Aromatase Inhibitors as Adjuvant Therapy for Postmenopausal Patients With Early Stage Breast Cancer

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ABSTRACT Endocrine therapy of hormone receptor-positive breast tumors is widely used as palliative therapy for metastatic breast cancer and as adjuvant therapy for early stage breast cancer. Tamoxifen has been the definitive standard of hormonal therapies for the last 30 years because of its documented efficacy and reasonable safety profile. Based on encouraging results from trials utilizing the selective, third generation aromatase inhibitors (AIs) in metastatic breast cancer, a number of trials were designed to examine these agents as adjuvant therapies. Trials directly comparing AIs with tamoxifen have, to date, demonstrated superior disease-free-survival with AIs. Likewise, trials examining the use of AIs after tamoxifen have demonstrated better outcomes compared with tamoxifen alone. Additionally, letrozole has been demonstrated to result in superior disease-free-survival after 5 years of adjuvant tamoxifen, compared with no further therapy. In general, the AIs are tolerated at least as well as tamoxifen but decrease bone mineral density and increase osteoporosis due to their lack of estrogenic effects on bone. Based on the fact that AIs appear more effective at preventing contralateral breast cancers than tamoxifen, they are being examined as breast cancer preventives. Despite available data using the AIs as adjuvant therapies, many questions remain unanswered, and further trials will be needed to address these important issues. (CA Cancer J Clin 2005;55:145–163.)

INTRODUCTION

It was more than a century ago when Beatson found that oophorectomy caused breast cancer regression in a premenopausal patient, long before either estrogen or the estrogen receptor (ER) had been discovered. Since then, a number of therapeutics have been developed with the goal of treating breast cancer via estrogen deprivation or by directly targeting the ER. Examples of such therapeutics are tamoxifen, a selective estrogen receptor modulator (SERM) that competitively blocks the ER, and the aromatase inhibitors (AIs), which reduce circulating estrogen levels. Both of these approaches result in inhibition of estrogen-regulated gene transcription. Tamoxifen has been established as an effective therapy for patients with all stages of hormone receptor-positive breast cancer, and more recently as a breast cancer preventive. However, AIs are proving to be at least as good as and perhaps better than tamoxifen as palliative treatment for hormone receptor-positive metastatic breast cancer, and more recently as effective adjuvant therapies for postmenopausal patients with early stage breast cancer. In this article, we will review available evidence on the use of tamoxifen and AIs in all stages of breast cancer.

MECHANISM OF ACTION

Aromatase Inhibitors

Aromatase is the enzyme that converts testosterone to estradiol and androstenedione to estrone (the main estrogen source in the postmenopausal female). After menopause, estrogens are produced mainly in adipose
tissue and adrenals by the conversion of androgens to estrogens via aromatization. Additionally, two-thirds of breast tumors demonstrate aromatase activity, making this enzyme a likely source of local estrogen for breast cancer cells. Therefore, AIs, which block aromatization, act not only by decreasing circulating levels of estrogen but also by directly blocking local estrogen production in the breast tumor. In premenopausal women, AIs cause an increase in gonadotropin secretion because of the reduced negative feedback of estrogen to the pituitary. This in turn leads to ovarian stimulation, an increase in ovarian size, which may result in ovarian cysts in premenopausal females. For all these reasons, AIs have been extensively studied for use in postmenopausal breast cancer patients and are currently not recommended for patients with intact ovarian function. AIs should not be used in patients with chemotherapy-induced amenorrhea, unless it is clear that menstrual function will not return.

There are now three generations of AIs, and those currently used in the United States are all third generation (Table 1). First generation AIs such as aminoglutethimide (Figure 1) are nonselective and block adrenal synthesis of both glucocorticoids and mineralocorticoids causing numerous unwanted side effects. AIs are classified into different types depending on their mechanisms of action. Type 1 inhibitors bind irreversibly to the steroid binding site on the aromatase molecule and are androstenedione steroidal analogs. Type 2 inhibitors bind reversibly to the heme group on the aromatase enzymes and are androstenedione steroidal analogs. Type 2 inhibitors bind reversibly to the heme group on the aromatase enzymes and are nonsteroidal.

**SERMs**

SERMs are a unique class of agents that act as estrogen antagonists on breast tissue while acting as estrogen agonists on other tissues such as endometrium and bone. SERMs work directly by manipulation of the ER, resulting in incomplete dimerization of the receptor. Tamoxifen is the most widely used SERM in the treatment and prevention of breast cancer. Raloxifene is another SERM that was initially developed as a breast cancer treatment but didn’t offer clear advantages over tamoxifen. Raloxifene was subsequently developed as an osteoporosis treatment and is currently approved for the prevention and treatment of osteoporosis in postmenopausal women. Toremifene is a chlorinated derivative of tamoxifen, which is approved in the United States as an alternative to tamoxifen in the first-line treatment of hormone-responsive metastatic breast cancer and appears as effective as tamoxifen in the adjuvant setting.

**Selective Estrogen Receptor Downregulators**

Selective estrogen receptor downregulators are another unique class of hormonal therapies, of which fulvestrant is the only one available clinically. Fulvestrant is a steroid analog that competitively binds to the ER with greater affinity than tamoxifen, resulting in marked downregulation of both the ER and progesterone receptor (PR). Fulvestrant is a pure ER antagonist and has antiestrogen effects not only on breast tissue but also on the endometrium and bone. Fulvestrant has poor oral bioavailability and must be given in monthly intramuscular injections, which may limit its adjuvant usage.

**TABLE 1 Aromatase Inhibitors by Class and Type**

| Class          | Type 1 (Steroidal) | Type 2 (Nonsteroidal) |
|----------------|--------------------|------------------------|
| First generation | None               | Aminoglutethimide      |
| Second generation | Formestane         | Fadrozole              |
| Third generation | Exemestane         | Anastrozole            |
|                |                    | Letrozole              |
|                |                    | Vorozole               |
Fulvestrant is currently approved in the United States for patients with metastatic breast cancer whose disease has progressed on antiestrogen therapy.

