Aromatase Inhibitors in Postmenopausal Breast Cancer Patients

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Abstract
Aromatase inhibitors (AIs) have greatly enriched the treatment of hormone receptor-positive breast cancer in postmenopausal patients. Before the introduction of the well-tolerated third-generation AIs, tamoxifen was the mainstay of endocrine therapy for hormone receptor-positive breast cancer. Many clinical trials have shown the superiority of AIs compared with tamoxifen in adjuvant breast cancer treatment, as well as their benefit in metastatic breast cancer. NCCN guidelines recommendations for their use are based on the evidence provided by these clinical trials. This discussion reviews the evidence supporting the current guidelines for use of AI therapy in the treatment of hormone receptor-positive postmenopausal breast cancer patients. (JNCCN 2005;3:309–314)

The concept of hormone therapy in breast cancer dates from 1896 when Beatson1 reported oophorectomy causing the regression of advanced breast cancer. Much work has been done in the interim, with endocrine therapies becoming a mainstay in the treatment of breast cancer. This discussion focuses on the treatment of hormone receptor-positive breast cancer with aromatase inhibitors (AIs) in postmenopausal women. To establish their place in the treatment of breast cancer, they first were compared against the standard of care, tamoxifen.

Tamoxifen is a selective estrogen receptor modulator (SERM) that has been used to treat breast cancer since the 1970s. It decreases estrogen’s effect on breast cancer cells by competing with estrogen for binding with the receptor. It is well tolerated but has associated side effects of hot flashes, vaginal dryness, and increased risk of thromboembolic events and uterine cancer.2 Its benefit in the treatment of hormone receptor-positive breast cancer has been well established. The Early Breast Cancer Trialists’ Group reviewed 55 randomized trials of 37,000 women treated with tamoxifen in the adjuvant setting. In the women with estrogen receptor (ER)-positive disease who took tamoxifen for 5 years, the decrease in disease recurrence was 50% and decrease in mortality was 26%.3 Recent trials have shown that the aromatase inhibitors are even more effective than tamoxifen in reducing the risks of breast cancer recurrence.

Development of Aromatase Inhibitors
Aromatase is part of the cytochrome P450-dependent enzyme family and a product of the CYP19 gene. Its expression in the placenta of pregnant women and granulosa cells of ovarian follicles in premenopausal women is regulated by gonadotropin stimulation. Other areas of expression include subcutaneous fat, brain, muscle, liver, and both normal and malignant breast tissue. In postmenopausal women, peripheral aromatase produces estrogen in subcutaneous fat. AIs block the enzymatic pathway of aromatase and therefore decrease the level of estrogen production and total circulating estrogen.

Aminoglutethimide is a first-generation aromatase inhibitor that became available for clinical use in the 1970s. It is a nonselective aromatase inhibitor with side effects of adrenal insufficiency, rash, nausea, somnolence, and blood dyscrasias. Second-generation aromatase inhibitors formestane and fadrozole have limited use because of extensive first-pass hepatic metabolism and adrenal mineralocorticoid suppression, respectively.4

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Because of these negative clinical effects, researchers needed to develop more selective aromatase inhibitors. Third-generation aromatase inhibitors were introduced for clinical use in the 1990s. Their classification, along with the classification of second-generation AIs is according to mechanism of action. Type 1 inhibitors, steroidal enzyme inhibitors, bind irreversibly to the androstenedione binding site. The effects of type 2, nonsteroidal inhibitors on aromatase enzyme are reversible. The nonsteroidal enzyme inhibitors bind to the heme component of aromatase via a basic nitrogen group (Figure 1). All third-generation AIs are highly selective and have good oral bioavailability. Exemestane is a type 1 inhibitor, and anastrozole and letrozole are type 2 inhibitors (Table 1).

**Advanced Disease**

The clinical benefit of the third-generation AIs was shown first in studies that compared AIs with megestrol acetate for second-line hormonal therapy after tamoxifen in metastatic breast cancer. These trials showed slight clinical benefit and, most importantly, an improved side effect profile compared with megestrol acetate. The AIs did not induce the weight gain seen with megestrol acetate and were relatively well tolerated.5

