ABSTRACT

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) clinical trial was the first large, randomized, double-blind study to show that treatment with an aromatase inhibitor (AI) improves clinical outcomes in postmenopausal women receiving adjuvant endocrine therapy for breast cancer. Since the publication of the initial findings from ATAC, several clinical reports, including longer-term follow-up evaluations from patients enrolled in ATAC, have shown that the AIs—anastrozole, letrozole, and exemestane— increase the likelihood of disease-free survival in hormone receptor-positive, postmenopausal women who have undergone surgical treatment for early breast cancer. In response to these clinical trial results, the American Society of Clinical Oncology (ASCO) convened an expert consensus panel to review the evidence supporting the use of AIs in breast cancer therapy and to develop a set of treatment guidelines. Since its original development this ASCO Technology Assessment has been revised several times as new clinical trial data became available, including a recent revision published in the January 20, 2005, issue of the Journal of Clinical Oncology. The consensus panel concluded that postmenopausal women with hormone receptor-positive breast cancer should receive an AI. AIs are preferred as initial therapy for women with contraindications to tamoxifen; other women may receive an AI for 5 years, or initial treatment with tamoxifen followed by an AI. A number of important issues have not been resolved by the available randomized trials, including the optimal duration of treatment and the long-term risks of adverse events.

(B)eginning with the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, the preliminary results of which were first presented at the San Antonio Breast Cancer Symposium in 2001, a series of large randomized clinical trials have evaluated the efficacy and safety of adjunctive treatment with an aromatase inhibitor (AI) for postmenopausal women with breast cancer. The ATAC trial found that the AI anastrozole significantly increased the likelihood of disease-free survival in postmenopausal women with early breast cancer compared with tamoxifen during 3 years of treatment. The combination of tamoxifen and anastrozole was not significantly more effective than tamoxifen alone. Anastrozole improved the disease-free survival rate of women who were hormone receptor-positive, but not of women who were hormone receptor negative. Since the publication of these initial ATAC findings, several additional reports have further characterized the role of AIs in postmenopausal women with breast cancer. Additional findings from the ATAC trial through 5 years of treatment confirmed that anastrozole produced a greater likelihood of remaining free of recurrence than did tamoxifen. In the Italian Tamoxifen Anastrozole (ITA) trial, a much smaller trial involving only 426 patients with...
node-positive, estrogen receptor (ER)-positive breast cancer, patients underwent 2 to 3 years of treatment with tamoxifen and were then randomized to either continue tamoxifen or to switch to anastrozole, for a total of 5 years of treatment. At a preliminary evaluation after a median of 3 years, the likelihood of disease recurrence was lower among the patients who switched to anastrozole than among those who continued with tamoxifen. The hazard ratio for disease recurrence with anastrozole was 0.35 (95% confidence interval [CI], 0.18-0.68; \( P = .001 \)). The Intergroup Exemestane Study (IES) employed a similar design to evaluate the efficacy of the AI exemestane. A total of 4742 women with node-positive or node-negative breast cancer who were either ER-positive or with unknown ER status were treated with tamoxifen for 2 to 3 years and were then randomized to continue tamoxifen or to switch to exemestane.\(^7\) After a median follow-up period of 30 months, the hazard ratio for metastatic disease, local recurrence, contralateral breast cancer, or death from any cause for the exemestane group was 0.68 (95% CI, 0.56-0.82; \( P < .001 \)) compared with tamoxifen. The MA-17 trial examined 5 years of letrozole or placebo treatment in 5187 women who had already completed 5 years of treatment with tamoxifen.\(^6\) At the first interim analysis, the estimated 4-year disease-free survival rates were 93% with letrozole and 87% with placebo (\( P \leq .001 \)). The hazard ratio for a local or metastatic recurrence or a new contralateral breast cancer with letrozole was 0.57 (95% CI, 0.43 to 0.75; \( P = .0008 \)). In none of these studies has an AI been shown to improve the likelihood of overall survival, though the MA-17 study demonstrated an improvement in survival for the node-positive subgroup.\(^7\)

