ADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL WOMEN WITH EARLY BREAST CANCER

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ABSTRACT

The safety and efficacy of tamoxifen as adjuvant endocrine therapy for postmenopausal patients with early breast cancer (BC) has been established. In the last decade, aromatase inhibitors (AIs) have also been evaluated in this setting. The results of several large, randomized clinical trials that investigated AIs as initial treatment for up to 5 years, after 2 to 3 years of tamoxifen, and for extended treatment after 5 years of tamoxifen have recently been reported. In all cases, AIs have shown greater efficacy than tamoxifen. However, the optimal role of AIs in postmenopausal patients with early BC remains unclear. The Technology Assessment Working Group of the American Society of Clinical Oncology has recommended that AIs be used for adjuvant therapy initially or after 2 to 3 years of tamoxifen for postmenopausal patients with hormone-receptor–positive BC. Differences in safety and efficacy among the AIs are emerging but are not yet fully understood. AIs are safe and generally well tolerated. They result in fewer hot flashes and gynecologic symptoms but more joint symptoms than tamoxifen. The greatest concern regarding the use of AIs is their association with an increased incidence of fractures because AIs reduce bone mineral density. The risk of cardiovascular events from AIs may vary with different AIs and remains to be further defined. AIs are less likely than tamoxifen to cause thromboembolic events.

T he first randomized clinical trial of adjuvant therapy for breast cancer (BC) was conducted approximately 60 years ago. Since then, hundreds of clinical trials have investigated a wide variety of treatment approaches. A meta-analysis conducted by the Early Breast Cancer Trialsists' Collaborative Group (EBCTG) established that adjuvant systemic chemotherapy improves the disease-free survival (DFS) time and overall survival (OS) time of patients with early stage BC.

The EBCTG also conducted a separate meta-analysis that showed the benefits of adjuvant endocrine therapy and helped establish 5 years of tamoxifen as the standard for adjuvant endocrine therapy in postmenopausal women with early BC. However, the benefits associated with tamoxifen—which were largely independent of age, menopausal status, daily tamoxifen dose, and previous chemotherapy—were not without risk. Treatment with tamoxifen increased the incidence of endometrial cancer; it approximately doubled the rate after 1 or 2 years of tamoxifen therapy and quadrupled it after 5 years of tamoxifen therapy. Furthermore, concerns regarding thromboembolic events and the development of resistance to tamoxifen leading to disease recurrence indicated a need for alternative adjuvant therapies.

ENDOCRINE THERAPY OPTIONS

The development of tamoxifen as adjuvant therapy for BC was based on the observation more than a century ago that oophorectomy caused BC regression in a premenopausal patient. Tamoxifen, a selective estrogen-receptor modulator (SERM), causes estrogen deprivation through competitive blockade of the estrogen receptor in breast tissue. At the same time, SERMs act as estrogen agonists on other tissues such as endometrium and bone. Other SERMs include raloxifene and toremifene. Raloxifene has no clinically significant antitumor activity in advanced BC and is not indicated for BC treatment. Toremifene is indicated as
an alternative to tamoxifen as first-line treatment of hormone-responsive metastatic BC and appears to be as effective as tamoxifen when given as adjuvant therapy to patients with metastatic disease. Fulvestrant is a steroid analog with pure estrogen-receptor antagonist activity that is also indicated for metastatic BC.

The use of aromatase inhibitors (AIs) is another approach to reducing the effects of estrogen in patients with BC. AIs reduce circulating estrogen levels by inhibiting aromatase, the enzyme that converts testosterone to estradiol and androstenedione to estrone. AIs also act by directly blocking local estrogen production in the breast tumor. Because AIs indirectly lead to ovarian stimulation, which may result in ovarian cysts in premenopausal females, they are not recommended in women with normal ovarian function.

Although 3 generations of AIs exist, only the third generation of AIs are used for the adjuvant treatment of BC in postmenopausal women because of their superior safety profile and convenient dosing features. AIs are classified as type 1 or type 2, depending on their mechanism of action. Type 1 AIs are androstenedione steroidal analogs and bind irreversibly to the aromatase enzyme, whereas type 2 AIs are nonsteroidal and bind reversibly to the heme group on the aromatase enzyme. Of the third-generation AIs, exemestane is a type 1 agent, whereas anastrozole and letrozole are type 2 AIs.

