

Anastrozole Data Show Continued Delay in Relapse, But No Clear Survival Advantage

For the first time in 20 years, another class of drugs—aromatase inhibitors—is challenging tamoxifen as the treatment of choice for postmenopausal women with early breast cancer. However, the higher cost of at least one of the aromatase inhibitors and the lack of a statistically significant advantage in breast cancer survival give some researchers pause in wholeheartedly endorsing the drugs.

Final results of the Arimidex, Tamoxifen, Alone or in Combination



Anthony Howell

(ATAC) trial, presented at this year's San Antonio Breast Cancer Symposium and published simultaneously in *The Lancet*, found that, compared with tamoxifen, anastrozole

(Arimidex) improved disease-free survival by 13% (17% among hormone-responsive patients) and increased time to recurrence by 21% (26% in hormone-responsive patients) in postmenopausal, estrogen receptor-positive women with early breast cancer; however, there was no statistically significant improvement in breast cancer survival or overall survival.

"Anastrozole is the initial treatment of choice for hormone receptor-positive early breast cancer in postmenopausal women," Anthony Howell, M.D., chairman of the ATAC Trialists' Group, concluded in his presentation in San Antonio.

The ATAC trial was the first randomized trial to test an aromatase inhibitor as first-line therapy in postmenopausal women with hormone-responsive early breast cancer. Between 1996 and 2000,

more than 9,000 women were randomly assigned to receive anastrozole, tamoxifen, or a combination of the two drugs as adjuvant therapy. The combination arm of the trial was shut down early because of a lack of efficacy beyond either of the agents alone.

Three aromatase inhibitors— anastrozole, letrozole (Femara), and exemestane (Aromasin)—are approved in the United States for use in women with metastatic breast cancer. Two major randomized trials in the adjuvant setting have found that women previously treated with tamoxifen who took an aromatase inhibitor had a lower risk of recurrence compared with women who continued tamoxifen or took placebo after 2 to 3 years of tamoxifen.

In November, the American Society of Clinical Oncology made public its updated technology assessment of aromatase inhibitors. "Optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen," the expert panel wrote in the assessment, which will be published this month in the *Journal of Clinical Oncology*. "Women with breast cancer and their physician must weigh the risks and benefits of all therapeutic options."

The latest update of ATAC, taken with results from earlier trials, shows that there is a substantial reduction in relapse rate after 2 to 3 years on an aromatase inhibitor, Howell said in an interview. "That's serious business. It's probably becoming unethical to give 5 years of tamoxifen [as initial therapy]."

Others are more cautious about the data, including Eric Winer, M.D., director of the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, who chaired the panel that authored the ASCO technology assessment. Winer pointed out that the data

from the three major trials point to two main strategies for incorporating an aromatase inhibitor into routine practice—either as initial therapy or after one or more years of tamoxifen. "Which of those approaches will ultimately lead to the longest and best lives for women with breast cancer—we don't know yet," Winer said.

"My fear is that we are creating a culture in which every single woman who's postmenopausal with breast cancer will feel that she must immediately go on an aromatase inhibitor as her only therapy," he continued. "We may find out in a year—or 2 or 3—that many of those women would have benefited from the sequential use of those drugs."

But some researchers questioned whether use of anastrozole was justified in light of its higher cost (\$6.56 per day for anastrozole versus \$1.33 per day for generic tamoxifen) and lack of a demonstrated survival benefit. Howell responded to the charge by comparing it to other expenditures on breast cancer treatment.

"If we treated everybody in the United Kingdom with aromatase inhibitors, it would only be 4% of the



Eric Winer

budget spent on breast cancer—£8 million, which is half the amount spent on taxanes, which are used for advanced disease where there's not much survival advantage,"

Howell said. "The cost-benefit analysis comes out in favor of anastrozole because of its side-effect profile."

Compared with women who took tamoxifen, women who took

anastrozole had fewer cases of endometrial cancer, thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, hot flashes, and vaginal discharge. However, rates of fracture—specifically, vertebral fractures—and arthralgia were higher among women who took anastrozole.

A cost-effectiveness analysis, which was also presented at the San Antonio meeting by the ATAC Trialists' Group, was based on a variety of assumptions, including outcome projections from the completed treatment analysis of ATAC and cost estimates for endometrial monitoring for patients on tamoxifen and for bone density scans and bisphosphonate use for women on anastrozole. It found that the estimated cumulative costs per patient after 25 years were \$28,278 for the anastrozole group and \$23,164 for the tamoxifen group. The incremental cost-effectiveness ratio—the additional cost of anastrozole over tamoxifen per quality-adjusted life-year—was \$23,740, which falls under the threshold of \$50,000 to \$100,000 generally considered acceptable in cost-effectiveness studies.

“Based on the data [from the ATAC trial], when a physician who chooses to start a woman on anastrozole, it's nice to know from a societal point of view that that decision is a cost-effective one,” said Gershon Y. Locker, M.D., of Evanston Northwestern Healthcare in Illinois, who presented the cost-effectiveness analysis in a poster session at the San Antonio meeting.

And although the data show a statistically nonsignificant 12% improvement in breast cancer survival at a median of 68 months of follow-up, Howell pointed out that it was not until 7 years that the overall survival advantage became apparent in the seminal B-14 trial of tamoxifen in women with lymph node–negative, estrogen receptor–positive breast cancer.

“This is a very good-prognosis group of patients,” Howell said of the women in the ATAC trial. “Many in this group will die of cardiovascular disease and not breast cancer. We think that we may see a survival advantage after another 2 years, but that is by no means certain.”

—Kate Travis