In response to the publication of these clinical trial findings, the American Society of Clinical Oncology (ASCO) has developed and published a series of technical assessments summarizing clinical research and treatment recommendations for the use of AIs for postmenopausal women with hormone receptor-positive breast cancer. An initial report was published in 2002, with updates in 2003 and 2005.\(^4\) Since the publication of the most recent assessment, preliminary results have become available from 2 additional large clinical trials, although these results are not likely to require significant modifications to the most recent ASCO recommendations. In January 2005, results from the Breast International Group (BIG) 1-98 clinical trial were presented at St Gallen, Switzerland.\(^9\) In BIG 1-98 more than 8000 women with early breast cancer were randomized to 1 of 4 treatment strategies: tamoxifen for 5 years; letrozole for 5 years; tamoxifen for 2 years followed by letrozole for 3 years; or letrozole for 2 years followed by tamoxifen for 2 years. The results of a preliminary analysis, which compared outcomes after a median follow-up of approximately 2 years, found that the cumulative incidence of breast cancer relapse over 5 years was 13.6% with tamoxifen and 10.2% with letrozole (\( P = .0002 \)). In August of 2005, a combined analysis of the Austrian Breast Cancer Study Group (ABCSG) trial 8 and Arimidex/Nolvadex (ARNO) 95 trial examined clinical outcomes in 3224 postmenopausal women with hormone-sensitive early breast cancer who were randomized to switch to anastrozole or continue tamoxifen after 2 years of treatment with adjuvant tamoxifen.\(^10\) After a median duration of follow-up of 28 months from randomization, the hazard ratio for recurrence-free survival was 0.60 (95% CI, 0.44-0.81; \( P = .0009 \)) in favor of the group who switched to anastrozole.

The ASCO technical assessment reviewed the available clinical trial data that compared AIs with placebo or with tamoxifen for postmenopausal patients with breast cancer and developed recommendations for treatment where possible, while acknowledging that there are questions for which no definite answers yet exist. The available evidence suggests that an AI should be used either as initial therapy or after initial treatment with tamoxifen. The use of an AI for 5 years was considered the treatment of choice for women with hormone receptor-positive invasive breast cancer for whom tamoxifen is contraindicated. For other women, neither the optimal timing (initial or after a course of tamoxifen) nor duration (2 to 5 years) of AI therapy is firmly established. The ASCO panel indicated, based on the results of the clinical trials, that a variety of strategies would be reasonable and that there is no evidence that either approach is associated with better overall survival. The results of the most recent ATAC trial update suggest that long-term overall survival is not different among patients randomized to tamoxifen or to anastrozole.\(^11\)

Many recurrences of hormone receptor-positive breast cancer take place more than 5 years after surgery, and the optimal approach to improve long-term outcomes remains unclear. The MA-17 study has revealed a significant survival advantage in women...
with node-positive disease. Further follow-up is needed to determine if this survival advantage is maintained or may even increase. An AI should be used for patients who have contraindications to tamoxifen. Perhaps the most significant contraindication to tamoxifen use is a history of a deep-vein thrombosis. Based on data presented by Dr Judy Garber from the Cancer and Leukemia Group B (CALGB), it has been suggested that even in the absence of thrombosis, a factor V Leiden mutation is sufficient reason to avoid tamoxifen.

A number of other questions are unanswered about the role of AIs as adjuvant therapy for breast cancer. The ASCO technology assessment panel was not able to reach consensus about the best treatment for patients with ER-positive, progesterone receptor (PgR)-negative disease. Some experts believe based on data from the ATAC study that women with PgR-negative disease should receive an AI as initial therapy. However, the BIG 1-98 study did not identify differences in outcomes based on PgR status. Many medical oncologists in both academic and community settings believe that AIs should be used for human epidermal growth factor receptor 2 (HER2)-positive patients. Beneficial effects of AI therapy have been demonstrated in a relatively small number of patients with HER2-positive disease in the preoperative setting, and it is not clear that these results can be extrapolated to longer durations of treatment.

Treatment exposure in the available trials lasted from 2 to 3 years in trials in which patients were crossed over from tamoxifen, and for up to 5 years in the MA-17 trial. It is not clear at present whether patients who switch from tamoxifen to an AI after 2 to 3 years should be treated for a total of 5 years, or should receive an AI for 5 years in addition to their previous tamoxifen treatment. No clinical trial data are available to guide the use of tamoxifen after treatment with an AI. This is an important unanswered question that may be answered by the BIG 1-98 trial.

There is no role for an AI as monotherapy in premenopausal women. The strategy of ovarian suppression using a luteinizing hormone-releasing hormone agonist followed by an AI should generally be reserved for patients in clinical trials. Caution should be exercised in women who appear to be postmenopausal as a result of chemotherapy. Amenorrhea induced by chemotherapy can be transient, and menstrual cycles may resume many months after the termination of chemotherapy.

**Conclusion**

The results of several large, randomized, placebo-controlled or tamoxifen-controlled trials have shown that treatment with an AI significantly improves the likelihood of disease-free survival following surgical treatment of early breast cancer in postmenopausal women. In general, the results of these trials have not clearly demonstrated improvement in overall survival with use of AIs. Early results from the MA-17 clinical trial have demonstrated an improvement in survival among patients with node-positive disease. Important questions about the optimal timing and duration of therapy as well as patient subpopulations most likely to benefit from AI therapy cannot be answered definitively on the basis of current clinical trial results. Further follow-up of completed studies, future studies, and analysis of correlative endpoints will be critical in the months and years ahead.

**References**