During the last few years, several trials testing AIs as adjuvant therapy for early BC in postmenopausal women have been completed or their preliminary results have been reported. These trials generally have compared AIs directly with tamoxifen or have used AIs in sequence with tamoxifen.

**Direct Comparison of Aromatase Inhibitors and Tamoxifen**

**The Arimidex, Tamoxifen, Alone or in Combination Trial**

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial enrolled postmenopausal women to compare the safety and efficacy of tamoxifen therapy with those of anastrozole therapy when given alone or with tamoxifen for 5 years. Women were eligible if they had invasive operable BC, had completed primary therapy, and could receive adjuvant hormonal therapy. Women (n = 9366) were randomized to receive tamoxifen, 20 mg; anastrozole, 1 mg; or both at the same dosages as were used in monotherapy.

After a median follow-up of 68 months, compared with tamoxifen, anastrozole prolonged DFS time (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.78–0.97, P = .01) and time to recurrence (HR 0.79, 95% CI 0.79–0.90, P = .0005). However, compared with tamoxifen, anastrozole produced the greatest benefit in women with hormone-receptor–positive BC (DFS HR 0.83, 95% CI 0.73–0.94; time to recurrence HR 0.74, 95% CI 0.64–0.87). Results of retrospective subgroup analysis suggested that the time to recurrence was substantially greater in the group with progesterone-receptor–negative BC. The benefit of anastrozole was independent of prior chemotherapy or type of chemotherapy. At 68 months’ median follow-up, the time to recurrence was not different between patients who had received prior chemotherapy and those who had not (HR 0.89 vs 0.74, respectively; P = .021). Time to distant metastases was longer (HR 0.86, 95% CI 0.74-0.99, P = .04) and incidence of contralateral BC was less (HR 0.58, 42% reduction, 95% CI 12%-62%, P = .01) in the group that received anastrozole than in the group that received tamoxifen. In terms of the latter measure, women with hormone-receptor–positive BC experienced the greatest benefit (53% reduction, 95% CI 25%-71%, P = .01). OS time was similar for the anastrozole and tamoxifen groups; although, given the relatively good prognosis of the patient population, it still may be too early for a difference to be seen.

**The Breast International Group 1-98 Trial**

The Breast International Group (BIG) 1-98 trial randomized 8010 postmenopausal women with operable invasive BC that was estrogen-receptor positive, progesterone-receptor positive, or both. Women received 5 years of treatment with letrozole, 2.5 mg daily; 5 years of treatment with tamoxifen, 20 mg daily; letrozole for 2 years then tamoxifen for 3 years; or tamoxifen for 2 years then letrozole for 3 years. After a median follow-up of 25.8 months, 4-year DFS was estimated to be 84% in the 2 groups that received letrozole initially combined and 81.4% in the 2 groups that received tamoxifen initially combined. Compared with tamoxifen, letrozole reduced the risk of experiencing an event that ended a period of DFS (HR 0.81, 95% CI 0.70-0.93; P = .003), especially the risk of distant recurrence (HR 0.73, 95% CI 0.60-0.88; P = .001). Although the supporting data were not provided, the investigators reported a beneficial effect of letrozole monotherapy compared with tamoxifen.
monotherapy. Planned subgroup analyses showed a 5-year DFS among women with node-positive cancer of 77.9% in the letrozole group and 71.4% in the tamoxifen group; in women with node-negative cancer, 5-year DFS was 88.7% in both groups. The DFS benefits of letrozole were similar for all combinations of estrogen-receptor and progesterone-receptor status.

**THE ARIMIDEX, TAMOXIFEN, ALONE OR IN COMBINATION AND BREAST INTERNATIONAL GROUP 1-98 TRIALS IN PERSPECTIVE**

Many of the benefits of AI therapy were similar in the ATAC and BIG 1-98 trials, although important differences exist. The ATAC trial showed that the relative treatment benefits of anastrozole did not differ between patients who received prior chemotherapy and those who did not. In contrast, the BIG 1-98 trial showed the greatest benefit of letrozole in women who had received chemotherapy and in those with node-positive disease. Similarly, the ATAC trial showed the greatest benefit of anastrozole in women with estrogen-receptor–positive and progesterone-receptor–negative tumors. Letrozole similarly reduced the risk of an event ending DFS irrespective of progesterone-receptor status. Despite these differences, both trials support the initial use of an AI instead of tamoxifen as adjuvant therapy.

