The aromatase inhibitors are regarded as standard approaches to first- or second-line endocrine therapy in women with hormone-responsive metastatic breast cancer. Their efficacy and apparent lack of toxicity have led to their evaluation as adjuvant therapy. Although initial results with these agents in early breast cancer are promising, our collective long-term experience documenting tamoxifen’s benefits and our uncertainty about the long-term effects of aromatase inhibitors suggest that it is too early to recommend their routine use in the adjuvant setting. However, anastrozole is also a reasonable therapeutic option in the adjuvant setting, particularly in individuals with a contraindication to tamoxifen such as those with thromboembolic disease or those who develop breast cancer while receiving tamoxifen or raloxifene (Evista) therapy. Anastrozole (Arimidex) was recently approved by the Food and Drug Administration for the adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer. Ongoing trials are assessing the potential role of aromatase inhibitors in the adjuvant, neoadjuvant, and preventive settings.

ABSTRACT: The aromatase inhibitors are regarded as standard approaches to first- or second-line endocrine therapy in women with hormone-responsive metastatic breast cancer. Their efficacy and apparent lack of toxicity have led to their evaluation as adjuvant therapy. Although initial results with these agents in early breast cancer are promising, our collective long-term experience documenting tamoxifen’s benefits and our uncertainty about the long-term effects of aromatase inhibitors suggest that it is too early to recommend their routine use in the adjuvant setting. However, anastrozole is also a reasonable therapeutic option in the adjuvant setting, particularly in individuals with a contraindication to tamoxifen such as those with thromboembolic disease or those who develop breast cancer while receiving tamoxifen or raloxifene (Evista) therapy. Anastrozole (Arimidex) was recently approved by the Food and Drug Administration for the adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer. Ongoing trials are assessing the potential role of aromatase inhibitors in the adjuvant, neoadjuvant, and preventive settings.

The modest decline in breast cancer mortality in the United States in the late 1990s (3.4% annually) has been attributed to early detection strategies and effective adjuvant systemic therapy.[1] Despite these promising statistics, the 15-year survival rate for breast cancer is still only about 60%.[2] These data highlight the need for innovative therapies such as the new generation of aromatase inhibitors, including anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara). These drugs specifically target the enzyme aromatase, in contrast to earlier aromatase inhibitors such as aminoglutethimide (Cytadren), which were less selective, less potent, and more toxic.[3] Currently, the use of tamoxifen for 5 years is regarded as standard treatment for postmenopausal women with early-stage hormone-responsive breast cancer.[4] However, initial data from the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial[5] suggest that anastrozole may be at least as effective as tamoxifen for postmenopausal women with estrogen-receptor (ER)-positive tumors.

In this article, we review our current understanding of the role of aromatase inhibitors in the adjuvant treatment of postmenopausal hormone-responsive breast cancer. The review will focus on (1) the function of aromatase inhibitors in breast cancer, (2) clinical trials with aromatase inhibitors in advanced breast cancer, (3) data from trials of aromatase inhibitors in the adjuvant setting including the recently published ATAC trial, (4) results from studies of aromatase inhibitors in the neoadjuvant setting, and (5) current recommendations about adjuvant use of aromatase inhibitors.
peripheral conversion of androstenedione to estrogen, the final step in the estrogen biosynthesis pathway.[6] Aromatase activity is more important in postmenopausal women than in their premenopausal counterparts because most estrogen is produced in the ovaries and regulated by gonadotropins in premenopausal women.[6] In postmenopausal women, conversion of androgen to estrogen in peripheral tissues is the primary source of estrogen.[6] Aromatase is present in a number of important tissues in females including muscle, fat, skin, neural structures, and breast tissue.[7] Elevated levels of both estrogen and aromatase have been demonstrated in malignant breast tissue, supporting a role for in situ production of estrogen in malignant breast cells. Extensive preclinical and clinical data show that estrogen increases the growth and proliferation of breast cancer cells,[6] and estrogen deprivation leads to tumor regression.[4]