The efficacy of AIs compared with tamoxifen as first-line therapy in advanced breast disease was addressed with randomized, multicenter, double-blind studies in the 1990s. Two trials in North America (North American trial) and Europe (TARGET trial) of anastrozole versus tamoxifen were designed for combined analysis, and they showed an equivalent median time to progression: 8.5 months in anastrozole group versus 7.0 months in tamoxifen group (P = .103). Tumor response was equivalent as well (29% vs. 27.1%; P = .1129).6 However, in the North American trial, in which the percentage of patients with ER-positive disease was greater than in the TARGET trial (90% vs. less than 50%), the results did have statistical differences. An unplanned retrospective analysis was performed to further evaluate anastrozole versus tamoxifen in patients with confirmed ER-positive disease. In the North American group, the median time to progression was 11.1 months for anastrozole versus 5.6 months for tamoxifen (P = .005), and the overall response rate was equivalent (21% vs. 17%). Clinical benefit, defined as complete or partial response and stable disease for 24 weeks or more, was significantly greater in the anastrozole group (59% vs. 46%; P = .0098).7

The International Letrozole Breast Cancer Group enrolled 916 patients with ER-positive advanced breast cancer in a randomized trial of letrozole versus tamoxifen. The initial report showed letrozole to be superior to tamoxifen in median time to progression (41 vs. 26 weeks), overall response rate (30% vs. 20%; P = .0006), and clinical benefit (49% vs. 38%; P = .001).8 Follow-up analysis at 32 months showed overall survival to be 34 versus 30 months (P = .53) and time to chemotherapy (total duration of endocrine therapy based on initial treatment arm) to be 16.3 versus 9.3 months for the letrozole and tamoxifen groups, respectively (P = .005).9

Trials of exemestane versus tamoxifen as first-line therapy of advanced breast cancer are ongoing. A phase II trial from the EORTC showed response rates of 41% versus 17% and clinical benefit of 57% versus 42%.10 This was a small trial of 120 patients that led to a phase III trial. These phase III results were presented at the American Society of Clinical Oncology.
(ASCO) annual meeting in 2004. The study included 382 evaluable patients with a median follow-up time of 29 months. Exemestane showed a superior overall response rate (46% vs. 31%; \( P = .005 \)) and clinical benefit rate (66% vs. 49%) than tamoxifen. Progression-free survival trended towards benefit with exemestane (9.9 months vs. 5.8 months) but did not reach significance.\(^1\)

These studies showed the equivalence or superiority of AIs versus tamoxifen in advanced disease. The National Comprehensive Cancer Network (NCCN) guidelines recommend AIs or antiestrogens as first-line therapy in postmenopausal breast cancer patients with hormone receptor-positive metastatic disease.\(^12\)

**Adjuvant Treatment**

The Early Breast Cancer Trialists’ Collaborative Group analyzed data from 55 trials of adjuvant tamoxifen versus placebo among women with early breast cancer. In patients with ER-positive breast cancer taking tamoxifen, the 5-year recurrence reduction was 50% and decrease in mortality was 26%.\(^1\) With this dramatic impact on the treatment of breast cancer, tamoxifen became the standard of care for adjuvant endocrine therapy.

The first reported adjuvant trial of a third-generation AI was the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study.\(^13\) In this study, 9,366 postmenopausal patients with ER-positive invasive breast cancers were treated with primary surgery and chemotherapy (when indicated) and then randomized to recived anastrozole, tamoxifen, or a combination of both. The first results were published in 2002 with 33.3 months median follow-up time. Disease-free survival favored anastrozole over tamoxifen alone, with 3-year survival rates of 89.4% versus 87.4% (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.71–0.96; \( P = .013 \)). Disease-free survival in the combination group (87.2) was not statistically different from that in the tamoxifen alone group (HR, 1.02; CI, 0.89–1.18; \( P = .8 \)). Anastrozole also significantly reduced the rate of contralateral breast cancer compared with tamoxifen (odds ratio, 0.42; CI, 0.22–0.79; \( P = .007 \)). Anastrozole-treated patients experienced fewer cerebrovascular events, thromboembolic events, hot flushes, and endometrial cancer than the tamoxifen-treated patients. Tamoxifen-treated patients had fewer musculoskeletal disorders and fractures than the anastrozole group.\(^1\)

Follow-up disease-free survival data with a median follow-up time of 47 months continued to significantly favor anastrozole over tamoxifen alone (86.9% vs. 84.5%; HR, 0.86; CI, 0.76–0.99; \( P = .03 \)). Contralateral breast cancers also were decreased in the anastrozole group with hormone receptor-positive disease (odds ratio, 0.56; CI, 0.32–0.98; \( P = .042 \)). Safety analysis confirmed the initial observations as well.\(^14\) Five-year data were published recently, with anastrozole continuing to prolong disease-free survival (HR, 0.87; CI, 0.78–0.97; \( P = .01 \)) and time to disease recurrence (HR, 0.79; CI, 0.70–0.89; \( P = .0005 \)). The number of distant metastases was lower in the anastrozole group (HR, 0.86; CI, 0.74–0.99; \( P = .04 \)), as was the number of contralateral breast cancers (42% reduction; CI, 12%–62%; \( P = .01 \)). Overall survival was not statistically significantly different (HR, 0.97; CI, 0.85–1.12; \( P = .7 \)).\(^13\) This study established anastrozole as the preferred initial adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer, and longer-term follow up has continued to support this.\(^1\)