The important role of an AI in initial adjuvant therapy is further supported by the results of a cost-effectiveness analysis that estimated the incremental cost per quality-adjusted life-year (QALY) gained from initial adjuvant therapy with letrozole compared with tamoxifen or from initial adjuvant therapy with anastrozole compared with tamoxifen. The incremental cost per QALY gained was estimated to be $33 536 (95% CI $20 409–$70 566) for letrozole and $38 967 (95% CI $23 826–$81 904) for anastrozole, which indicates that therapy with an AI is cost effective for the healthcare system.

**AROMATASE INHIBITOR THERAPY AFTER 2 TO 3 YEARS OF TAMOXIFEN THERAPY**

An overall survival benefit when tamoxifen was given for less than 5 years and followed by AI therapy was preliminarily shown for aminoglutethimide, a first-generation AI, in the GROCTA 4 trial. Other studies have confirmed these results.

**THE ITALIAN TAMOXIFEN ANASTROZOLE TRIAL**

The Italian Tamoxifen Anastrozole (ITA) trial was conducted by the GROCTA 4 investigators using the same study design as was used in GROCTA 4. Postmenopausal women (n = 448) with node-positive, estrogen-receptor–positive tumors who had been treated with 2 to 3 years of tamoxifen were randomized to receive anastrozole, 1 mg daily, or to continue to receive tamoxifen, 20 mg daily, for a total of 5 years. At a median follow-up of 36 months, DFS and local recurrence-free survival (LRFS) times were longer in the anastrozole group than in the tamoxifen group (DFS HR 0.35, 95% CI 0.18–0.68, P = .001; LRFS HR 0.15, 95% CI 0.03–0.65, P = .003).

An updated and pooled analysis of the GROCTA 4 and ITA trials showed that all-cause mortality and breast-cancer–specific mortality were decreased (P = .007 or .03, respectively) by switching to anastrozole.

**THE AUSTRIAN BREAST AND COLORECTAL CANCER STUDY GROUP TRIAL 8 AND ARIMIDEX-NOLVADEX95 TRIAL**

A prospectively planned, event-driven, combined analysis was done of the Austrian Breast and Colorectal Cancer Study Group Trial 8 (ABCSD 8) and Arimidex-Nolvadex (ARNO) 95 trial. The data analyzed were obtained from studying 3224 postmenopausal women with hormone-sensitive early BC. After completing 2 years of adjuvant tamoxifen therapy, patients were randomized to continue to receive tamoxifen, 20 or 30 mg daily, or to receive anastrozole, 1 mg daily, for a total treatment period of 5 years. DFS 3 years after the switch was longer in the anastrozole group than in the tamoxifen group (HR 0.60, 95% CI 0.44–0.81, P = .0009); the absolute benefit at 3 years was 3.1%. A separate analysis of the ARNO 95 trial with a median follow-up of 30.1 months showed that switching to anastrozole improved DFS (HR 0.66, 95% CI 0.44–1.00, P = .049) and OS (HR 0.53, 95% CI 0.28–0.99, P = .045).

**THE INTERGROUP EXEMESTANE STUDY**

Postmenopausal women who had received tamoxifen for 2 to 3 years were randomized to continue receiving tamoxifen, 20 mg daily, or to switch to exemestane, 25 mg daily, for a total of 5 years of adjuvant therapy. After a median follow-up of 58 months, DFS was greater in the exemestane group than in the tamoxifen group (HR 0.76; 95% CI 0.66–0.88, P = .0001). The time to distant recurrence (HR 0.83, 95% CI 0.70–0.98) and contralateral BC (HR 0.56, 95% CI 0.32–0.97) were reduced (P = .03 or .04, respectively) in the exemestane group. OS time
was not different between the 2 groups (HR 0.85, 95% CI 0.71–1.02, \( P = .08 \)), except in those with estrogen-receptor–positive/unknown, unilateral BC (HR 0.83, 95% CI 0.69–1.00, \( P = .05 \)). \(^{18} \)