Mechanisms of Action

Aromatase inhibitors use two distinct mechanisms to block the action of aromatase and thereby reduce estrogen production. Type I inhibitors such as exemestane and formestane (Lentaron) are androgen-like compounds that bind irreversibly to the substrate-complex, causing permanent inactivation of the enzyme.[8,9] This could potentially lead to prolonged estrogen deprivation even after the drug is cleared. These drugs are also known as aromatase inactivators. Type II inhibitors such as aminoglutethimide, letrozole, and anastrozole are nonsteroidal compounds that reversibly bind to the heme-iron component of the aromatase enzyme, thereby inhibiting the conversion of androgen to estrogen in an indirect fashion.[8]

Pharmacokinetic Properties

Aminoglutethimide, the first clinically available aromatase inhibitor, was introduced in the late 1970s for the second-line treatment of postmenopausal women with advanced breast cancer.[10] The widespread use of this inhibitor was limited by its toxicity and lack of selectivity for the aromatase enzyme, leading to suppression of other steroidal synthetic pathways such as those for glucocorticoids and mineralocorticoids.[11] In 1993, 4-hydroxyandrostenedione, or formestane, became available as an intramuscular injection. It was more specific and associated with fewer systemic side effects but had to be given frequently and in large doses because of its extensive first-pass metabolism.[9] In the mid-1990s, a new generation of aromatase inhibitors including letrozole, anastrozole, and exemestane became available in the United States, and fadrozole was released abroad. These new drugs are administered orally and have long half-lives, enabling once-daily dosing. All three aromatase inhibitors have been shown to almost completely suppress aromatase activity (97%-99%) in postmenopausal women, leading to a significant decrease in estrogen production within 7 days. Maximal estradiol suppression occurs 50% earlier in women taking anastrozole and letrozole compared to exemestane.[8] Aminoglutethimide also suppresses aromatase activity in postmenopausal women by up to 85% but does not reduce estrogen levels to the same degree.[8,12-15] Of note, aromatase inhibitors have been shown to suppress estrogen alone in premenopausal women who are already receiving gonadotropin-releasing hormone agonists.[3,16,17] The new aromatase inhibitors are also more selective and potent, resulting in decreased toxicity compared with aminoglutethimide, although type I steroidal inhibitors like exemestane can cause dose-related androgenic side effects.[18] Neither anastrozole nor exemestane affects cortisol and aldosterone levels, but both can suppress sex hormone-binding globulin levels. Letrozole can decrease cortisol and increase both aldosterone and sex hormone-binding globulin levels.[8] Whether any of these biochemical and pharmacologic differences translate into significant clinical differences remains to be seen.[3,8]

There are also differences in how the aromatase inhibitors interact with tamoxifen. The simultaneous use of aminoglutethimide and tamoxifen leads to a 70% decrease in tamoxifen concentrations.[19] On the other hand, the combination of tamoxifen and letrozole results in a 40% reduction in plasma concentrations of letrozole.[20-21] Anastrozole does not seem to interact with tamoxifen when given in combination.[22,23] These results are important in the consideration of combined endocrine therapy.
Second-Line Therapy

All three aromatase inhibitors- letrozole (2.5 mg/d), anastrozole (1 mg/d), and exemestane (25 mg/d)- have been approved by the US Food and Drug Administration (FDA) as second-line hormonal therapy in postmenopausal women with estrogen-responsive disease. In randomized trials comparing letrozole, anastrozole, or exemestane to megestrol acetate in women who had received tamoxifen, time to progression and overall survival were as good, if not slightly better, with the newer drugs.[24-29] Similar results were observed in a randomized trial comparing letrozole with aminoglutethimide.[30]

Equally important in the setting of advanced disease, the aromatase inhibitors had superior toxicity profiles. Women taking either anastrozole or letrozole experienced less weight gain, dyspnea, peripheral edema, and vaginal bleeding compared to those taking megestrol acetate.[25-29] However, there was a mild increase in the likelihood of hot flashes, nausea, vomiting, and diarrhea, and hair thinning was also reported with letrozole. A similar toxicity profile was observed when exemestane was compared to megestrol acetate.[24] Not unexpectedly, significantly more women developed side effects to aminoglutethimide than to letrozole.[30]

