The Aromatase Inhibitors as Adjuvant Therapy for Hormone Receptor-Positive Breast Cancer

Jennifer A. Ligibel, MD, and Eric P. Winer, MD, Boston, Massachusetts

With the widespread use of screening mammography, the vast majority of breast cancers in the United States are diagnosed in the early stages, before distant metastases have developed. Many of these women will enjoy long-term disease-free survival; however, a proportion will suffer a disease relapse months to years later. New agents are continuously being tested for use in the adjuvant setting in an attempt to further decrease the rate of breast cancer recurrence and subsequent breast cancer deaths.

Adjuvant hormonal therapy has been shown to reduce the risk of breast cancer recurrence and increase survival in women with estrogen or progesterone receptor-positive tumors. The Scottish tamoxifen trial showed an increase in both disease free and overall survival in women with estrogen receptor (ER)-positive tumors treated with tamoxifen. This benefit was seen in both node-negative and node-negative patients and was not dependent on menopausal status. The National Surgical Adjuvant Breast Program (NSABP) B-14 trial also showed an increase in disease-free and overall survival in node-negative patients treated with 5 years of adjuvant tamoxifen after resection of an ER-positive breast cancer. Based on the results of these trials and the Early Breast Cancer Trialists’ Collaborative Group meta-analysis, tamoxifen became standard treatment for women with ER-positive tumors, regardless of menopausal or nodal status.

Given the long follow-up duration in these adjuvant tamoxifen studies, the side effect profile of tamoxifen has been well documented. Many women experience hot flashes and vaginal discharge. More rarely, tamoxifen can lead to an increased risk of uterine cancer and venous
clotting. There is also a slightly increased risk of cerebral vascular events, especially in women over the age of 50. Many of these toxicities did not become evident until hundreds of thousands of patient-years of follow-up data were available, both from the adjuvant tamoxifen studies and from the use of tamoxifen in large, randomized prevention trials.

Although these studies have shown that adjuvant tamoxifen does increase survival in women with ER-positive breast cancer, work is ongoing to find newer agents with better efficacy and less toxicity. Efforts have been made to target the estrogen-dependence of breast tumors in novel ways. Tamoxifen acts as a mixed estrogen agonist-antagonist and blocks the ER proteins on breast cancer cells. This depletes tumor cells from the growth-stimulating effects of endogenous estrogen. In recent years, a newer class of agents, the aromatase inhibitors, has been developed. These agents prevent conversion of adrenal androgens into estrogens via inhibition of the cytochrome-p450-dependent enzyme aromatase. This enzyme complex is responsible for the majority of estrogen production in postmenopausal women and men.

Aminoglutethimide, the first aromatase inhibitor developed, was introduced in the late 1970s. The drug was shown to have efficacy in hormone receptor-positive breast cancer, but its use was limited by its concomitant suppression of cortisol and aldosterone production. In the mid 1990s, aromatase inhibitors with much greater specificity for the aromatase enzyme were developed, which produced no clinically relevant suppression of cortisol or aldosterone. These third-generation inhibitors include the steroidal drug exemestane and the nonsteroidal drugs letrozole and anastrozole. The steroidal inhibitor binds irreversibly to the aromatase enzyme, while the nonsteroidal inhibitors form covalent, reversible bonds. Despite this slight difference in mechanism of action, both classes of drugs are very potent inhibitors of aromatase and have been shown to decrease estrogen levels to below the lower level of detection of most clinical assays.

The aromatase inhibitors are currently used only as monotherapy in postmenopausal women and in men. In premenopausal women, studies with first- and second-generation aromatase inhibitors have shown that high levels of endogenous androstenedione compete with the drugs as substrates for the aromatase enzyme complex. Therefore, estrogen synthesis is not completely blocked. Lower estrogen levels in premenopausal women also trigger increased gonadotropin levels, resulting in increased ovarian aromatization. At this time, no information is available regarding the use of third-generation aromatase inhibitors as monotherapy in premenopausal women. Therefore, these drugs are used only in combination with ovarian suppression in this patient population, and there is relatively limited experience with this approach.