**ITA, ABCSG 8, ARNO 95, and INTERGROUP EXEMESTANE STUDY IN PERSPECTIVE**

Combined analysis of these trials showed that switching to AI therapy after only 2 to 3 years of tamoxifen improved event-free and recurrence-free survival (\( P < .00001 \)) compared with 5 years of tamoxifen therapy. \(^{19} \)

**AROMATASE INHIBITORS AFTER 5 YEARS OF TAMOXIFEN**

The National Surgical Adjuvant Breast and Bowel Project B-14 trial showed that extending the duration of tamoxifen therapy beyond 5 years offered no benefit and instead shortened DFS time. \(^{20} \) For this reason, and because 50% of all recurrences and two thirds of all deaths from hormone-dependent BC occur after 5 years of tamoxifen therapy, \(^{21} \) the role of AI therapy when given after 5 years of tamoxifen therapy has been investigated.

**THE MA.17 TRIAL**

Postmenopausal women who were completing 5 years of tamoxifen were randomized to receive 5 years of letrozole, 2.5 mg daily (\( n = 2593 \)), or placebo (\( n = 2594 \)). \(^{21} \) After a median follow-up of 30 months, women in the letrozole group had better DFS time (HR 0.58, 95% CI 0.45–0.76, \( P = .001 \)) and distant DFS time (HR 0.60, 95% CI 0.43–0.84, \( P = .002 \)). Although OS time was the same in both groups, those with node-positive tumors in the letrozole group fared better (HR 0.61, 95% CI 0.38–0.98, \( P = .044 \)). At a median follow-up of 2.4 years, the estimated 4-year DFS time in the letrozole group was 93% compared with 87% in the placebo group (\( P < .001 \)), which represents an absolute reduction in recurrence of 6% caused by letrozole. Because this difference exceeded a predesignated cutoff point, the trial was closed, even though most patients had not completed 5 years of therapy.

After the trial was unblinded, women in the placebo group were offered letrozole. An intent-to-treat analysis was conducted at a median follow-up of 54 months. Patients originally randomized to receive letrozole fared better than patients whose therapy was switched from placebo to letrozole in terms of DFS (94.3% vs 91.4%, respectively; HR 0.64, 95% CI 0.52–0.79, \( P = .00002 \)), distant DFS (96.2% vs 94.9%, respectively; HR 0.76, 95% CI 0.58–0.99, \( P = .041 \)), and incidence of contralateral BC (0.29% vs 0.47%, respectively; HR 0.61, 95% CI 0.38–0.98, \( P = .037 \)), but not in terms of OS (95.0% vs 95.1%, respectively; HR 1.00, 95% CI 0.78–1.28, \( P = .99 \)). \(^{22} \) A separate analysis showed that the patients in the group whose therapy was switched from placebo to letrozole fared better than those in the placebo group who elected no further treatment, which suggests that AI therapy produced a benefit despite a substantial delay in treatment after 5 years of tamoxifen therapy. \(^{23} \)

In addition to producing clinical benefits, adding letrozole to 5 years of tamoxifen therapy also reduces costs. A separate analysis compared the direct medical costs (excluding surgery) of adding 4 years of letrozole therapy with those of not extending therapy. \(^{24} \) In spite of its additional cost, by reducing BC recurrences, adding 4 years of letrozole therapy produced a net savings of $36 314 per 100 patients treated.

**THE AUSTRIAN BREAST AND COLORECTAL CANCER STUDY GROUP TRIAL 6A**

The ABCSG 6 trial showed that postmenopausal women treated with 2 years of tamoxifen plus aminoglutethimide then 3 years of tamoxifen had a similar prognosis when compared with that of patients treated with tamoxifen alone for 5 years. The ABCSG 6a trial randomized patients from ABCSG 6 to receive anastrozole, 1 mg daily, or no treatment for an additional 3 years. \(^{25} \) At 5 years’ median follow-up, fewer patients in the anastrozole group experienced disease recurrence (HR 0.64, 95% CI 0.41–0.99, \( P = .047 \)). OS time was not different between the 2 groups.