AROMATASE INHIBITORS IN ADVANCED DISEASE

Metastatic breast cancer remains an incurable disease, where the primary goal of therapy is palliative. Treatment with SERMs, particularly tamoxifen, has not only prolonged time to progression but has also improved quality of life. Until recently, tamoxifen was the first-line hormonal treatment of choice for patients with hormone-responsive metastatic breast cancer. The third generation aromatase inhibitors were initially compared with megestrol acetate as second-line agents in patients whose disease had become resistant to tamoxifen.13–16 Each of the aromatase inhibitors was noted to be as effective as megestrol acetate, with superior tolerability and the advantage of once daily dosing (Table 2).13–17 Subsequently, the third generation AIs have been examined for first-line treatment of advanced disease.

Two trials evaluated anastrozole as primary treatment for metastatic, hormone receptor-positive breast cancer (Table 3).18–21 The first trial was performed in North America and randomized 353 women to tamoxifen and anastrozole until disease progression.18 Anastrozole significantly increased time to progression at 11.1 months compared with 5.6 months for tamoxifen. There was, however, no significant difference in response rate or in survival between the two treatment groups. In a second trial performed in Europe and the rest of the world,19 there was no significant difference in the time to progression between the two groups, both being approximately 8 months. Additionally, there was no significant difference in response rate or in survival. A likely explanation for the different results in the two trials was the difference in percentage of patients on each trial with known hormone receptor-positive tumors. In the North American trial, the majority of patients had known hormone receptor-positive disease, compared with only 50% on the other trial. Overall, anastrozole was at least as effective as tamoxifen as first-line therapy of advanced breast cancer and was superior in terms of time to progression, when only the patients with known hormone receptor-positive disease were analyzed.

Letrozole was compared with tamoxifen as first-line treatment of hormone-responsive
metastatic breast cancer in a large, randomized, double-blind trial. Approximately 900 patients with ER-positive or unknown receptor-status metastatic breast cancer were randomized to letrozole or tamoxifen until the time of disease progression. Letrozole significantly improved response rates and significantly increased time to progression compared with tamoxifen (9 months and 6 months, respectively). To evaluate overall survival, patients on this trial were prospectively offered the option of crossing over to the opposite agent at the time of disease progression. Approximately 50% of patients on each arm crossed over to the opposite agent, and median time to crossover was not significantly different between the two arms. Overall, there was no significant difference in overall survival between the patients crossing from letrozole to tamoxifen and from tamoxifen to letrozole. Importantly, this finding demonstrated that patients had similar outcome regardless of whether they were initially treated with tamoxifen or with an AI, which is of particular relevance because there is increasing use of AIs in the adjuvant setting.

Final results of a randomized trial comparing exemestane to tamoxifen as primary treatment of hormone-responsive metastatic disease were recently presented. Approximately 400 patients with metastatic breast cancer were randomized to exemestane or tamoxifen as first-line treatment. Response rate was significantly

### TABLE 2 Results of Second-line Trials Examining AIs Versus Megestrol Acetate in Tamoxifen-refractory Metastatic Breast Cancer

| Trial                  | LET* vs MA† | ANAST‡ vs MA | EXEM§ vs MA |
|------------------------|-------------|--------------|-------------|
| Number of Patients     | 174 vs. 189 | 128 vs. 128  | 366 vs. 403 |
| CRf1 + PR**            | LET > MA    | ANAST = MA   | EXEM = MA   |
| Duration of clinical benefit | LET > MA    | Not reported  | EXEM > MA   |
| Time to treatment progression | LET = MA    | ANAST = MA   | EXEM > MA   |
| Time to treatment failure | LET > MA    | ANAST = MA   | EXEM > MA   |
| Overall survival       | LET = MA    | ANAST > MA   | EXEM > MA   |

*LET, letrozole.
†MA, megestrol acetate.
‡ANAST, anastrozole.
§EXEM, exemestane.
¶CR, complete response.
**PR, partial response.
Buzdar et al.13,17; Dombernowsky et al.15; Kaufmann et al.14

### TABLE 3 Results of First-line Trials Examining AIs Versus Tamoxifen in Metastatic Breast Cancer

| Results                  | LET* vs TAM† | ANAST‡ vs TAM | EXEM§ vs TAM |
|--------------------------|-------------|--------------|-------------|
| Number of patients (total) | 907         | 353          | 371         |
| Overall response         | LET > TAM   | ANAST = TAM  | EXEM > TAM  |
| Clinical benefit         | LET > TAM   | ANAST > TAM  | Not reported |
| TTP¶                     | LET > TAM   | ANAST > TAM  | EXEM > TAM  |
| TTP (AI** vs. TAM) mos.  | 9.4 vs. 6.0 | 11.1 vs. 5.6 | 9.9 vs. 5.8 |
| Overall survival         | LET = TAM   | ANAST = TAM  | EXEM = TAM  |

*LET, letrozole.
†TAM, tamoxifen.
‡ANAST, anastrozole.
§EXEM, exemestane.
¶TTP, time to progression.
**AI, aromatase inhibitor.
Nabholtz et al.18; Mouridsen et al.20,21; Parideans et al.22
higher in patients treated with exemestane at 46%, compared with 31% for patients treated with tamoxifen. Time to progression was also significantly longer in patients treated with exemestane at 9.9 months, compared with 5.8 months for patients treated with tamoxifen. There was no significant difference in overall survival between the two arms.

In summary, these trials demonstrate that the AIs are superior to tamoxifen in terms of time to progression as first-line hormonal therapies for patients with known hormone receptor metastatic breast cancer. Additionally, AIs result in similar survival rates compared with tamoxifen, with an acceptable safety profile.

**ADJUVANT THERAPY**

**Tamoxifen**

The substantial evidence supporting the use of antiestrogen therapy in advanced disease led to further studies in patients with early stages of breast cancer (ie, cancer confined to the breast and/or local lymph nodes). Based on trials performed in the 1980s, tamoxifen was approved as an adjuvant therapy to reduce the risk of recurrence and remains widely used for this indication.