The third-generation aromatase inhibitors initially gained FDA approval for second-line therapy of metastatic, hormone receptor-positive breast cancer. Anastrozole, letrozole, and exemestane each were shown to be equivalent or superior to megestrol acetate in women with metastatic breast cancer whose tumors had progressed on tamoxifen. Given their favorable side effect profile, the drugs became widely used in the metastatic setting. More recently, letrozole and anastrozole each were compared with tamoxifen as first-line therapy for advanced breast cancer. Again, the drugs were found to have equivalent efficacy and were granted FDA approval for use as first-line therapy of advanced, hormone receptor-positive breast cancer. Trials comparing exemestane and tamoxifen are underway.

Given the lack of toxicity and efficacy of the third-generation aromatase inhibitors in advanced disease, researchers have shown much interest in evaluating these drugs in the adjuvant setting. Many trials are currently underway to determine the optimal adjuvant hormonal therapy in terms of efficacy and tolerability. Some of these trials directly compare the aromatase inhibitors and tamoxifen, while others look at sequential treatments using both tamoxifen and aromatase inhibitors.

### Aromatase Inhibitors in the Adjuvant Setting

Few published studies evaluating the use of aromatase inhibitors in the adjuvant setting are currently available. Most of the studies reported to date have looked at the use of the first-generation aromatase inhibitor aminoglutethimide. These studies are not comparable with those using the newer third-generation agents, because the third-generation compounds lead to a more complete suppression of aromatization and therefore lower estrogen levels. The newer agents are also more tolerable than aminoglutethimide, probably
leading to better treatment adherence and fewer adverse events. Nevertheless, the aminoglutethimide trials did establish the feasibility of using aromatase inhibitors in the adjuvant setting.

Jones et al. performed the first trial using aminoglutethimide in the adjuvant setting. The investigators randomized 354 postmenopausal, node-positive women to receive aminoglutethimide or placebo. Local therapy was left to the discretion of the treating physician, but patients did not receive chemotherapy or any other form of adjuvant treatment. Aminoglutethimide was initially dosed at 250 mg twice daily, with dose escalation to 250 mg 4 times a day if tolerated. Hydrocortisone replacement was also administered to women in the aminoglutethimide arm. Adjuvant therapy was continued for 2 years. The primary end point was event-free survival, defined as time to breast cancer recurrence or death. Baseline characteristics were well balanced between the groups. The average age was 61 years; 58% of women had more than 4 nodes involved, and local therapies were similar in the 2 treatment arms. Estrogen receptor status was available for only 52% of patients; 73% of the patients in whom hormonal status was known were ER negative.

An interim analysis at 26 months median follow-up reported significantly better event-free survival in the aminoglutethimide arm. At 2 years, the log hazard ratio for events in the aminoglutethimide arm was –0.5 [95% confidence interval, –0.1 to –0.9]. No survival analysis was reported at that time. However, an update was published after a median follow-up of 8.1 years. At that time, the study showed no benefit for aminoglutethimide in terms of overall or event-free survival. There were 105 events in the aminoglutethimide group compared with 107 events in the placebo group (P = .41). Ninety-three deaths occurred in each group. Subset analysis showed a trend toward increased event-free survival in patients with ER-positive tumors treated with aminoglutethimide versus placebo; however, this did not reach statistical significance (64% vs 58%; P = .054). Toxicity was significantly higher in the aminoglutethimide group. Common side effects included lethargy, astasia, and rash. Multiple studies of tamoxifen in the adjuvant setting have suggested that a 5-year course of adjuvant hormonal therapy is most efficacious and that only hormone receptor-positive patients gain benefit from this type of adjuvant therapy. Thus, the abbreviated course of adjuvant hormonal therapy administered in this study, as well as the large number of ER negative and unknown patients included, make these data difficult to interpret.