**THE MA.17 AND AUSTRIAN BREAST AND COLORECTAL CANCER STUDY GROUP 6A TRIALS IN PERSPECTIVE**

The benefits of adding AI therapy after 5 years of tamoxifen therapy are clearly evident, particularly with respect to DFS time. The benefit of AI therapy persisted despite a substantial delay in its initiation after 5 years of tamoxifen therapy, although this benefit was blunted compared with the benefit obtainable when AI therapy was given without delay.

**DIRECT COMPARISONS OF AROMATASE INHIBITORS**

Cumulative evidence suggests that there may be differences among AIs with respect to efficacy and safety. To determine whether 5 years of letrozole, 2.5 mg daily, and 5 years of anastrozole, 1 mg daily, pro-
duce different results in terms of 5-year DFS time, a phase IIIB open-label, randomized study of 4000 postmenopausal women has begun. Preliminary results indicate that letrozole, 2.5 mg daily, suppresses estradiol to a greater degree than anastrozole, 1 mg daily. Postmenopausal women with invasive, estrogen-receptor–positive BC received 12 weeks of letrozole, 2.5 mg daily, then 12 weeks of anastrozole, 1 mg daily (n = 27), or 12 weeks of anastrozole, 2.5 mg daily, then 12 weeks of letrozole, 1 mg daily (n = 27). At study end, the mean estradiol levels were 2.91 pmol/L after anastrozole therapy and 1.87 pmol/L after letrozole therapy (P < .0001). Compared with baseline, the mean residual percentage of estradiol was 9.2% after anastrozole therapy and 5.6% after letrozole therapy. The clinical significance of more profound suppression of estradiol by letrozole, if any, remains to be defined.

SAFETY OF AROMATASE INHIBITORS COMPARED WITH TAMOXIFEN

AIs are generally well tolerated, and their side-effect profile seems to be better than that of tamoxifen. However, the long-term safety of AIs remains unclear. Assessments generally show little impact of AIs on quality of life. Vasomotor and gynecologic symptoms, such as hot flashes and vaginal dryness, in addition to bone/muscle aches, are the most common adverse side effects of AI therapy. Despite this, other serious side effects, such as osteoporosis, cardiovascular events, thromboembolic events, and endometrial cancer have received greater attention than the more common adverse side effects (Table 1).

OSTEOPOROSIS

Many adjuvant studies have shown an increase in osteoporosis in women treated with an AI, which generally leads to an increase in bone fracture rate. The yearly fracture rate was higher for anastrozole than for tamoxifen after 68 months of follow-up in the ATAC trial and remained constant over the treatment period. The BIG 1-98 trial showed that letrozole therapy was associated with a greater incidence of fractures compared with tamoxifen therapy, whereas the MA.17 trial showed no difference between letrozole therapy and placebo in this regard. This finding reaffirms an earlier observation that tamoxifen has a protective effect on bone mineral density. Early experience with exemestane