*Early Breast Cancer Trialist Collaborative Group*

Every 5 years in Oxford, England, a meta-analysis, which includes 55 trials with approximately 37,000 patients, is performed comparing outcomes from trials in which patients with early stage breast cancer were randomized to tamoxifen or to placebo. After excluding women with ER-negative tumors, the absolute risk reduction for recurrence was 14.9% ($P < 0.0001$) for patients with node-negative tumors (relative risk reduction of 49%) and 15.2% ($P < 0.0001$) in those with node-positive disease (relative risk reduction of 43%) after 5 years of tamoxifen, compared with 5 years of placebo. Mortality reduction was also significant, with an absolute reduction of 5.6% and 10.9% ($P < 0.0001$) in patients with node-negative (relative risk reduction of 25%) and node-positive (relative risk reduction of 28%) tumors, respectively. Five years of tamoxifen was significantly more effective than 2- or 1-year duration. The NSABP B-1423 trial is included in the meta-analysis and initially randomized 2,818 women with node-negative, ER-positive disease to tamoxifen or placebo for 5 years. Many of the patients who initially received 5 years of tamoxifen were rerandomized to a further 5 years of tamoxifen or to no further therapy. This extension trial revealed no further improvement in outcome by continuing tamoxifen for 10 years. In fact, the most recent analysis of this trial demonstrated a significantly shorter disease-free survival of 78% for patients who received 10 years of tamoxifen, compared with 82% for patients who stopped the drug at 5 years. Additionally, overall survival was worse in patients treated for 10 years, compared with patients stopping the drug at 5 years. Based on the result of this trial, the National Cancer Institute recommended stopping tamoxifen after 5 years in patients with early stage breast cancer. However, it was not clear that the results of this trial could be applied to patients with node-positive disease.

The meta-analysis clearly demonstrated that tamoxifen significantly reduced the rate of contralateral breast cancer by 50%. The 2000 Oxford Overview Analysis demonstrates that tamoxifen is only effective in decreasing the incidence of contralateral breast cancer if the primary breast cancer was ER-positive [presented at Oxford, United Kingdom, 2000]. The fact that tamoxifen effectively decreases the risk of contralateral breast cancer was a major reason why the drug was subsequently developed as a breast cancer chemopreventive.

These adjuvant trials identified several serious side effects of tamoxifen, mainly related to its estrogen agonistic effects, including uterine cancer and thromboembolic disease. These side effects of tamoxifen and the fact that many patients with early stage breast cancer develop drug resistance, leading to disease recurrence, opened the door for the development of AIs as adjuvant therapies.
Aromatase Inhibitors

Over the past 4 years, preliminary results of several trials evaluating the use of AIs as adjuvant therapies have become available. Two main approaches have been taken in these trials. The first is to compare the AIs head to head with tamoxifen, and the second is to sequence the AIs after tamoxifen.

Efficacy From Adjuvant AI Trials

HEAD-TO-HEAD TRIALS

Results of two trials comparing AIs to tamoxifen are available. Data from other trials are eagerly awaited.

ATAC TRIAL

The ATAC (Figure 2) trial was the first trial published that examined the use of AIs as adjuvant therapy in postmenopausal women with early stage breast cancer. Enrolling over 9,000 patients, the ATAC trial is the largest adjuvant breast cancer study to date. Postmenopausal patients were randomized, after primary therapy, to receive anastrozole alone, tamoxifen alone, or the two drugs in combination, for a total of 5 years. The rationale behind the combination arm was to increase the efficacy of the two agents and to reduce toxicity. The results were first presented at a follow-up of 3 years and demonstrated a significantly improved disease-free survival for patients treated with anastrozole, compared with those treated with tamoxifen. Interestingly, disease-free survival was not found to be statistically different between patients treated with the combination or with tamoxifen-alone arm. The ATAC trial was more recently published at a follow-up of 4 years. The absolute improvement in disease-free survival was 2.4% and 2.7%, with relative risk reductions of 14% and 18% in the overall population and hormone receptor-positive population, respectively. Based on the results of the ATAC trial, anastrozole was approved as an alternative to tamoxifen in the adjuvant therapy of hormone receptor-positive early stage breast cancer in postmenopausal patients. However, an expert committee from the American Society of Clinical Oncology urged caution because of the premature nature of the results from the ATAC trial and have recommended that 5 years of adjuvant tamoxifen remain the standard therapy for postmenopausal patients with early stage breast cancer.27,28 The 5-year disease-free survival and overall survival results of the ATAC trial were, therefore, eagerly awaited.

Anastrozole was also demonstrated to reduce the incidence of contralateral breast cancers (Figure 3). At the initial 3-year follow up, there was a significant reduction in contralateral breast cancers in patients treated with anastrozole, compared with those treated with tamoxifen, with 13
and 30 cases, respectively. At 4 years, the difference in incidence of contralateral breast cancers is no longer significant, with 25 in the anastrozole-treated patients and 40 in the tamoxifen-treated patients. However, there continues to be significantly less invasive contralateral breast cancers in the anastrozole-treated patients, compared with those treated with tamoxifen. This reduction in contralateral breast cancers seen with anastrozole has led to the design of trials evaluating the drug as a chemopreventive.

The ATAC trial was recently updated at 5 years of follow up (Howell A. ATAC, ‘Arimide’, Tamoxifen, Alone or in Combination) completed treatment analysis. Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen. Patients randomized to anastrozole continue to have improved disease-free survival and longer time to recurrence, compared to patients treated with tamoxifen. At 5 years, the absolute benefit for disease-free survival and time to recurrence are 2.5% (relative reduction 17%, \( P = .005 \)) and 2.8% (relative reduction 26%, \( P = .0002 \)) for patients with hormone receptor-positive disease treated with anastrozole, compared to those treated with tamoxifen. There are 26 contralateral breast cancers in the anastrozole group, compared to 53 in the tamoxifen group (relative reduction 53% in patients with hormone receptor-positive disease). Time to distant recurrence is also longer in patients treated with anastrozole, compared with those treated with tamoxifen (relative reduction 16%, \( P = .06 \)) in patients with hormone receptor-positive tumors. However, there is, as yet, no significant difference in survival, overall or due to breast cancer (relative reduction 3% overall survival and 13% time to breast cancer death), in patients with hormone receptor-positive disease. Interestingly, patients with ER-positive, PR-negative tumors continue to obtain the greatest benefit in disease-free survival from anastrozole (relative reduction 57%, compared to 16% for patients with ER-positive, PR-positive tumors). Subgroup analyses remain the same as previous reports, with patients with node-negative tumors and those who did not receive adjuvant chemotherapy achieving more benefit from anastrozole. Differences in adverse events between the two groups are similar to previous reports. Overall, a significantly greater number of patients treated with tamoxifen experienced adverse events, including serious adverse events, resulting in significantly greater withdrawals from treatment. A fivefold higher rate of hysterectomies was noted in the tamoxifen arm, compared with the anastrozole arm, although it is
unclear why these hysterectomies were performed, as the number was much higher than the number of endometrial cancers reported. Fracture rate was higher in the anastrozole arm, but the rate declined when patients discontinued the aromatase inhibitor. In summary, at 5 years, disease-free survival is improved in patients receiving upfront aromatase inhibitors, but a survival advantage is yet to be reported.