Another adjuvant aminoglutethimide trial compared the standard 5 years of adjuvant tamoxifen to sequential treatment with tamoxifen followed by aminoglutethimide. In this trial, 380 postmenopausal women who were free of disease after 3 years of adjuvant tamoxifen were randomized to receive 2 additional years of tamoxifen or 2 years of aminoglutethimide at a dose of 250 mg/d. All patients had ER-positive or unknown disease.

The trial was stopped early due to a high incidence of toxicity in the aminoglutethimide arm. At a median follow-up of 61 months, 114 events had occurred: 59 events in the tamoxifen arm, including 10 non-breast cancer deaths, and 55 events in the aminoglutethimide arm, including 2 non-breast cancer deaths. Most of the non-breast cancer deaths in the tamoxifen group were attributable to myocardial infarctions or other cardiovascular events. Forty-two patients in each arm developed metastatic disease. There were 19 breast cancer deaths in the tamoxifen arm and 10 in the aminoglutethimide arm. Overall, no difference was found in event-free survival between the 2 groups, but the study did show a statistically significant improvement in overall survival in the aminoglutethimide group (P = .005) and a trend toward an improvement in breast cancer-specific survival in this group as well (P = .06). However, treatment-related side effects were much more common in the aminoglutethimide group and led to discontinuation of the study medication in 14% of patients, as compared with 4% in the tamoxifen group.

**Third-Generation Aromatase Inhibitors in the Adjuvant Setting**

At this time, only one trial comparing a third-generation aromatase inhibitor and tamoxifen in the adjuvant setting has been reported. In the ATAC trial (Anastrozole or Tamoxifen Alone or in Combination), 9,366 postmenopausal women with invasive breast cancer were randomized to receive 5 years of adjuvant anastrozole, tamoxifen, or a combination of the two. Primary end points were disease-free survival and tolerability.

Baseline characteristics were well balanced across the 3 groups. The average age was 64; one-third of the
patients had positive lymph nodes, and 64% had tumors less than 2 cm. Almost 84% of patients had estrogen receptor-positive tumors, and another 8% had unknown receptor status. Only 8% of patients were known to be ER negative, and these patients were equally distributed among the 3 arms. Prior treatments also were similar between the groups: 48% had undergone mastectomy, 62% had received radiation, and 21% had been treated with chemotherapy.

The group published an interim analysis after 33.3 months median follow-up. At that time, a total of 1,079 events had occurred: 317 in the anastrozole arm, 379 in the tamoxifen arm, and 383 in the combination arm. There was a statistically significant improvement in disease-free survival in the patients treated with anastrozole as compared with tamoxifen, with a hazard ratio of 0.83 (95% confidence interval [CI], 0.71–0.96). There was no difference in disease-free survival between the combination arm and the tamoxifen arm. Survival analysis was not performed. There was also a significant decrease in the incidence of contralateral breast cancers in the anastrozole group as compared with the tamoxifen group (odds ratio [OR] 0.42; 95% CI, 0.22–0.79).

The study also looked at the incidence of adverse events. Hot flashes, vaginal bleeding, endometrial cancer, stroke, and venous clotting were all more common in the tamoxifen arm, whereas musculoskeletal disorders, loss of bone density, and fractures were more common in the anastrozole arm. Toxicity in the combination arm was similar to that seen in the tamoxifen arm.

A second update at 47 months median follow-up was presented at the 2002 San Antonio Breast Conference. At the time of this analysis, a total of 1,373 first events had occurred. The hazard ratio for first events was 0.86 (95% CI, 0.76-0.99), favoring the anastrozole arm. There were 413 events in the anastrozole arm and 472 events in the tamoxifen arm (Table 1). The difference in the rate of contralateral breast cancers was no longer significant. There were an insufficient number of deaths across the 3 arms to perform a survival analysis.