The next group of patients to be evaluated was the patient population that had completed the recommended 5 years of tamoxifen therapy. The National Surgical Adjuvant Breast and Bowel Project B14 trial showed significantly superior disease-free survival in patients who underwent 5 years of tamoxifen therapy compared with those who continued tamoxifen therapy for more than 5 years (82% vs. 78%; \( P = .03 \)), and overall survival trend was towards a benefit for 5 years of therapy (94% vs. 91%; \( P = .07 \)).\(^15\) With the addition of AIs to the endocrine therapy of breast cancer, a trial was begun to compare 5 years of tamoxifen with the sequential addition AI therapy or placebo.

The MA17 trial was a double-blind, placebo-controlled, multicenter trial comparing letrozole with placebo in patients who had completed 4.5 to 6 years of tamoxifen therapy.\(^16\) At study entry, 5,187 women who had completed 4.5 to 6 years of tamoxifen and were disease free at that time were randomized to receive letrozole 2.5 mg daily or placebo. At 4-year follow-up, disease-free survival was 93% versus 87% (\( P = .001 \)) for the letrozole and placebo groups, respectively. Overall survival was not statistically significantly different. The letrozole group experienced more hot flashes, arthralgias, myalgias, and arthritis. More women in the letrozole group were diagnosed with osteoporosis (5.8% vs. 4.5%; \( P = .07 \)), but the rate...
Neoadjuvant Treatment

In 2001, a randomized double-blind multicenter study was published comparing letrozole with tamoxifen in the neoadjuvant setting. Three hundred thirty-seven postmenopausal women with untreated hormone receptor-positive breast cancer were treated with letrozole 2.5 mg daily or tamoxifen 20 mg daily for 4 months. None of the patients was eligible for breast-conserving surgical therapy at diagnosis, and 14% of the cancers were considered inoperable. The overall objective response rate (determined by clinical palpation) was 55% in the letrozole group and 36% in the tamoxifen group \( (P < .001) \). Breast ultrasound response was 35% versus 25% \( (P = .042) \); mammographic response was 34% versus 16% \( (P < .001) \); and the rate of breast-conserving surgery was 45% versus 35% \( (P = .022) \).

Another study evaluated neoadjuvant exemestane versus tamoxifen in postmenopausal ER-positive breast cancer patients. Seventy-three patients were treated with exemestane 25 mg daily or tamoxifen 20 mg daily for 3 months and evaluated for response. Clinical response was higher in the exemestane group \( (88.6\% \text{ vs. } 57.3\%; P < .05) \), and the rate of breast-conserving surgery was higher in the exemestane group \( (38.7\% \text{ vs. } 10.8\%; P < .05) \).

A recently presented study evaluated chemotherapy versus endocrine therapy in the neoadjuvant setting. In this study, 146 women with hormone receptor-positive breast cancer were randomized to chemotherapy with doxorubicin and paclitaxel for four cycles or 3 months of anastrozole (1 mg daily) or exemestane (25 mg daily). The tumors were AJCC stage T2N1-2, T3N0-1, or T4N0M0 (excluding inflammatory). The overall objective response rate, determined by clinical palpation and mammography, was not statistically significantly different \( (chemotherapy, 76\% \text{ and } 61.9\%; \text{ anastrozole, } 75.6\% \text{ and } 62.1\%; \text{ and exemestane, } 81.5\% \text{ and } 71\%) \). The rate of breast-conserving surgical therapy trended toward benefit of endocrine therapy \( (chemotherapy, 23.9\%; \text{ anastrozole, } 33.3\%; \text{ and exemestane, } 34\%; P = .058) \). Endocrine therapy was well tolerated with less toxicity than chemotherapy.23 These trials show the benefit of AIs in the neoadjuvant setting. This option provides an alternative to chemotherapy for patients opposed to chemotherapy or those with comorbidities. The NCCN guidelines state that hormonal therapy may be considered for treatment in the preoperative setting.

