ATAC Investigators Back Anastrozole as Adjuvant

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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.

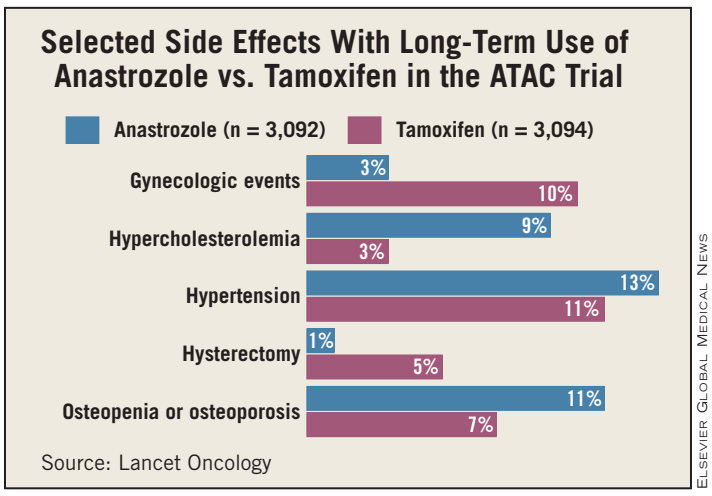
"This benefit was greatest at 1-2 years of treatment, which indicates that a prospective strategy to start tamoxifen treatment but switch to an aromatase inhibitor afterward puts patients at risk of preventable recurrences and excess adverse events during the initial period of tamoxifen treatment," the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

In an interview, Dr. Aman U. Buzdar, the principal investigator, said that 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]," he said.

Dr. Buzdar, professor of breast medical oncology at the University of Texas MD 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 National 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.



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"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. "Even though their efficacy may be the same, their safety may be different," Dr. Buzdar said.

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 centers in 21 countries. A combination arm using tamoxifen and anastrozole was dropped after 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). 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. ■

Expert Panel Backs Aromatase Inhibitors but Questions Remain

Dr. Buzdar is also the first author of a consensus statement published by an international panel of 24 breast cancer experts who met in December 2005 to review the major randomized trials of adjuvant treatment with tamoxifen and aromatase inhibitors.

The International Aromatase Inhibitor Expert Panel 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).

They 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. "It is possible that shorter or longer periods of adjuvant therapy may be suitable for different patients, depending upon their specific disease characteristics," the panel wrote.

► **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.

Some studies have associated tamoxifen with increased risk of stroke, endometrial cancer, and possibly deep venous thrombosis. The panel found that these risks are not predictable in individual patients, however. It also suggested that stroke risk may be reduced with one or more aromatase inhibitors, but more evidence is needed.

Tamoxifen-to-Exemestane Switch of Benefit in Early Breast Cancer

Atlanta — Postmenopausal women with early-stage hormone-receptive breast cancer who have done well on 2-3 years of tamoxifen therapy have significantly improved disease-free and overall survival if they are switched to exemestane midway through their hormonal treatment, researchers reported at the annual meeting of the American Society of Clinical Oncology.

The beneficial effects of tamoxifen tend to wane the longer women are treated, said Dr. Judith Bliss, director of the Clinical Trials and Statistics Unit at the Institute for Cancer Research in London. "Five years of tamoxifen has been the gold standard of treatment for hormone-sensitive postmenopausal breast cancer patients. But we know that the amount of benefit for tamoxifen is greater in the early years, compared with the later years of its use. We wanted to determine what we could add to this treatment to improve on the good results we already have," she said.

Accordingly, Dr. Bliss and her colleagues initiated the Intergroup Exemestane Study of more than 4,700 patients from 37 countries and 366 centers worldwide. In the study, patients who remained disease free after 2-3 years of tamoxifen therapy were randomized to continue on tamoxifen, or to start treatment with exemestane, an aromatase inhibitor approved for this purpose by the Food and Drug Administration and marketed as Aromasin by Pfizer. Disease-free survival, the trial's primary end point, was increased by approximately 25% in the women who were switched to exemestane, compared with women who remained on tamoxifen, Dr. Bliss reported.

At the time Dr. Bliss and her colleagues started the trial, routine testing of estrogen-receptor status was not being done in several countries. When they went back to determine estrogen-receptor status in their population, they were able to identify 122 women as hormone-receptor negative. After omitting them and reanalyzing the data, the results remained virtually the same, Dr. Bliss said in an interview.

Serious side effects overall were very low. Cardiovascular side effects were equal for both treatments. There was a slight increase in musculoskeletal side effects in women switched to exemestane. However, it is difficult to determine whether this increase was due to cessation of tamoxifen, which is known to be protective of bone, or due to exemestane, Dr. Bliss noted. "I think what we are seeing here is very exciting. By incorporating this switch, we add to the early benefit from treatment with tamoxifen," she said.

—Fran Lowry