ONGOING HEAD-TO-HEAD TRIALS

The Tamoxifen Exemestane Adjuvant Multinational trial randomizes postmenopausal patients with early stage breast cancer to tamoxifen or to exemestane for 5 years (Figure 2). A subprotocol that compares the incidence of menopausal symptoms between the two drugs has been presented twice, but no efficacy data are available at this time.

Sequencing Trials

AIS AFTER 5 YEARS OF TAMOXIFEN

Based on the results of the extension trial of NSABP B-14 demonstrating no benefit, and in fact a shorter disease-free survival when patients continued tamoxifen through 10 years compared with stopping at 5 years, two trials (MA-17 and NSABP B-33) were initiated to evaluate the role of AIs after 5 years of tamoxifen.

In the MA-17 trial (Figure 4), approximately 5,000 postmenopausal patients were randomized to either letrozole or to placebo after approximately 5 years of adjuvant tamoxifen. Approximately one-half of the patients had negative axillary lymph nodes, and 98% of patients had tumors with positive hormone receptors. The trial was closed prematurely after the first planned interim analysis at 171 events and a follow up of 2.4 years, based on significantly improved outcome in the letrozole-treated patients. The estimated 4-year disease-free survival in the letrozole-treated patients was 93%, compared with 87% in the placebo arm, resulting in a highly significant reduction in recurrence of 43%. There were a total of 75 events in the letrozole-treated patients, compared with 132 events in the placebo group. The letrozole-treated patients had 47 distant metastases, compared with 76 in the placebo group, which was not significantly different at this follow up. There were 14 contralateral breast cancers in the letrozole-treated patients, compared with 26 in the placebo group. There was no significant difference in estimated 4-year overall survival between the groups, which was 96% in the letrozole-treated patients and 94% in the placebo-treated patients. Before the trial being initiated, a cutoff significant difference in 4-year disease-free survival between the groups, which would require stopping the trial, was designated at a P value of ≤0.0008. The difference in 4-year disease-free survival in favor of the letrozole-treated patients resulted in a P value of 0.00008, and the trial was therefore closed at a follow up of only 2.4 years, despite the fact that most of the patients had not completed the total 5 years of assigned therapies.

Final results of the MA-17 trial were recently presented. With follow up of 30 months, there were 247 events and 113 deaths. Estimated 4-year disease-free survival continues to be significantly better in the letrozole-treated patients at 95%, compared with 90% in the placebo-treated patients. Estimated 4-year disease-free survival was significantly better in patients regardless of axillary nodal status (Table 4). Overall, distant disease-free survival was not significantly different between the two groups, but patients with node-positive tumors had significantly longer distant disease-free survival compared with the placebo group. Likewise, overall survival was not significantly different between the two groups. However, overall survival was significantly better in patients with node-positive tumors treated with letrozole, compared with patients with node-positive tumors who received placebo.

In summary, at a relatively short follow up, letrozole significantly improved disease-free survival, compared with no further treatment in patients treated with 5 years of adjuvant tamoxifen. Additionally, in the patients with node-positive breast cancer, letrozole after 5 years of tamoxifen resulted in improved distant disease-free survival and overall survival. Based on the results of this trial, further accrual to the NSABP B-33 trial was suspended, and this trial
is now closed. Letrozole was approved in October 2004 for extended adjuvant hormonal therapy in patients completing 5 years of tamoxifen.

**AIs AFTER 2 TO 3 YEARS OF TAMOXIFEN**

An Italian trial\(^ {33} \) previously demonstrated an improved survival for patients randomized to the AI, aminoglutethimide, after 2 to 3 years of tamoxifen, compared with patients receiving a total of 5 years of tamoxifen. With the advent of the selective AIs, the same group developed a follow-up trial, the Italian Tamoxifen Arimidex (ITA) trial (Figure 4), in which approximately 500 patients, all with node-positive breast cancer who had completed approximately 3 years of adjuvant tamoxifen, were randomized to continue tamoxifen or to switch to anastrozole for the remaining 2 years. The total duration of hormonal therapy in both arms was 5 years. At a short follow up of 36 months (range, 1 to 70 months), patients who switched to anastrozole had a significantly longer event-free and progression-free survival than those who continued on tamoxifen.\(^ {34} \) There were significantly fewer local events in the patients who switched to anastrozole, and there was a marked trend to fewer distant events in the anastrozole-treated patients but no significant difference in overall survival between the groups.\(^ {34} \) The authors urged caution in applying these results to clinical practice due...
to the small size of the trial and the short follow-up.

The Intergroup Exemestane Study (IES) trial (Figure 4) randomized nearly 5,000 postmenopausal patients who had completed approximately 3 years of adjuvant tamoxifen to either continue tamoxifen or to switch to exemestane for the remaining 2 years. The total duration of hormonal therapy in both arms was 5 years, and the median time on tamoxifen before randomization was 2.4 years. Approximately one-half of the patients on the trial had positive axillary lymph nodes. Although the follow up is short (30.6 months), 90% of patients on the trial have completed the assigned treatment. Disease-free survival was significantly better in the patients who switched to exemestane, with an absolute improvement of 4.7%.35 The total number of events in the patients who continued tamoxifen was 266, compared with 183 in the patients who switched to exemestane. There were 174 distant recurrences and 20 contralateral breast cancers in the tamoxifen arm, compared with 114 distant recurrences and 9 contralateral cancers in the exemestane arm (Figure 3). Breast cancer survival was also significantly better in the patients who switched to exemestane. At this follow up, there was no significant difference in overall survival. In summary, the IES trial demonstrates that adding the AI after 3 years of tamoxifen significantly improved disease-free survival over the standard 5-year treatment with tamoxifen. Disease-free survival was improved by switching to exemestane regardless of nodal status.