Table 1. Safety Overview of Aromatase Inhibitors

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Arthralgia</th>
<th>Thromboembolic Event</th>
<th>Invasive Endometrial Cancer</th>
<th>Serious/Life-threatening/Fatal Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC7</td>
<td>A (11%)</td>
<td>A (35.6%)</td>
<td>A (2.8%)</td>
<td>A (0.2%)</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>T (7.7%)</td>
<td>T (29.4%)</td>
<td>T (4.5%)</td>
<td>T (0.8%)</td>
</tr>
<tr>
<td>vs tamoxifen</td>
<td>(P &lt; .0001)</td>
<td>(P &lt; .001)</td>
<td>(P = .0004)</td>
<td>(P = .02)</td>
</tr>
<tr>
<td>BIG 1-9810</td>
<td>L (5.7%)</td>
<td>L (20.3%)</td>
<td>L (1.5%)</td>
<td>L (0.1%)</td>
</tr>
<tr>
<td>Letrozole</td>
<td>T (4.0%)</td>
<td>T (12.3%)</td>
<td>T (3.5%)</td>
<td>T (0.3%)</td>
</tr>
<tr>
<td>vs tamoxifen</td>
<td>(P &lt; .001)</td>
<td>(P &lt; .001)</td>
<td>(P &lt; .001)</td>
<td>(P = .18)</td>
</tr>
<tr>
<td>ITA13</td>
<td>A (1.0%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>T (1.3%)</td>
<td>—</td>
<td>—</td>
<td>A (10.8%)</td>
</tr>
<tr>
<td>vs tamoxifen</td>
<td>(P = 6)</td>
<td>—</td>
<td>—</td>
<td>T (12.9%)</td>
</tr>
<tr>
<td>IES17</td>
<td>E (3.1%)</td>
<td>E (5.4%)</td>
<td>E (1.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Exemestane</td>
<td>T (2.3%)</td>
<td>T (3.6%)</td>
<td>T (2.4%)</td>
<td>—</td>
</tr>
<tr>
<td>vs tamoxifen</td>
<td>(P = .08)</td>
<td>(P = .01)</td>
<td>(P = .007)</td>
<td>—</td>
</tr>
<tr>
<td>MA.1732</td>
<td>L (5.3%)</td>
<td>L (25%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Letrozole</td>
<td>P (4.6%)</td>
<td>P (2.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>vs placebo</td>
<td>(P = .25)</td>
<td>(P &lt; .001)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

A = anastrozole; ATAC = Arimidex, Tamoxifen, Alone or in Combination trial; BIG 1-98 = Breast International Group 1-98 trial; E = exemestane; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole trial; L = letrozole; T = tamoxifen; — = data unavailable.

Data from Howell et al7; Thurlimann et al10; Boccardo et al13; Coombes et al17; and Goss.19
suggests that use of this AI results in a modest loss of bone from the femoral neck and a minimal loss of lumbar bone. Moreover, the Intergroup Exemestane Study (IES) trial found more fractures in the group that switched to exemestane than in the group that continued to receive tamoxifen after a median of 58 months of follow-up ($P = .003$). The estimated increase in fracture rate with exemestane was similar to what has been observed in trials of anastrozole and letrozole.

**CARDIOVASCULAR**

A definitive conclusion regarding the cardiovascular risk of AIs as a group cannot be made because of the small number of events that have been reported thus far. The ATAC trial afforded the greatest amount of evidence regarding the cardiovascular effects of AIs and suggested that anastrozole has no deleterious effect on cardiac health. After 68 months’ median follow-up, no difference was found between anastrozole and tamoxifen in the incidence of myocardial infarction, cardiac death, or ischemic cardiovascular death in the ATAC trial. The BIG 1-98 trial showed an increase in grade 3 to 5 cardiac events for letrozole compared with tamoxifen at 26 months, whereas no differences were observed in the MA.17 trial at 2.5 years of follow-up. For exemestane, with a median follow-up of 58 months, the IES trial found that the incidence of myocardial infarction and cardiac death were not different for exemestane compared with tamoxifen.

**THROMBOEMBOLIC**

Direct comparative trials have shown that thromboembolic events occur more frequently in patients treated with tamoxifen than in those treated with anastrozole, exemestane, or letrozole. Because AIs do not have estrogenic effects, this finding is not surprising. Furthermore, in the ATAC trial, cerebrovascular events occurred less frequently in patients treated with anastrozole than in those treated with tamoxifen.

**ENDOMETRIAL CANCER**

Because of their lack of estrogenic effects on the uterus, AIs would not be expected to increase the incidence of uterine cancer. The ATAC trial showed that compared with tamoxifen, anastrozole caused significantly fewer endometrial cancers, whereas the BIG 1-98 trial showed that compared with tamoxifen, letrozole produced a reduction in endometrial cancers that was not statistically significant.

**AROMATASE INHIBITION: TRANSLATION INTO A SUCCESSFUL THERAPEUTIC APPROACH**

The results of the clinical trials discussed help clarify the role of AIs as adjuvant therapy in postmenopausal women with early BC. However, some uncertainty remains, in part because the trials have studied different third-generation AIs and have administered them at different times.

