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. At the recent 2004 San Antonio meeting, data were presented from the third analysis at 68 months. An advantage to anastrozole in disease-free survival continued to be present with about one in four relapses on tamoxifen avoided with anastrozole.

CONCLUSIONS FROM THE ATAC TRIALISTS’ GROUP

The present data suggest that it is not appropriate to wait five years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1–3), and the balanced numbers of adverse events and treatment withdrawals associated with tamoxifen support the approach of offering the most effective and well-tolerated therapy at the earliest opportunity. Five years of anastrozole should now be considered as the preferred initial endocrine treatment for postmenopausal women with hormone receptor-positive localized breast cancer.


6-MONTH FOLLOW-UP OF THE ATAC TRIAL

The ATAC trial had a very important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have seen one year of follow-up after the therapy was completed.

I believe this is probably the most important of the three analyses, and this latest analysis allows me, as a practicing clinician, to change my mind and change therapy. I was still a practicing clinician when the data came out and I was the principal investigator of the trial. A Lancet article was published in parallel with the 2004 San Antonio presentation and, as a group, we have stuck our necks out and now would say that anastrozole is the preferred initial treatment for postmenopausal women with hormone receptor-positive disease.

The simplest interpretation of the results is that anastrozole prevents one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival. We can see this month-to-month with certain curves, which are useful for the statistical analyst but don’t really reflect what happens as the hazard rate dies off. A higher narrow peak for relapse occurs at two years, which then comes down again. Then a second, much flatter peak occurs after five years.

In the hazard rate analysis plot from the ATAC trial, we saw two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial — not only to help make therapeutic decisions, but also to give a fascinat- ing biological insight.

The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost abolishes that peak that if you wait two to three years, as some of the trials are reporting, the effects are wane. However, I believe you lose those patients who will relapse and ultimately die in those first two years.

— Michael Dowsett, MD, CMF

ADJUVANT AROMATASE INHIBITORS AS INITIAL THERAPY IN POSTMENOPAUSAL WOMEN

Since the third-generation aromatase inhibitors are better than tamoxifen, my postmenopausal patients with ER positive disease who have not yet started adjuvant hormonal therapy will initially receive an aromatase inhibitor — preferably anastrozole. We started using adjuvant anastrozole instead of tamoxifen after the first presentation of the ATAC trial results.

Even if tamoxifen and anastrozole had been therapeu- tically equivalent, anastrozole would still be prefere- able because it was better tolerated. For us, the issue of osteoporosis was always secondary. We already had experience with the biopharmaceutics and monitoring patients for osteoporosis because chemotherapy and ovarian ablation produce amenorrhea, menopause and accelerated bone resorption. We felt quite comfortable in matching our front-line adjuvant therapy to anastrozole.

— Gabriel N Hortobagyi, MD