The Breast International Group/Femara R-Tamoxifen (BIG FEMTA) trial (Figures 2 and 4) was initially designed to compare 5 years of letrozole to 5 years of tamoxifen upfront in postmenopausal patients with hormone receptor-positive early stage breast cancer. In 1999, the trial was amended to include two other arms, in which patients would be treated with 2 years of tamoxifen, followed by 3 years of letrozole, or with 2 years of letrozole, followed by 3 years of tamoxifen. The initial analysis accrued 1,835 patients from March 1998 to March 2000. The amended protocol accrued a further 6,193 patients from September 1999 to May 2003. The primary core analysis of this trial, which includes patients treated with tamoxifen (arms A and C), and patients treated with letrozole (arms B and D), was recently reported at a follow up of 26 months.35a This analysis was censored before patients had crossed over to the opposite hormonal agent (arms C and D), and, therefore, contains no information regarding sequencing. Patients were balanced for age and basic tumor characteristics. Approximately 40% of patients had node-positive disease, and 25% had received prior adjuvant chemotherapy. All patients had hormone receptor-positive disease. Disease-free survival was significantly improved in patients treated with letrozole, compared to those treated with tamoxifen (relative reduction 19%, \( P = .003 \)), with an absolute difference at 3 years of 1.5%. Local and distant recurrences and contralateral breast cancers were seen less often in patients treated with letrozole. To date, there is no significant difference in survival in patients treated with letrozole or tamoxifen. Interestingly, disease-free survival was improved for all patients, regardless of tumor PR-status. Additionally, patients who had received prior adjuvant chemotherapy, and who had node-positive disease, had an improved disease-free survival with letrozole. Side effects and adverse events were similar to what has been previously reported with adjuvant aromatase inhibitor trials. Thromboembolic and gynecologic events were higher in patients treated with tamoxifen. There was a nonsignificant increase in fractures in patients treated with letrozole. Although more patients in the letrozole arm had hypercholesterolemia, there is no significant difference in severe cardiovascular events at this follow up. In summary, the BIG FEMTA trial confirms the superiority of 5 years of an aromatase inhibitor over tamoxifen upfront. Unfortunately, the results, to date, do not determine if the use of upfront aromatase inhibitors is superior to a short period of tamoxifen followed by an aromatase inhibitor. Mature results of this trial are, therefore, eagerly awaited.
Efficacy in Specific Subgroups in Adjuvant AI Trials

The large size of the available adjuvant AI trials has allowed for prospective evaluation of specific subgroups. These subgroups are needed to determine which patients will specifically benefit from AIs rather than tamoxifen.

**AXILLARY NODAL STATUS**

In general, patients had improved outcomes from AIs compared with tamoxifen, regardless of axillary nodal status (Table 5). AIs would be expected to have their greatest benefit compared with tamoxifen in patients at the highest risk of recurrence (ie, patients with involved axillary lymph nodes). Interestingly, anastrozole was significantly more effective than tamoxifen for improving disease-free survival of patients with node-negative tumors but not for patients with node-positive tumors.

In contrast, in the MA-17 trial, patients treated with letrozole with positive lymph nodes had a significantly improved distant disease-free and overall survival, while patients with negative lymph nodes did not. In the IES trial, switching to exemestane resulted in an improved disease-free survival regardless of lymph node status. The BIG-1-98 trial demonstrates improved DFS in node-positive disease, but not as yet in node-negative disease.

**HORMONE RECEPTOR STATUS**

As stated above, the benefits of anastrozole were greater in patients with known hormone receptor-positive tumors, compared with the overall population. A retrospective study examined the expression of both ER and PR on a large subset of tumors from patients randomized on the ATAC trial (Table 6). In the largest group of patients whose tumors expressed both ER and PR, there was no significant difference in disease-free survival in the patients treated with tamoxifen or anastrozole. In contrast, in patients with ER-positive, PR-negative tumors, anastrozole resulted in a statistically significantly improved disease-free survival, resulting in a hazard ratio of approximately 0.5, compared with tamoxifen-treated patients. No significant difference was seen between the anastrozole- and tamoxifen-treated patients in the small group of patients with ER-negative, PR-positive tumors. As would be expected, neither drug improved disease-free survival in the 8% of patients with ER-negative, PR-negative tumors. However, BIG-1-98 does not confirm these findings, demonstrating a benefit for letrozole and tamoxifen, regardless of PR status.

**HER2/neu STATUS**

In preclinical studies, HER2/neu overexpression appears to produce tamoxifen-resistance. Data from retrospective studies of patients with metastatic disease have produced conflicting results. Data from neoadjuvant hormonal trials have demonstrated an improved clinical response rate in patients with HER2/neu overexpressing tumors treated with AIs compared with...
tamoxifen (Table 7)\(^{39,40}\) but little difference in response rates of tumors that do not overexpress HER2/neu. To date, there are no data on the impact of HER2/neu status on outcome in any of the adjuvant trials.