First-Line Therapy

Anastrozole and letrozole have also been approved by the FDA for first-line hormonal therapy in postmenopausal women with estrogen-responsive disease, as an alternative to tamoxifen. In phase III randomized studies, time to progression was observed to be at least equivalent when letrozole and anastrozole were compared to tamoxifen,[31-33] and the impact on survival is under evaluation. In aggregate, these studies confirm the side-effect profiles described earlier. In phase III trials comparing anastrozole to tamoxifen, the incidence of thromboembolic disease, vaginal bleeding, and lethargy was lower, and the incidence of hot flashes and diarrhea was higher among women taking anastrozole.[31,33] A randomized comparison of letrozole and tamoxifen showed similar side-effect profiles except that hot flushes and hair thinning were slightly increased in women in the letrozole arm.[32] A phase III trial comparing exemestane to tamoxifen is under way.

Relative Efficacy

Investigators have begun to question whether one aromatase inhibitor is superior to another. A small crossover trial examining the endocrine effects of anastrozole and letrozole suggested that letrozole leads to greater suppression of aromatization and estrogen levels.[34] However, preliminary data from a trial comparing letrozole to anastrozole as first-line therapy in postmenopausal women with advanced breast cancer showed no difference in time to progression, the primary end point of the study.[35] That said, patients who develop resistance to the nonsteroidal inhibitors anastrozole, letrozole, or aminoglutethimide have a documented response rate and clinical benefit after exposure to a steroidal inhibitor like exemestane.[36] Thus, it is possible that clinically relevant differences in the effects of the various aromatase inhibitors will emerge with further testing. In aggregate, these trials have shown that aromatase inhibitors are effective and well tolerated in postmenopausal women with hormoneresponsive advanced breast cancer. These findings supported the testing of aromatase inhibitors in the setting of early-stage breast cancer. However, these trials cannot provide information about long-term toxicity, a major concern in the adjuvant setting.

Adjuvant Setting

Aminoglutethimide

Aminoglutethimide was the first aromatase inhibitor to be evaluated in the adjuvant setting. In a multicenter trial in the United Kingdom, 354 women with node-positive breast cancer were randomized to receive either aminoglutethimide (250 mg po qid) and hydrocortisone (20 mg po bid) or placebo for 2 years after surgical treatment. Aminoglutethimide appeared to be superior to placebo for disease-free survival in the 4-year interim analysis, but no difference in disease-free or overall survival was observed at a median follow-up of 8.1 years.[37] Excess toxicity was seen with aminoglutethimide, leading to premature closure of the trial. Agranulocytosis developed in three patients receiving aminoglutethimide; in one case, the condition was irreversible and fatal despite discontinuation of the drug. Although not statistically significant, more cardiovascular deaths occurred among women taking aminoglutethimide compared to placebo, and an increase in the incidence of nausea, lethargy, ataxia, and skin rash was also observed.
Another randomized trial accrued 380 postmenopausal women to receive either 3 years of tamoxifen therapy followed by 2 years of aminoglutethimide or 5 years of tamoxifen therapy.[38] At 5 years, there was no difference in disease-free survival, but a marginal benefit was seen in overall survival ($P = .005$) and breast cancer-specific survival ($P = .06$). The pattern of relapse was also different between the two groups: Women on tamoxifen therapy were more likely to relapse viscerally compared to women on sequential therapy ($P = .02$). Not surprisingly, aminoglutethimide was not tolerated as well as tamoxifen. In fact, excess toxicity and the availability of the third-generation aromatase inhibitors led to early closure of this trial as well.

