

Commentary: Optimal Adjuvant Endocrine Therapy of Postmenopausal Breast Cancer

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ABSTRACT: There is a growing body of evidence that the optimal adjuvant endocrine therapy for hormone-sensitive breast cancer in postmenopausal women should include an aromatase inhibitor. However, further research is required to establish the optimal aromatase inhibitor and whether such a drug should be used as monotherapy or in sequence after 2 to 3 years of tamoxifen. *Int J Fertil* 50(5):00–00, 2005

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ANTI-AROMATASE AGENTS INHIBIT the cytochrome P-450 component of the aromatase enzyme complex responsible for the final step of estrogen biosynthesis in peripheral tissues. Third-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) are now considered the gold standard for endocrine therapy in the first-line and second-line settings for estrogen receptor (ER) and/or progesterone receptor (PgR) positive advanced breast cancer in postmenopausal women [1]. Furthermore, there is growing evidence that they are superior to tamoxifen in the adjuvant setting. The latter is the focus of this commentary.

The ATAC (Arimidex, Tamoxifen, Alone or in Combination) study has shown that 5 years of anastrozole is superior to tamoxifen in terms of efficacy and tolerability in treating postmenopausal women with ER-positive breast cancer [2]. There was a 12% statistically non-significant reduction in breast cancer-related deaths in the anastrozole group, compared with the tamoxifen group, and a reduction of borderline significance in distant metastases (hazard ratio: 0.84, $P = 0.056$). However, no significant dif-

ference in overall survival (OS) was seen after 68 months. This may be due to the fact that the follow-up interval is currently too short to see such a difference. However, another potential contributing factor to the similarity in OS is the increase in non-breast cancer deaths in the anastrozole group. The latter was due largely to an excess of new non-breast cancers (statistically nonsignificant). The incidence of fatal myocardial infarction events has not yet been analyzed or reported.

Several studies appear to have shown the aromatase inhibitors (AIs) to be superior in the adjuvant setting for postmenopausal women with ER-positive breast cancer during the first 5 years [2–4]. However, it is not clear when to start AIs. The ATAC study recommends a 5-year initial course of anastrozole instead of tamoxifen [2]. Two recent studies that switched patients from tamoxifen to an AI after 2 to 3 years showed a larger improvement in 5-year disease-free survival [DFS] (hazard ratios: 0.68, $P < 0.001$ and 0.60, $P = 0.0009$, respectively, in favor of the AI compared with 0.87 for ATAC), suggesting that patients may benefit from using both drugs sequentially [3,4]. Furthermore, there was a lower

incidence of non-breast malignancies in the exemestane arm of the International Exemestane Study (IES) [3]. However, it is important to note that cross-trial comparison among different population settings is inappropriate and can potentially lead to flawed conclusions. In addition, both switch studies' patients were disease-free at the time of randomization to either continued tamoxifen or AI (i.e., disease-free at 2 to 3 years of follow-up), making such a direct comparison with ATAC invalid.

The incidence of venous thromboses and endometrial tumors is lower in women taking an AI, compared with those taking tamoxifen. However, AIs are associated with a higher incidence of osteoporosis and fractures, and two of them (anastrozole and letrozole) have been shown to have an adverse influence on serum lipids [1–4].

One potential advantage of the sequencing approach would be the bone protection conferred by tamoxifen before starting an AI. It remains to be proven whether a sequencing approach will lead to a reduction in fractures. Data from the bone sub-protocol of the IES show that the gain in bone mineral density (BMD) in patients treated with tamoxifen for 2 to 3 years is rapidly lost. Differences in BMD appear within 6 months of switching, and the loss is similar to that seen with other aromatase inhibitors at 2% to 3% in the first year of therapy with exemestane.

Using Markov models to simulate 10-year disease-free survival among postmenopausal women with ER-positive breast cancer, Punglia et al, analyzed three treatment strategies: 5 years of tamoxifen alone, 5 years of an aromatase inhibitor alone, and sequential treatment consisting of tamoxifen with crossover to an aromatase inhibitor at 2.5 or 5 years [5]. The authors found that sequential therapy with tamoxifen followed by crossover to an aromatase inhibitor at 2.5 years yielded a significant improvement in DFS, compared with planned aromatase inhibitor monotherapy. At 10 years, the cross-over strategy achieved absolute DFS rates of 83.7% and 67.6% for node-negative and node-positive patients, respectively, compared with 82.6%

and 65.5%, respectively, for aromatase inhibitor monotherapy; this is a 6% relative risk reduction. The DFS improvement was apparent after 6 years. Later crossover from tamoxifen to an aromatase inhibitor at 5 years did not further improve 10-year disease-free survival estimates. This analysis suggests that sequential treatment could be superior to AI monotherapy in terms of DFS. A prospective comparison between 5 years AI and a tamoxifen/AI switch with upfront randomization (e.g., the BIG 1-98 study) will answer this question in due course [6].

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