An updated safety analysis was also presented at the conference. Endometrial cancer and vaginal complaints continued to be more common in the tamoxifen arm, with 15 cases of endometrial cancer in the tamoxifen arm versus 3 in the anastrozole arm (OR 0.2). Thromboembolic events and cerebrovascular events were also more common in the tamoxifen arm. Musculoskeletal disorders were slightly more common in the anastrozole group, and the risk of fracture in this group was also elevated (219 events vs 137; OR 1.60). Significantly fewer patients discontinued anastrozole for drug-related toxicity as compared with tamoxifen (5.1% vs 7.2%; P < .0001). The investigators also looked at differences in quality of life between the tamoxifen and anastrozole arms using the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument and found no overall difference in quality of life between the 2 groups. Patients treated with anastrozole reported fewer colds and night sweats (OR 0.83) as well as less vaginal discharge (OR 0.79). Those treated with tamoxifen were less likely to experience vaginal dryness (OR 0.66), pain during intercourse (OR 0.55), and loss of interest in sex (OR 0.53).

Based on the results of the ATAC trial, anastrozole was granted fast-track approval by the FDA for use as adjuvant therapy of postmenopausal women with hormone receptor-positive breast cancer. This approval was based on the analysis of recurrence-free survival after a median of 31 months of treatment, and the FDA stipulated that further follow-up of patients would be required to determine the long-term outcomes of patients treated with anastrozole in the adjuvant setting. The ATAC trial and other trials of

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<th>Table 1 Distribution of First Events in the ATAC Trial</th>
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<tr>
<td>33 Months</td>
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<tr>
<td>Anastrozole</td>
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<td>Total first events</td>
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<td>Local recurrence</td>
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<td>Distant recurrence</td>
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<td>Contralateral breast cancer</td>
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<td>Deaths without known recurrence</td>
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adjuvant anastrozole will continue to collect these data over the next several years.

After the initial release of data from the ATAC trial, the American Society of Clinical Oncology (ASCO) convened a multidisciplinary panel of experts to conduct a technology assessment on the role of aromatase inhibitors in the adjuvant setting. The group reviewed the published data describing the use of aromatase inhibitors in this setting and recommended that tamoxifen continue to be the standard adjuvant therapy in early stage breast cancer until additional data from the ATAC trial and other trials become available. In reaching this conclusion, the group cited concerns over the unknown effects of long-term treatment with aromatase inhibitors, especially on bone density. The group noted that the absolute difference in distant disease-free survival was less than 1%, and there has been no difference reported in overall survival. Studies have shown that the full benefit of tamoxifen requires 5 years of treatment, and that there is additional benefit even after tamoxifen is stopped. It is not clear if the same profile will exist for...

### Table 2 Selected Postmenopausal Adjuvant Breast Cancer Trials With Third-Generation Aromatase Inhibitors

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<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
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<tr>
<td>Aromatase inhibitors vs tamoxifen</td>
<td>Anastrozole and Tamoxifen Alone or in Combination (ATAC)</td>
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<tr>
<td>International Breast Cancer Study Group (IBCSG – 98) BIG-FEMTA</td>
<td>Tamoxifen 20 mg/d × 5 y versus Anastrozole 1 mg/d × 5 y versus Combination (placebo use)</td>
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<tr>
<td>Trials Evaluating Exemestane as Adjuvant Therapy (CRC-TU-TEAM)</td>
<td>Tamoxifen 20 mg/d × 5 y versus Letrozole 2.5 mg/d × 5 y versus Tamoxifen × 2 y → Letrozole versus Letrozole × 2 y → Tamoxifen</td>
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<tr>
<td>ABCSG AU08 Trial</td>
<td>Tamoxifen 20–30 mg/d × 3 y versus Anastrozole 1 mg/d × 3 y (placebo use)</td>
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<tr>
<td>German Adjuvant Breast Cancer Group (GR0001 trial) ARNO trial</td>
<td>Tamoxifen 20-30 mg/d × 3 y versus Anastrozole 1 mg/d × 3 y</td>
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<tr>
<td>Worldwide Intergroup Study Breast Cancer International Group (BIG) 031/BIG9702</td>
<td>Tamoxifen 20 mg/d × 2–3 y versus Exemestane 25 mg/d × 2–3 y (5 y total for hormonal therapy)</td>
</tr>
<tr>
<td>Austrian Breast Cancer Study Group (ABCsG) AU06 trial Adjuvant anastrozole after 5 years of endocrine therapy</td>
<td>Anastrozole 1 mg/d × 3 y versus Control</td>
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<tr>
<td>National Cancer Institute of Canada Clinical Trial Group (NCIC CTG MA17)</td>
<td>Letrozole 2.5 mg/d × 5 y versus Placebo</td>
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<tr>
<td>National Surgical Adjuvant Breast Project (NSABP B-33)</td>
<td>Exemestane 25 mg/d × 5 y versus Placebo</td>
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anastrozole, thus raising further concern about the short follow-up in this study.