**USE OF HORMONAL THERAPIES IN THE NEOADJUVANT SETTING**

The use of neoadjuvant chemotherapy has been established as an effective means of downstaging breast tumors before surgery.\(^{41–43}\) There is increasing evidence to suggest that patients with tumors that express hormone receptors are less likely to achieve a pathologic complete response.\(^{44}\) Additionally, elderly patients or patients with a poor performance status may not be candidates for chemotherapy. Neoadjuvant hormonal treatment is being used increasingly and is emerging as an excellent method to downstage tumors and avoid mastectomy. Selected patients with hormone responsive tumors may be able to avoid cytotoxic chemotherapy. Multiple Phase II trials have evaluated hormonal therapies in the neoadjuvant setting.\(^{45}\) Recent randomized trials have demonstrated that aromatase inhibitors may be more effective than tamoxifen in the neoadjuvant setting. Eiermann et al\(^{46}\) compared 4 months of neoadjuvant letrozole with 4 months of neoadjuvant tamoxifen in approximately 300 postmenopausal women with ER- and/or PR-positive breast cancers. The participants in this study had tumors that would have required mastectomy and/or were locally advanced and inoperable. Clinical response rates were significantly better in the letrozole group (55%), compared with the tamoxifen group (36%).\(^{47}\) Forty-five percent of patients randomized to letrozole and 35% of the tamoxifen group, respectively, were able to undergo breast-conserving surgery.\(^{46}\) The Immediate Preoperative Arimidex Alone or in Combination with Tamoxifen\(^{40}\) trial randomized patients with operable hormone receptor-positive breast cancers to anastrozole alone, tamoxifen alone, or a combination of tamoxifen and anastrozole. Although there was no significant difference in clinical response between the three arms,\(^{40}\) anastrozole was significantly more effective than tamoxifen in downstaging tumors and allowing breast conservation for patients who would otherwise have required a mastectomy.\(^{40}\)

An interesting comparison of neoadjuvant chemotherapy (four cycles of doxorubicin and paclitaxel) with neoadjuvant hormonal therapy (either anastrozole or exemestane for 3 months) in patients with hormone receptor-positive breast cancers was recently reported.\(^{47}\) There was no significant difference in either clinical response or pathologic complete response rates between the chemotherapy and hormonal therapy arms (Table 8).\(^{47}\) Interestingly, significantly more patients were rendered eligible for breast-conserving therapy in the hormonal therapy arm (24%), compared with the chemotherapy arm (15%).\(^{47}\) There is no long-term outcome available from this trial as of yet, but it validates the use of neoadjuvant hormonal therapy in certain patients. Considering the fact that hormone receptor-positive tumors may be less likely to respond to neoadjuvant chemotherapy,\(^{44}\) neoadjuvant hormonal therapy could be examined in these patients.

**Hormonal Therapy and Ductal Carcinoma In Situ**

Lumpectomy with radiation has been proven as an acceptable treatment for localized ductal carcinoma in situ (DCIS). The NSABP B-24\(^{48}\) study demonstrated that tamoxifen reduces breast cancer events by about 50% in patients treated

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**TABLE 7** Clinical Response Rate in Patients With HER2/neu-positive and -negative Tumors Treated With AIs Versus Tamoxifen in Neoadjuvant Setting

| Clinical Response | Numbers (Responding/ Total) | P Value |
|-------------------|-----------------------------|---------|
| **LET**           |                             |         |
| HER2+             | 69% 11/16                   | 0.25    |
| HER2−             | 53% 64/120                  |         |
| **TAM†**          |                             |         |
| HER2+             | 17% 4/23                    | 0.045   |
| HER2−             | 40% 48/119                  |         |
| **ANAST‡**        |                             |         |
| HER2+             | 58% 7/12                    | 0.09    |
| TAM               | 22% 29                      |         |

*LET, letrozole. †TAM, tamoxifen. ‡ANAST, anastrozole. Ellis et al.;\(^{39}\) Smith et al.\(^{40}\)
with lumpectomy and radiation for localized DCIS. A retrospective analysis of ER status of DCIS from patients randomized on NSABP B-24 demonstrated, as would be expected, that tamoxifen was only effective in reducing breast cancer events in patients who had ER-positive DCIS. The use of AIs as therapy for localized DCIS is being investigated in the NSABP B-35 trial. This trial randomizes postmenopausal patients with localized ER- and/or PR-positive DCIS treated with lumpectomy and radiation to tamoxifen or anastrozole for 5 years.

### CHEMOPREVENTION

A number of randomized controlled trials compared tamoxifen with placebo in women at high risk of breast cancer. The Breast Cancer Prevention Trial (BCPT) evaluated the effect of tamoxifen on 13,000 high-risk women. Women were determined to be high risk if they met the following criteria: aged 60 or greater, between 35 to 59 years with a Gail score of at least 1.66%, or a history of lobular carcinoma in situ. There were significantly less cancers, both invasive and DCIS, in the tamoxifen-treated patients, compared with the placebo-treated patients, with 124 and 244, respectively. The relative risk reduction was 50% for both invasive and noninvasive breast cancer. As would be expected, tamoxifen resulted in a lower occurrence of invasive, ER-positive cancers but did not affect occurrence of ER-negative cancers. Benign breast disease was also reduced in the tamoxifen-treated patients, compared with placebo-treated patients. Based on the results of this trial, tamoxifen was approved by the Food and Drug Administration for prevention of breast cancer in high-risk women. The International Breast Cancer Intervention Study demonstrated a 32% reduction in both invasive and noninvasive cancer in patients treated with tamoxifen compared with placebo. Similar to the BCPT, there was a decrease in ER-positive tumors but no significant change in the number of ER-negative tumors. Two smaller studies, the Royal Marsden Hospital Trial pilot trial and the Italian Tamoxifen Prevention Study, did not show a statistically significant decrease in breast cancer in patients treated with tamoxifen. Various reasons are given for the discrepancy in results, including sample size, differences in risk of breast cancer in the samples, and/or use of hormonal therapy by participants.

The Study of Tamoxifen and Raloxifene trial is the follow up to the BCPT trial. This trial is randomizing 19,000 postmenopausal women at high risk according to age, Gail model score, and history of lobular carcinoma in situ to either tamoxifen or raloxifene for 5 years. The primary endpoint of this trial is breast cancer incidence, but given the fact that raloxifene has no estrogenic effects on the uterus in preclinical models, an important secondary endpoint is the incidence of uterine cancer.

### Aromatase Inhibitors and Prevention

One of the main reasons tamoxifen was examined as a chemopreventive was the fact that it reduces the incidence of contralateral breast cancer. The adjuvant AI trials have demonstrated that AIs may be more effective than tamoxifen in reducing the risk of contralateral breast cancers (Figure 3). Based on these findings, chemoprevention trials in high-risk women with AIs are underway. A European trial is randomizing postmenopausal women at high risk to either anastrozole or placebo. The National Cancer Institute Canada is randomizing postmenopausal women at high risk to exemestane plus the COX II inhibitor, celecoxib, or to exemestane plus placebo.