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of fracture was not statistically significantly different. Because of these results, the study was closed early. Letrozole is recommended for 5 years after tamoxifen therapy. Further studies will further clarify the benefit of AIs after tamoxifen and the appropriate duration of therapy.

Other studies have explored the benefit of changing endocrine therapy to AIs after the patient has begun tamoxifen therapy. The Intergroup Exemestane Study (IES) evaluated switching to exemestane after 2 to 3 years of tamoxifen adjuvant therapy in postmenopausal, hormone receptor-positive breast cancer patients. In this study, 4,742 patients who had taken tamoxifen for 2 to 3 years were randomized to continue tamoxifen (20 mg daily) or change to exemestane (25 mg daily) to complete a total of 5 years of endocrine therapy. After a median follow-up time of 30.6 months, the exemestane group had improved disease-free survival \( (HR, 0.68; CI, 0.56–0.82; P < .0001) \). This corresponded to an absolute risk reduction of 4.7% \( (CI, 2.6–6.8) \) at 3 years. Overall survival was not statistically significantly different at 3 years \( (HR, 0.88; CI, 0.67–1.16; P = .37) \). Exemestane was also found to decrease risk of contralateral breast cancers \( (HR, 0.44; CI, 0.2–0.98; P = .04) \). Based on this study, the current NCCN recommendation is to consider switching to exemestane for patients who have completed 2 to 3 years of tamoxifen.22

The Italian trial (ITA) was an open-label prospective trial of 426 postmenopausal women with hormone receptor-positive breast cancer who had completed 2 to 3 years of tamoxifen therapy. They were randomized to receive anastrozole or tamoxifen to complete 5 years of endocrine therapy. The findings were consistent with anastrozole decreasing the risk of recurrent disease \( (HR, 0.36; CI, 0.17–0.75; P = .006) \).22

The current NCCN guidelines recommend the following therapeutic algorithm for postmenopausal women with hormone receptor-positive breast cancer:22

- Initial adjuvant endocrine treatment
  - Anastrozole 1 mg daily for 5 years
  - Treatment with tamoxifen for 2 to 3 years, discuss
    - Exemestane 25 mg daily to complete 5 years total therapy
    - Anastrozole 1 mg daily to complete 5 years total therapy
  - Treatment with tamoxifen for 4.5 to 6 years, discuss
    - Letrozole 2.5 mg daily for 5 years
for postmenopausal women with hormone receptor-positive breast cancer. The preferred hormonal therapy is an aromatase inhibitor.22

**Comparison of Aromatase Inhibitors**

With many studies demonstrating the superiority of the three available AIs compared with tamoxifen, the issue arises as to which of the AIs is superior. Are they to be used interchangeably, and can the data from one study be extrapolated to the other AIs? One comparison study was an open randomized trial comparing letrozole with anastrozole in the second-line setting of advanced breast cancer. In this study, 713 patients with hormone receptor-positive or unknown cancers were randomized to receive letrozole 2.5 mg daily or anastrozole 1 mg daily and evaluated for time to disease progression. No difference was found in time to progression, with 5.7 months for both treatments (P = .92), and no statistically significant difference was seen in overall survival (22.0 vs. 20.3 months; P = .624). The overall clinical benefit trended towards favoring letrozole, and the overall response rate was greater for letrozole (19.1% vs. 12.3%; P = .013). Cancers with disease primarily in the soft tissue and viscera had higher response rates to letrozole than anastrozole. In patients with known hormone receptor-positive disease, anastrozole had a longer median time to progression of 6.5 versus 5.8 months with letrozole.23 This study did not show a significant difference in time to progression. At this time, no major clinical differences among the AIs have been shown. The NCCN guidelines for advanced disease do not designate which AI to use as initial therapy, but in the adjuvant setting the AI that was studied in each particular clinical situation is recommended.

**Conclusions**

Many studies have shown the benefit of AIs in hormone receptor-positive breast cancer in postmenopausal women. The guidelines for each clinical situation are based on the evidence generated by these trials. Studies in advanced disease revealed AIs to be superior or equal to tamoxifen. Studies in early breast cancer have shown the superiority of AIs compared with tamoxifen, and preoperative studies have shown the benefit of AIs in tumor response rate and rate of breast-conserving surgery. Further studies are needed to evaluate the length of therapy in the adjuvant setting, comparison of the efficacy and toxicity of AIs, and their role in chemoprevention for breast disease (two studies are pending).24 In all, aromatase inhibitors have dramatically impacted the treatment of hormone receptor-positive breast cancer in postmenopausal women and will continue to be an asset to clinicians in the treatment of disease.

**References**


