ATAC Trialists Back Up-Front Use of Anastrozole

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Investigators of a key international trial comparing anastrozole to tamoxifen have concluded that their long-term safety results support up-front use of the aromatase inhibitor as an adjuvant treatment for hormone-sensitive early-stage breast cancer in postmenopausal women.

Risk-benefit analysis of adverse event and recurrence data from more than 6,000 women, most of whom had completed 5 years of hormonal therapy, demonstrated a significant advantage for anastrozole (Arimidex) over tamoxifen (Nolvadex), according to the Armidex, Tamoxifen, Alone or in Combination (ATAC) trialists' group.

"This benefit was greatest at 1-2 years of treatment, which indicates that a prospective strategy to start tamoxifen treatment but switch to an aromatase inhibitor afterward puts patients at risk of preventable recurrences and excess adverse events during the initial period of tamoxifen treatment," the investigators said (Lancet Oncol. 2006;7:633-43).

In an interview, Dr. Aman U. Buzdar, the principal investigator, said he did not think the ATAC findings would be the last word in the quandary over up-front vs. sequential use of aromatase inhibitors after a number of years of tamoxifen therapy. "I don't think it is resolved, but the evidence points to [up-front use]."

Dr. Buzdar, professor of breast medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston, said that the risk of recurrence peaks 2-3 years after treatment in women with either node-negative or node-positive breast cancer. "We can't predict which one will not get disease up front," he said in support of starting the more effective therapy immediately in all patients.

Current guidelines from the American Society of Clinical Oncology and the Na-

Expert Panel Eyes Inhibitor Issues

The International Aromatase Inhibitor Expert Panel of 24 breast cancer experts reviewed the major randomized trials of adjuvant treatment and concluded that aromatase inhibitors are superior to tamoxifen, whether given as an initial hormonal therapy or sequentially in patients who started on tamoxifen (Curr. Med. Res. Opin. 2006;22:1575-85). The panel also found, however, that the best way to use aromatase inhibitors is yet to be determined.

Among the issues addressed by the panel, which was supported by an unrestricted grant from AstraZeneca, are:

► **Patient populations.** Patients who were switched to aromatase inhibitors after they did not recur while on tamoxifen are not the same as patients who were randomized to a sequence of tamoxifen followed by an aromatase inhibitor. "Switching-study patient populations are by default enriched with patients who respond well to endocrine therapy by excluding patients who have had an early recurrence despite tamoxifen treatment," the panel wrote.

► **No direct comparisons.** Until the Breast International Group–98 trial publishes mature data comparing 5 years of letrozole therapy with sequence therapy, no data are available from trials comparing a sequential strategy with monotherapy. For now, the panel found that the best researchers can do is to construct models based on existing data.

► **Duration of therapy.** Although the optimal duration of tamoxifen therapy is 5 years, and 5 years has been adopted as the standard for endocrine therapy, the optimal duration of aromatase inhibition is not known.

► **Cardiac, stroke, and endometrial cancer risk.** Data on patients with preexisting coronary heart disease are not available for tamoxifen or aromatase inhibitors, according to the panel. Although there is no evidence that these patients should be excluded from treatment with aromatase inhibitors, this needs to be studied.

tional Comprehensive Cancer Network state that aromatase inhibitors alone or in combination with tamoxifen are better than tamoxifen alone. They recommend specific up-front and sequential strategies without stating a preference.

Category 1 evidence from randomized trials comparing aromatase inhibitors with tamoxifen supports up-front and sequential approaches, according to Dr. J. Leonard Lichtenfeld, deputy chief medical officer for the American Cancer Society in Atlanta. Without a head-to-head comparison of strategies in a randomized clinical trial, the decision remains up to clinician judgment, he said in an interview.

"There are obvious questions people will ask to which there are not obvious answers available," he said.

That the ATAC long-term analysis did not introduce any late side effects is perhaps its most salient contribution to the literature, according to the physicians interviewed.

"If there were any skeptics at the first ATAC report, the data have held up over time," Dr. Lichtenfeld said.

"Nothing new has emerged from that data," Dr. Buzdar said. "It is reassuring that there is nothing in the back that is lurking and may show up."

The ATAC investigators warned that their safety findings should not be extrapolated to letrozole and exemestane, the other two aromatase inhibitors in large clinical trials as adjuvant treatments for early-stage hormone-sensitive breast cancer. They noted that cardiovascular adverse events were no worse with anastrozole than with tamoxifen, whereas the other studies have raised concern about cardiovascular safety.

"Even though their efficacy may be the same, their safety may be different," Dr. Buzdar said. "We can't assume the other aromatase inhibitors will have the same safety data."

The ATAC trial and many of the investigators, including Dr. Buzdar, received financial support from AstraZeneca, maker of anastrozole and of Nolvadex, a trademarked form of tamoxifen, which recently became a generic drug.

Clinicians enrolled 9,366 postmenopausal women at 381 participating centers in 21 countries. A combination arm in which women were randomized to tamoxifen and anastrozole was dropped after an initial analysis showed no benefit over tamoxifen as a single agent.

In the latest analysis, 3,125 women assigned to monotherapy with anastrozole and 3,116 women on tamoxifen were followed for a median of 68 months (range 1-90 months). Dr. Buzdar noted that this is significantly longer than the follow-up so far in ongoing letrozole and exemestane trials. Only 8% of patients were still on their trial medication, with less than a year of treatment remaining.

Efficacy measures were based on the intent-to-treat population, but safety was based on the treatment of 3,092 women on anastrozole and 3,094 women on tamoxifen.

Women in the anastrozole group had fewer treatment-related adverse events (61% vs. 68%) and fewer serious adverse events that were treatment related (5% vs. 9%). They also were less likely to withdraw because of adverse events (11% vs. 14%).

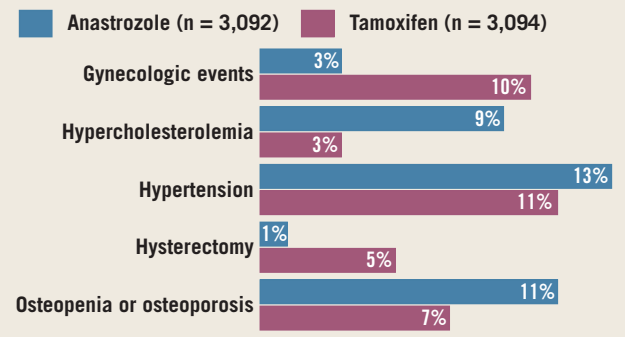
About 13% of both cohorts had died, but the tamoxifen patients were more likely to have died of breast cancer (9% vs. 8% of the anastrozole arm) and less likely to die without a recurrence of breast cancer (5% vs. 6%).

The analysis calculated the hazard ratio of death from breast cancer as 0.88 for anastrozole in comparison with tamoxifen.

In both groups, the women who died of breast cancer tended to be younger, with a median age 68 years vs. 74 years for those who died of other causes.

"There are a lot more women free of cancer down the line," Dr. Buzdar said, adding that the fact that they are dying older and of other causes "means we can prevent cancer in a much larger population, and they are having a normal life span." ■

Selected Side Effects With Long-Term Use of Anastrozole vs. Tamoxifen in the ATAC Trial



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