	Placebo	Difference (95% CI)
Disease-free survival (%)			
1 year	98.6	97.8	0.8 (0.0–1.5)
2 years	96.7	94.8	1.9 (0.6–3.3)
3 years	95.2	90.2	5.0 (2.7–7.3)
4 years	92.8	86.8	6.0 (2.0–10.1)
Overall survival (%)			
1 year	99.8	99.7	0.1 (–0.2–0.4)
2 years	98.9	98.6	0.3 (–0.5–1.1)
3 years	97.7	96.9	0.8 (–0.8–2.3)
4 years	96.0	93.6	2.4 (–0.9–5.6)

CI = confidence interval. From Goss et al.⁵ Used with permission from the *New England Journal of Medicine*. Copyright © 2003 Massachusetts Medical Society. All rights reserved.

bo group. The estimated 4-year disease-free survival rate in the letrozole group was significantly greater than that in the placebo group (92.8% vs 86.8%, $P \leq 0.001$ [Table 3]). Overall survival did not differ significantly between the two groups.

Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group; vagi-

nal bleeding was more frequent in the placebo group. New diagnoses of osteoporosis occurred in 5.8% of the letrozole group and 4.5% of the placebo group; the two groups had similar rates of fracture.

Given the finding of prolonged disease-free survival and an apparent trend in improved overall survival with letrozole treatment, it was rec-

ommended that the trial be halted after the first interim analysis.

References

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The community oncologists' view

WE ASKED TWO COMMUNITY ONCOLOGISTS whether the results of the ATAC trial and other research on aromatase inhibitors have impacted their choice of adjuvant therapy for patients with breast cancer.

Dr. Shamoan Ahmad, US Oncology, Las Vegas, NV, believes the data are still maturing but look promising. Concerns about the potential risk of osteoporosis with letrozole (Femara) has made him cautious, however. The availability of more osteoporosis data and recommendations for its prevention in letrozole-treated patients will likely sway his opinion regarding use of this drug in the future.

Currently, he is prescribing anastrozole (Arimidex) in lieu of tamox-

ifen for about half of his clinic's breast cancer patients. As more experience is gained, Dr. Ahmad reported, physicians will most likely convert most of their patients to aromatase inhibitors. "If a patient requests Arimidex," he said, "after a discussion of options, it is prescribed."

Aromatase inhibitors will likely be started earlier

Our other responder, a medical oncologist who heads a community practice in southern California, feels that as even more data indicate the benefits of aromatase inhibitors over tamoxifen, they are likely to be introduced earlier in the treatment of breast cancer, just as adjuvant therapy itself has moved from use in meta-

static disease to treating cancer at earlier and earlier stages.

She started using anastrozole because of the long duration of follow-up data available from the ATAC trial but encountered "significant intolerance due to arthritis, especially in younger postmenopausal women." These patients are switched to letrozole or exemestane (Aromasin). More recently, she has begun using letrozole as first-line therapy with fewer arthritic complaints but is contemplating switching to exemestane based on newer data and the low incidence of hot flashes associated with this drug.

Is reimbursement an issue? No, says Dr. Ahmad, but our California oncologist points out that "when

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patients have to pay, the current cost of tamoxifen versus that for an aromatase inhibitor has had several patients come back requesting tamoxifen." She added, "When cost is not an issue, patients almost invariably

choose aromatase inhibitors. Their concern about the risk of blood clots and uterine cancer makes my patients overwhelmingly choose an aromatase inhibitor over tamoxifen, even with the increased risk of bone loss. Having just dealt with one cancer, even a very rare risk of uterine cancer is not acceptable to my patients when

there is an alternative available that may even be more effective."

"Certainly, if a patient has a fairly low risk of recurrence and significant bone loss," she concluded, "use of tamoxifen along with exercise, calcium, and vitamin D can be a cost-effective alternative to aromatase inhibitors used with bisphosphonates."