Adjuvant Endocrine Therapy Trials in Postmenopausal Patients

The ATAC trial reported initial results in December 2001, demonstrating an advantage in disease-free survival (DFS) with the third-generation aromatase inhibitor anastrozole compared to tamoxifen. An advantage was also seen in safety and tolerability with regard to thrombotic events and endometrial cancer, although fractures and arthralgias were more common in women treated with anastrozole. At the 2003 San Antonio Breast Cancer Symposium, further data were presented demonstrating an even greater advantage to anastrozole compared to tamoxifen in women with ER-positive, PR-negative tumors. The first overall survival analysis from the ATAC trial will be presented at this meeting, and other trials evaluating letrozole and exemestane as up-front therapy in postmenopausal patients are maturing and are likely to have initial data available in the near future.

### ATAC ADJUVANT TRIAL: SUBGROUP ANALYSIS OF PATIENTS WITH ER-POSITIVE, PR-NEGATIVE DISEASE

The ATAC trial enrolled 9,366 patients, and the first report demonstrated a significant benefit for the patients with hormone receptor-positive disease who were treated with anastrozole compared to tamoxifen. The hazard ratio for disease-free survival in this group was 0.78. The 47-month analysis had a similar hazard ratio. Because the ATAC trial was designed in 1994 and initiated in 1996, it didn't require the patients to have ER- and/or PR-positive disease for enrollment. Hence, a very small proportion of patients had ER- and PR-negative disease, and a larger cohort had ER- or PR-unlabeled disease. We retrospectively analyzed the historical blocks from those patients for their ER and PR status to obtain a more comprehensive view of the influence of the ER and PR status on the outcomes of the trial. We asked whether the PR status had any impact on the relative benefit associated with anastrozole and tamoxifen in patients with ER-positive disease.

In the patients with ER- and PR-negative disease, which consisted of approximately 5,700 patients, anastrozole was more beneficial than tamoxifen, with a hazard ratio of 0.82. In the patients with ER-positive and PR-negative disease, a very substantial difference was noted, with a hazard ratio of 0.48, indicating that patients treated with anastrozole had almost as many relapses as patients treated with adjuvant tamoxifen. The comparison between patients with ER- and PR-positive disease to patients with ER-positive and PR-negative disease was borderline for significance, although this was a retrospective subgroup analysis, I hope that other aromatase inhibitor trials will perform the same analyses to substantiate this finding.

— Mitchell Dowsett, PhD

We don’t know why the ER-positive, PR-negative phenotype behaves so differently, but Dowsett and Osborne have formulated a hypothesis that involves contrasting the effect of tamoxifen versus anastrozole on the classical nuclear versus nonclassical membrane estrogen receptor pathways. When the nuclear pathway is intact, estrogen activates the estrogen receptor, which induces the synthesis of the progesterone receptor; however, we can hypothesize that pathway is not functioning in ER-positive, PR-negative tumors, and if the membrane pathway is activated, it can lead to the activation of growth factor receptors and induce cell growth. Tamoxifen is an antagonist in the nuclear pathway (hypothetically, the nonfunctioning pathway in the ER-positive, PR-negative subset) and it’s an agonist in the membrane pathway, which may result in stimulating growth factors and tumor growth. On the other hand, aromatase inhibitors reduce estrogen levels to nearly zero and are antagonists on both pathways. This may explain the striking additional benefit of anastrozole seen in the ER-positive, PR-negative subset, which is the phenotype for 20 percent of breast cancer patients. The HER2 assays have not yet been performed in the ATAC trial, but some have speculated that the subset of patients with the ER-positive, PR-negative phenotype may also be HER2-positive. However, we’ve known for years that only 10 or 15 percent of HER2-positive tumors are ER-positive and, while most of those are PR-negative, I don’t believe that small subset could be entirely responsible for these intriguing results.

— Craig Allard, MD

**TIME COURSE OF BONE FRACTURES IN ATC**

“Sex-monthly fractures remain constant for both an (anastrozole) (range 0.93 to 1.57) T (tamoxifen) (0.58 to 1.37), with the greatest difference between A and T seen at 18 and 24 months. After 24 months, the 6-monthly fracture rates seen with A reached a plateau. Overall, clinical presentation sites of hip + spine + wrist, showed similar patterns. Anastrozole leads to an increased fracture incidence compared with T, a drug known to have a positive effect on bone. Importantly, the fracture rate in the A-treated group appeared to have stabilized after reaching a peak at 2 years.”