**New Generation of Aromatase Inhibitors**

The promising results and sideeffect profile of the new generation of aromatase inhibitors in the advanced disease setting led to the initiation of several adjuvant trials in postmenopausal women. These studies address four areas of research: (1) direct comparison of an aromatase inhibitor to tamoxifen as the "gold standard," (2) sequential treatment with tamoxifen followed by an aromatase inhibitor (or the reverse) for 5 years compared to 5 years of either tamoxifen or the aromatase inhibitor, (3) the role of an aromatase inhibitor in women who have completed 5 years of tamoxifen, and (4) the comparison of steroidal and nonsteroidal aromatase inhibitors. In addition, the value of aromatase inhibitors as an adjunct to ovarian suppression in premenopausal women is under evaluation.

**Anastrozole**

The ATAC trial is the only adjuvant trial of a new aromatase inhibitor that has been published so far.[5] This large multinational double-blind placebo-controlled trial began in July 1996 and ended accrual in March 2000. The aim of the trial was to compare the efficacy and sideeffect profile of 5 years of anastrozole (1 mg po qd), tamoxifen (20 mg po qd), and the combination of tamoxifen and anastrozole in the management of postmenopausal women with early stage breast cancer. TABLE 1

![Key Features of the ATAC Trial](image)

A total of 9,366 postmenopausal women with histologically proven operable breast cancer of any steroid receptor phenotype who had completed local therapy with or without chemotherapy were randomized to one of the three study arms. Patient characteristics are summarized in Table 1. Compliance was good, with 84% of patients receiving 99% of the allocated treatment. At the time of analysis, 43% of patients had received 2 to 3 years of the allocated 5-year treatment, and the median duration of follow-up was 33 months.

- **ATAC Results**—The estimated 3-year disease-free survival was 89.4% in the anastrozole arm compared to 87.4% in the tamoxifen arm (hazard ratio: 0.83, 95% confidence interval [CI]: 0.71-0.96, $P = .013$) and 87.2% in the combination arm (hazard ratio: 0.81, 95% CI: 0.70-0.94, $P = .006$). Thus, there was a statistically significant 2% difference in disease-free survival between women who received anastrozole and those who received tamoxifen. A similar difference was observed favoring anastrozole over the combination arm.

In absolute terms, local recurrences occurred in 16 more women, and distant recurrences occurred in 24 more women who took tamoxifen compared to those who took anastrozole. When women who were hormone-receptor-negative were excluded from the analysis, disease-free survival at 3 years increased to 91.2% in the anastrozole arm and 89.3% in the tamoxifen arm. Thus, the difference in outcome between patients given anastrozole vs tamoxifen remained the same.
In a subgroup analysis, the investigators found no difference in disease-free survival for women whose tumors were hormone-receptor-negative, confirming the lack of benefit of endocrine therapy in these women. Notably, there was also no difference in outcome for tamoxifen and anastrozole in the minority of women who had received prior chemotherapy. These tumors may have been largely steroid receptor-negative, but a ready explanation for this observation is not available.

From the published data, overall survival has been similar in all three arms of the trial; 200 deaths were reported in the anastrozole arm, compared with 203 in the tamoxifen arm, and 215 in the combination arm. The number of deaths thought to be unrelated to breast cancer in each arm was between 33% and 40%. A formal comparison of these results is planned for after at least 704 deaths have occurred in the anastrozole and tamoxifen arms.

An unexpected finding in this study was that the combination of tamoxifen and anastrozole resulted in the same benefit as that seen with tamoxifen alone. This does not appear to be related to an adverse pharmacokinetic interaction between the two drugs, as noted earlier. Based on preclinical models, it has been suggested that tamoxifen may act as an estrogen agonist rather than an antagonist in a setting of extreme estrogen deprivation.[39]

Anastrozole also had a superior effect on the incidence of contralateral breast cancer in the ATAC trial. Women taking anastrozole had a 58% decrease in the risk of developing a contralateral breast cancer compared to tamoxifen (odds ratio: 0.42, 95% CI: 0.22-0.79, \( P = .007 \)). However, the numbers in each group were small: 30 cases of invasive carcinoma and 3 cases of ductal carcinoma in situ were diagnosed in the tamoxifen group, whereas 9 cases of invasive cancer and 5 cases of ductal carcinoma were diagnosed in the anastrozole group.