Several additional trials are underway comparing aromatase inhibitors to tamoxifen in the adjuvant setting (Table 2). These trials have several basic designs: some compare 5 years of adjuvant tamoxifen with an aromatase inhibitor; others evaluate the use of sequential therapy with tamoxifen and an aromatase inhibitor; and the last group of studies randomizes patients to receive an aromatase inhibitor or placebo after completing 5 years of adjuvant tamoxifen. There is also a large adjuvant trial planned that will compare anastrozole with exemestane. Data from these trials should be available within the next few years and will help guide further adjuvant treatment recommendations for women with early stage breast cancer.

Conclusions

The third-generation aromatase inhibitors have gained widespread use in the treatment of metastatic breast cancer. Studies have shown that letrozole, anastrozole, and exemestane possess equivalent or superior efficacy to both megestrol acetate and tamoxifen in the metastatic setting. Most studies also have indicated that aromatase inhibitors are less likely than tamoxifen to lead to serious adverse events, such as venous clotting, stroke, and endometrial cancer. Incidence of hot flashes and nausea appear to be similar in patients treated with aromatase inhibitors and tamoxifen.

The precise role of aromatase inhibitors in postmenopausal women with early stage breast cancer remains uncertain. Previous studies using aminogluthethimide in this setting are not likely to be relevant because of the diminished efficacy and increased toxicity of this agent as compared with the third-generation aromatase inhibitors. Early results from the ATAC trial suggest that anastrozole may be more effective than tamoxifen in preventing breast cancer recurrence, but sufficient events have not yet occurred to allow for a survival analysis. In addition, because most patients have not yet completed a 5-year course of therapy, the long-term impact of an adjuvant course of anastrozole on breast cancer recurrence and other health parameters, such as osteoporosis and cardiovascular health, is not yet known. Further information is needed to determine whether aromatase inhibitors should be routinely used in place of tamoxifen. The ASCO technology panel did conclude that sufficient data exist to recommend anastrozole for postmenopausal women who have a contraindication to tamoxifen, and the FDA approved anastrozole in the adjuvant setting. At this time, no published data exist regarding the use of other aromatase inhibitors in the adjuvant setting.

Ongoing studies will provide more information regarding the efficacy and toxicity of anastrozole and other aromatase inhibitors in the adjuvant setting. These trials should answer many important questions, including whether the aromatase inhibitors should replace tamoxifen as adjuvant therapy for postmenopausal women, whether sequential therapy with aromatase inhibitors and tamoxifen provides any additional benefit to single-agent therapy, and whether one aromatase inhibitor is superior to the others in the adjuvant setting. The results of these trials will help guide the choice of hormonal agents in postmenopausal women and hopefully will help reduce the number of women who experience a breast cancer recurrence or other adverse event after their initial breast cancer diagnosis.

References

Aromatase Inhibitors in the Adjuvant Setting


24. Buzdar A. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer-updated efficacy results based on a median follow-up of 47 months [oral presentation]. San Antonio Breast Conference, 2002.