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**TABLE 8. Comparison of Tumor Response in Patients Treated With Neoadjuvant Chemotherapy Compared With Neoadjuvant Hormonal Therapy**

|                      | Chemo | Endocrine |
|----------------------|-------|-----------|
| Clinical response    | 76%   | 75.6%     |
| Mammographic response| 61.9% | 62.1%     |
| Pathologic complete response | 7.4% | 3.3%      |
| Breast conserving surgery | 23.9% | 33.3%     |

*AT, paclitaxel plus doxorubicin. ANAST, anastrozole. EXEM, exemestane.

§$P = 0.054$.

Semiglazov et al.47
ADVERSE EVENTS

Both AIs and SERMs are well tolerated by most patients. However, both classes of drugs have both short-term and long-term side-effects, which can be predicted by their mechanisms of action (Table 9). Tamoxifen is a SERM and has estrogenic effects on several target tissues. In contrast, the AIs do not have any demonstrable estrogenic effects. The most common adverse events with both SERMs and AIs are hot flashes and vaginal dryness, both of which seem to be somewhat worse with tamoxifen. Overall, the adjuvant trials comparing AIs and tamoxifen have demonstrated an equivalent to slightly improved side-effect profile with AIs. However, it is important to remember that unlike tamoxifen, the long-term toxicities of the AIs are unclear.

Musculoskeletal Effects

The majority of adjuvant studies have shown an increase in osteoporosis in women treated with AIs (Table 10). The difference in rate of osteoporosis is more marked in trials where AIs were compared with tamoxifen, because tamoxifen has a protective effect on bone mineral density. The ATAC trial reported a significantly greater number of fractures both at its 3-year and 4-year follow up. The IES trial at a follow up of 30 months reports a significant increase in osteoporosis but not in fracture rate. It seems likely that with longer follow up, there may be a significant difference in fractures in this trial. The MA-17 trial to date does not show a significant difference in fractures between the letrozole and placebo arms but does demonstrate a trend toward more osteoporosis in the letrozole-treated patients. These data suggest that the AIs will reduce bone mineral density and increase the risk of osteoporotic-related fractures over time. Interestingly, preclinical data have suggested that exemestane, because of its androgenic effects at high doses, would not be associated with reduced bone density and fractures. However, a European trial that randomized patients with low-risk breast cancers to exemestane and placebo has failed to show a beneficial effect for exemestane on bone mineral density. This finding, in combination with the results of the IES trial, does not demonstrate a clear difference between exemestane and the other AIs on bones. To date, there are no standard guidelines on the management of osteoporosis in patients treated with AIs. It seems reasonable to get a baseline bone density study and then repeat at regular intervals while patients are receiving AIs. Also, the use of bisphosphonates may prevent or modify the incidence of osteopenia in women treated with AIs. If a patient is at significant risk of an osteoporotic fracture at baseline, bisphosphonate therapy should be considered when initiating endocrine treatment with aromatase inhibitors.

All the adjuvant AI trials have demonstrated an increase in arthralgias and myalgias in pa-

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**TABLE 9** Summary of Adverse Events Across Trials Examining AIs Versus Tamoxifen

| Adverse Event                      | ATAC* (ANAST† vs. TAM‡) | TEAM§ (EXEM¶ vs. TAM) | IES** (EXEM vs. TAM) |
|------------------------------------|-------------------------|----------------------|---------------------|
| Hot flashes TAM                    | AI > Al††               | Al = TAM             | Al = TAM            |
| Vaginal bleeding TAM               | AI > Al                 | Al = TAM             | TAM > Al            |
| Vaginal discharge TAM              | TAM > AI                | TAM > AI             | Not reported        |
| Endometrial cancer TAM             | TAM > AI                | Not reported         | Not reported        |
| Arthralgia/musculoskeletal AI      | AI > TAM                | AI > TAM             | AI > TAM            |
| Osteoporosis/fractures AI          | AI > TAM                | Not reported         | Not reported        |
| Thromboembolic disease TAM         | TAM > AI                | Not reported         | TAM > Al            |

*ATAC, arimidex, tamoxifen and combination.  
†ANAST, anastrozole.  
‡TAM, tamoxifen.  
§TEAM, Tamoxifen Exemestane Adjuvant Multinational.  
¶EXEM, exemestane.  
**IES, Intergroup Exemestane Study.  
††AI, aromatase inhibitor.  
Baum et al., Asmar et al., Coombes et al.
Patients treated with AIs. Symptoms are usually mild and include joint pains and muscle aches. The etiology of these musculoskeletal complaints is unknown, but they can usually be managed with anti-inflammatories and rarely result in discontinuation of therapy.

**Cardiovascular Effects**

SERMs have estrogenic effects on the cholesterol panel, resulting in a reduction in low density lipoprotein cholesterol. However, this has not to date resulted in a reduction of coronary artery disease. This is not surprising given the recent findings that hormone replacement therapy does not impact the incidence of coronary artery disease. Nonetheless, tamoxifen does not appear to increase the incidence of coronary artery events. On the other hand, AIs do not have estrogenic effects and therefore may increase cholesterol and possibly coronary artery events. The small Italian Tamoxifen Arimidex trial and the BIG-1-98 trial have demonstrated an increase in cholesterol in patients treated with anastrozole after tamoxifen. The IES trial has repeated a non-significant rate of MI patients on AIs, but should be mentioned for cardiovascular risk factors.

**Thromboembolic Effects**

SERMs, likely due to their estrogenic effects, have been demonstrated to increase the incidence of thromboembolic events, including deep venous thromboses and pulmonary emboli, particularly in postmenopausal women. Because the AIs do not have estrogenic effects, they would not be expected to increase the incidence of thromboembolic events. Overall, the incidence of thromboembolic events is higher in patients treated with tamoxifen, compared with those treated with AIs in the head-to-head trials. Tamoxifen has also been demonstrated to increase the incidence of cerebrovascular accidents. In the ATAC trial, there were less cerebrovascular accidents in patients treated with anastrozole, compared with those treated with placebo.