**Toxicity in the ATAC Trial**—This large blinded study provides excellent insight into the toxicity of these two agents. Fewer treatment-related withdrawals occurred among women taking anastrozole compared to tamoxifen. Anastrozole was associated with a significant reduction in hot flashes, vaginal bleeding and discharge, endometrial cancers, ischemic cerebrovascular events, and venous thromboembolic events.

However, use of the aromatase inhibitor also resulted in a significant increase in polyarthralgias and fractures of the spine (23 vs 10) and wrist (36 vs 25). The increased incidence of fractures is of concern given that the majority of the women in the trial have taken less than half the planned 5-year treatment, and it is likely that fractures will increase with time. The validity of this trial is supported by the observation that the number of events that occurred in the tamoxifen arm was similar to that reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of tamoxifen in 30,000 postmenopausal women with ER-positive breast cancer.[40]

**Considerations About ATAC**—Although the results of the ATAC trial are promising, caution is warranted in applying the results to clinical practice. This is because our knowledge base of anastrozole is limited, compared to the extensive literature on adjuvant tamoxifen that has been compiled over 20 years through metaanalysis and individual trials such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial—the largest single study of adjuvant tamoxifen.[40,41] Several concerns arise that suggest that it may be too early to translate the ATAC data into clinical practice outside a clinical trial. In this regard, the following points are worth considering:

1. In the ATAC trial, no survival difference between anastrozole and tamoxifen has emerged thus far. Nevertheless, it may emerge with time, as in the EBCTCG overview—5 years of adjuvant tamoxifen therapy resulted in a 47% decrease in disease recurrence and a 26% decrease in mortality after 10 years of follow-up.[5,40]

2. In the EBCTCG overview, the reduction in breast cancer recurrence, mortality, and contralateral cancers was significantly greater among women who received 5 years of tamoxifen therapy compared to 1 or 2 years of therapy. In the ATAC trial, the median duration of therapy so far is less than 3 years. Because the optimal treatment time with anastrozole is not known, we do not know what the ultimate impact of anastrozole will be and whether it will exceed that seen with 5 years of tamoxifen.[5,40]

3. The EBCTCG has shown that tamoxifen's beneficial effects on survival are sustained for at least 5 years after the cessation of tamoxifen therapy. Thus, many more years of follow-up will be required to demonstrate the overall benefit of tamoxifen and to permit an accurate comparison with anastrozole therapy.[40]

4. Tamoxifen's side effects have been well documented over many years of use. Widespread use of tamoxifen for nearly a decade was needed to confirm an increased incidence of endometrial cancer associated with the drug. Compared to tamoxifen, very little is known about the long-term side effects of anastrozole because this agent has been given largely to women with advanced breast
cancer. The increased fracture rate with anastrozole after less than 3 years of treatment is a concern, suggesting that some women taking anastrozole may also have to take a second drug to prevent bone loss. In addition, it is possible that other late and rare side effects will emerge.[5,40,41]

**Neoadjuvant Setting**

Aromatase inhibitors may also have a role in the neoadjuvant setting. Biochemical studies show that letrozole and anastrozole can significantly suppress both tissue and plasma concentrations of estrogen and its derivatives.[42,43] Postmenopausal women with ER-positive locally advanced breast cancer who receive 3 to 4 months of anastrozole, letrozole, or exemestane therapy have shown a decrease in tumor volume of between 75% and 90%.[42,44-47] In a small randomized trial comparing 1 or 10 mg of anastrozole daily over a 3-month period, 15 of the 17 patients who would have required a mastectomy achieved the option of breast-conserving surgery.[45]

Similar results were observed with letrozole.[48] In addition, a phase III randomized study comparing letrozole (2.5 mg po qd) with tamoxifen (20 mg po qd) in 337 postmenopausal women with ER-positive tumors demonstrated a significant improvement in response rate (60% vs 41%) favoring letrozole, as judged by clinical examination, ultrasound, and mammography.[49] More importantly, 48% of women were able to undergo breast-conserving surgery after treatment with letrozole compared to 36% after treatment with tamoxifen. Women with ER-positive tumors that expressed ErbB-1 and/or ErbB-2 had the greatest response to letrozole and the weakest response to tamoxifen, but the numbers were small in each stratum. Survival data from these studies are not yet available but are unlikely to be useful, given the small patient numbers in these trials.

