Safety Data Reassuring

Anastrozole *from page 1*

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 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. The guidelines 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.

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.

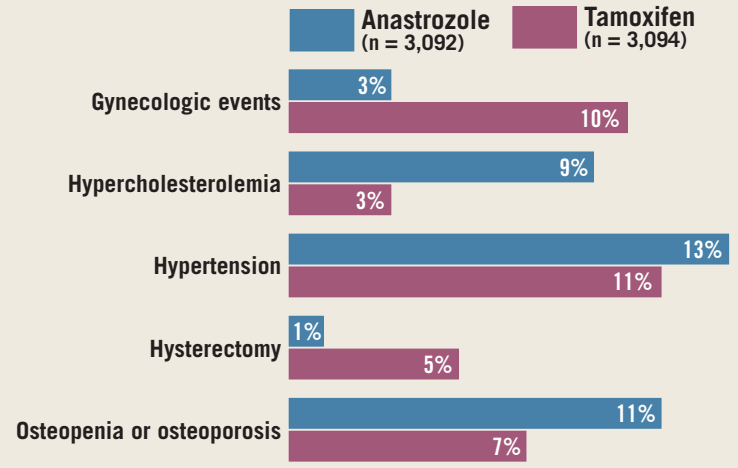
The ATAC trial and many of the investigators, including Dr. Buzdar, received financial support from AstraZeneca, maker of anastrozole and of Nolvadex, a trademarked form of tamoxifen, which recently became a generic drug.

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. ■

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



Source: Lancet Oncology

Elsevier Global Medical News

Panel Cautiously Supports Use of Aromatase Inhibitors

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 linked 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.

Aromatase Inhibitors Aid Cancer Survival

BY JANE SALODOF MACNEIL
Southwest Bureau

ATLANTA — Switching from tamoxifen to aromatase inhibitors improved overall survival for 8,794 breast cancer patients in four randomized phase III trials, according to a pooled analysis presented at the annual meeting of the American Society of Clinical Oncology.

Despite reporting benefits in progression-free survival, none of the individual published trials had shown that significantly more patients lived if they were switched to an individual aromatase inhibitor after 2-3 years of adjuvant hormonal therapy with tamoxifen.

Dr. Emilio Bria of Italy's Regina Elena National Cancer Institute in Rome and his coinvestigators found an absolute overall survival gain of 1.2% with aromatase inhibitors in the pooled data. They translated this into 100 patients who were cured as a result of the substitution. Patients switched to an aromatase inhibitor had a relative risk of 0.76 for death from any cause, compared with patients who continued on tamoxifen.

In looking for the effect of the whole class of drugs, 'we found there is a benefit in survival when you pool all the results.'

DR. BRIA

"We were looking not for the effect of a single drug, but the effect of a class of drugs," Dr. Bria said in an interview alongside the poster, where he was joined by the lead author, Dr. Mariangela Ciccarese. "We found there is a benefit in survival when you pool all the results."

The pooled analysis only addressed an early-switch strategy, as Dr. Bria said he could not find enough trials that have so far reported outcomes for up-front hormonal therapy with an aromatase inhibitor or for late switching to an aromatase inhibitor. He said he hopes to pool additional studies and compare early, up-front, and late strategies when more trials become available.

The pooled trials compared continued tamoxifen use to initial tamoxifen followed by aminoglutethimide, exemestane, or anastrozole (J. Clin. Oncol. 2001;19:4209-15, N. Engl. J. Med. 2004;350:1081-92, J. Clin. Oncol. 2005;23:5138-47, Lancet 2005;366: 455-62).

Other highly significant findings in the pooled analyses included a relative risk ratio of 0.67 for any event (local or distant relapse, secondary breast cancer, or death from any cause) in the aromatase inhibitor group. The relative risk of distant recurrence was 0.65 with aromatase inhibitors, with an absolute benefit of 2.4% and a need-to-treat estimate of 43 patients to prevent one death.

Patients switched to aromatase inhibitors were significantly more likely than patients who continued on tamoxifen to have fractures and musculoskeletal pain. The relative risk ratios were 1.50 and 1.33, respectively. Cardiovascular events also increased slightly, with a relative risk ratio of 1.22. ■