**Endometrial Cancer**

Tamoxifen has been clearly demonstrated to increase the incidence of endometrial cancer. In the BCPT, there was a fourfold increase in the incidence of uterine cancer in postmenopausal treated with tamoxifen compared with those treated with placebo. No such increase in uterine cancer was noted in premenopausal women. The AIs would not be expected to increase the incidence of uterine cancer, because they do not exhibit any estrogen-like effects on the uterus. The ATAC trial reports significantly less endometrial cancers in the anastrozole-treated patients, compared with those treated with tamoxifen. Likewise, both the ATAC and IES trials report less vaginal discharge and bleeding in the AI-treated patients, compared with the tamoxifen-treated patients.

**Table 10: Available Data on the Effects of AIs on Bone**

| Bone Outcome | Trial          | AI*  | TAM†  | P Value | Follow Up |
|--------------|----------------|------|-------|---------|-----------|
| Fractures    | ATAC‡          | 5.9% | 3.7%  | <0.0001 | 33.3 mos. |
|              | ATAC           | 7.1% | 4.4%  | <0.001  | 48 mos.   |
|              | ITA§           | 0.9% | 0.9%  | 0.9     | 36 mos.   |
| Osteoporosis | IES¶          | 7.4% | 5.7%  | 0.05    | 30.6 mos. |
|              | MA             |      |       |         |           |
| Fractures    | 17             | 3.6% | 2.9%**| 0.24    | 28.8 mos. |
| Osteoporosis |                | 5.8% | 4.5%**| 0.07    |           |

*AI, aromatase inhibitor.
†AM, tamoxifen.
‡ATAC, Arimidex, Tamoxifen and Combination.
§TA, Italian Tamoxifen Arimidex.
¶IES, Intergroup Exemestane Study.
**Placebo.
Baum et al.; Goss et al.; Boccardo et al.; Coombes et al.
In summary, to date, AIs have been demonstrated to increase the risk of osteoporosis but are not associated with an increase in endometrial cancer. The incidence of vasomotor symptoms is similar between the two classes of agents. Patients on long-term AIs are being monitored closely for unforeseen side effects, including effects on cognitive function.

**AIs in Premenopausal Women**

As stated above, the AIs are not effective in patients with intact ovarian function. However, there are several trials that are examining the AIs with ovarian ablation in premenopausal patients (Figure 5). The Suppression of Ovarian Function trial randomizes premenopausal woman who do not receive adjuvant chemotherapy or who continue to menstruate after adjuvant chemotherapy to tamoxifen alone for 5 years, tamoxifen plus ovarian ablation for 5 years, or to exemestane plus ovarian ablation for 5 years. Ovarian ablation can be accomplished by surgery, ovarian radiation, or by a luteinizing hormone-releasing hormone (LHRH) agonist administered for 5 years. The tamoxifen and exemestane trial randomizes premenopausal patients who have not received adjuvant chemotherapy to tamoxifen plus ovarian suppression with an LHRH agonist for 5 years or to exemestane plus ovarian suppression with an LHRH agonist for 5 years. These trials will determine whether AIs are effective in premenopausal patients. AIs are not currently recommended for patients who become amenorrheic following adjuvant chemotherapy, because they may not be truly postmenopausal and would not be, therefore, likely to benefit from an AI.

**WHO SHOULD GET AN ADJUVANT AI?**

Available data from the adjuvant AI trials does not, as yet, provide definitive guidelines on how patients should be treated with adjuvant AIs. The American Society of Clinical Oncology committee recently concluded that AIs are reasonable adjuvant therapy for postmenopausal patients, but did not state whether AIs should be used alone, or after some duration of tamoxifen. The only conclusion that can be taken from their recommendations is that no patient should receive just tamoxifen, and that an AI is indicated as part of adjuvant therapy in postmenopausal patients.
Based on this other available data, it would seem appropriate to look at the outcome of specific subgroups in the adjuvant trials, and most importantly, weigh up the side-effect profiles of the agents, prior to making a recommendation to an individual patient. For example, based on the final analysis of the MA-17 trial, patients with positive axillary lymph nodes may benefit, both in terms of recurrence rate and survival, from letrozole after 5 years of tamoxifen. In contrast, patients with uninvolved axillary lymph nodes benefit much less from letrozole after tamoxifen, and it would seem reasonable to discontinue hormonal therapy after 5 years in these patients, particularly when osteoporosis is a concern. In patients where available data demonstrate a similar outcome with tamoxifen or AIs (for example patients with ER-positive, PR-positive tumors), the agent’s side-effect profile and cost should be taken into account and these patients may be best treated with a short duration of tamoxifen followed by an AI. Overall, it seems appropriate to make decisions regarding optimal adjuvant hormonal therapy on an individual patient basis, taking into account tumor-related factors, as well as the side-effect profile of the agent.

CONCLUSION

Endocrine therapy for breast cancer is a rapidly evolving field. In the treatment of advanced breast cancer, the AIs are at least as good as tamoxifen, and are widely used as first-line therapies. Likewise, the AIs are at least as effective, and perhaps better in specific subsets of patients, than tamoxifen, in the adjuvant treatment of early stage breast cancer in postmenopausal women. Trials examining neoadjuvant hormonal therapies are promising, and hormonal therapy may be more appropriate than chemotherapy for selected patients with low grade, hormone receptor-positive tumors. Prevention trials using the AIs in high risk women have been initiated based on the observation that these agents are at least as effective as tamoxifen in reducing the rate of contralateral breast cancer. The AIs are being examined along with ovarian suppression in premenopausal women.

Despite the available data, many questions remain unanswered. Will the use of adjuvant AIs translate into a survival advantage? What is the optimal sequence of endocrine therapies in the advanced and adjuvant disease settings? Is there a difference between the third generation inhibitors? What is the optimal duration of AIs in the adjuvant setting, and do patients still require tamoxifen? Lastly, and most importantly, what are the long term side effects of aromatase inhibitors? Ongoing trials will answer some of these questions, but it seems likely that further trials will be needed.

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