**Recommendations on Aromatase Inhibitors in the Adjuvant Setting**

Both the 2000 US National Institutes of Health Consensus Conference on Treatment of Early Breast Cancer[50] and the 2001 St. Gallen Consensus Conference[51] endorsed the use of 5 years of tamoxifen as adjuvant therapy for virtually all women with invasive steroid-receptor-positive breast cancer. With the emergence of new data on adjuvant use of aromatase inhibitors, the American Society of Clinical Oncology carried out and published a technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone-receptor-positive breast cancer.[52] Members of the expert panel concluded that although the results of the ATAC trial were promising, they were insufficient to change standard practice and that a 5-year course of tamoxifen remains the standard adjuvant endocrine therapy for women with postmenopausal breast cancer.
Aromatase Inhibitors as Adjuvant Therapy in Breast Cancer

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hormone-receptor-positive breast cancer.

An aromatase inhibitor might be considered for women who have a contraindication to tamoxifen or who develop breast cancer while receiving raloxifene (Evista) or tamoxifen therapy. If an aromatase inhibitor is indicated, the available data support the use of anastrozole for 2 to 3 years with a plan to reassess the duration of treatment as more information becomes available. Because the only reported large-scale trial used anastrozole, it would be appropriate to use this agent rather than other aromatase inhibitors for adjuvant therapy at this time. If a patient is receiving adjuvant tamoxifen without incident, changing her therapy to an aromatase inhibitor is discouraged in the absence of supportive data. Similarly, the administration of an aromatase inhibitor after 5 years of tamoxifen therapy is not recommended.

Finally, there is no information to justify the use of an aromatase inhibitor as monotherapy in premenopausal women or women with steroid-receptor-negative breast cancer. Long-term data from the ATAC study and other large randomized trials will allow us to refine these recommendations in time.

**Future Directions**

A 47-month update of the ATAC trial reported trends in disease-free survival and side-effect profiles that were similar to what had previously been reported. Further results from the ATAC trial (for which blinded follow-up continues) and other ongoing adjuvant trials are eagerly awaited. The designs of several of these trials are shown in Tables 2 and 3. **REFERENCE GUIDE**

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Aromatase inhibitors will also be evaluated in the management of ductal carcinoma in situ and in the preventive setting. The possible longterm side effects are of even greater concern in these situations, and shorter term studies with biologic end points are in progress to complement the results of the adjuvant trials. For example, a trial of 3 months of letrozole in 32 women without breast disease demonstrated marked suppression of estradiol levels, no significant changes in lipid profile, and a 25% increase in the level of C-telopeptide, a bone resorption marker.[53] Given the side effects of anastrozole in the adjuvant setting and these types of biologic findings, one potential strategy would be to evaluate lower doses of aromatase inhibitors in the preventive setting. This may not be an unreasonable proposition, as complete suppression of estradiol activity may not be necessary to achieve a significant reduction in the incidence of breast cancer.[54]

Conclusions

In summary, aromatase inhibitors currently represent an excellent choice for first- or second-line endocrine therapy for postmenopausal women with advanced hormonereceptor-positive breast cancer. The routine adjuvant use of these agents is not recommended, but anastrozole is a second therapeutic option, particularly in women who are not candidates for tamoxifen. Results from numerous trials should crystallize our understanding about the appropriate use of aromatase inhibitors in early breast cancer and risk reduction in the next few years.

References:


 Therapeutic Agents Mentioned in This Article

- Aminoglutethimide (Cytadren)
- Anastrozole (Arimidex)
- Exemestane (Aromasin)
- Fadrozole (Formestane) (Lentaron)
- Megestrol acetate
- Raloxifene (Evista)
- Tamoxifen

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically. References continued on following page.


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