Nonetheless, the Technology Assessment Working Group convened by the American Society of Clinical Oncology in 2004 concluded that adjuvant endocrine therapy for a postmenopausal woman with hormone-receptor–positive BC should include an AI as initial therapy or after tamoxifen therapy. Moreover, the favorable reduction in recurrence obtained from using an AI compared with using tamoxifen in the ATAC and BIG 1-98 trials supports the initial use of an AI rather than tamoxifen as adjuvant therapy (Table 2). Furthermore, the ABCSG 8/ARNO 95, ITA, and IES trials have shown the benefits obtainable by switching to AI therapy after 2 to 3 years of adjuvant tamoxifen therapy in postmenopausal women with hormone-sensitive early BC. Moreover, data from the ATAC trial showed that, during the first 2.5 years of adjuvant treatment, patients treated with anastrozole had almost 50% of recurrences and death after recurrence of patients treated with tamoxifen. This finding suggests that anastrozole suppresses the early peak in recurrence that is well established to occur with tamoxifen therapy during years 1 to 3. Moreover, the risk of recurrence was lower with anastrozole than with tamoxifen throughout the entire treatment period. Thus, instead of introducing an AI after 2 to 3 years of tamoxifen therapy, using an AI as initial therapy might be expected to avoid some recurrences, especially early ones.

In the absence of definitive data from clinical trials, various investigators have utilized existing efficacy and safety data to construct models that identify the best role for an AI. One such model predicted the percentage of years of life lost to recurrence in patients with estrogen-receptor–positive BC on the basis of the adjuvant therapy they received. At 10 years of follow-up, the model predicted that 12.1% of years would be lost to recurrence if tamoxifen were used alone for 5 years as adjuvant therapy. If 5 years of treatment with an AI were added to 5 years of treatment with tamoxifen, 10.9% of years of life would be lost to recurrence. This percentage would decrease to 9.6% if patients received 2 years of tamoxifen.
therapy then 3 years of AI therapy. However, according to the model, the best choice is 5 years of therapy with an AI alone because only 9% of years of life would be lost to recurrence with this treatment option. The superiority of this regimen was seen at all points up to 10 years (Figure).

A different model developed by Burstein et al provided somewhat different results. This model determined that switching to AI therapy after 2 years of tamoxifen therapy yielded slightly better 10-year DFS than therapy with an AI alone in women with estrogen-receptor–positive/progesterone-receptor–positive BC, irrespective of lymph-node status. However, in women with estrogen-receptor–positive/progesterone-receptor–negative BC, 5 years of treatment with an AI alone yielded slightly better 10-year DFS than switching from tamoxifen to AI therapy, irrespective of node status. Until definitive data from clinical trials are available, the best approach may be to select adjuvant hormonal therapy individually after an adequate discussion of available data with each patient.

### Managing the Toxicities of Aromatase Inhibitors

Various strategies for managing or preventing AI toxicities have been investigated. However, whether therapy should be switched to another AI or tamoxifen when the toxicity of one AI becomes intolerable is unclear.

### Osteoporosis

The ability of bisphosphonates to preserve bone mineral density in otherwise healthy postmenopausal women is well established. However, the long-term

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**Table 2. Recurrence Rates for Adjuvant Aromatase Inhibitor Therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>AI</th>
<th>Sample Size (months)</th>
<th>Median Follow-up (months)</th>
<th>All ER+</th>
<th>ER+/PgR+</th>
<th>ER+/PgR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC*</td>
<td>ANA</td>
<td>8028</td>
<td></td>
<td>0.72</td>
<td>0.72†</td>
<td>0.72‡</td>
</tr>
<tr>
<td>BIG 1-98†</td>
<td>LET</td>
<td>4742</td>
<td>31</td>
<td>0.70</td>
<td>0.72‡</td>
<td>0.63‡</td>
</tr>
<tr>
<td>IES‡</td>
<td>EXE</td>
<td>448</td>
<td>52</td>
<td>0.43</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ITA§</td>
<td>ANA</td>
<td>3224</td>
<td>28 (0.44–0.81)</td>
<td>0.60</td>
<td>0.66</td>
<td>0.42</td>
</tr>
<tr>
<td>ABCSG 8/ARNO‖</td>
<td>ANA</td>
<td>5157</td>
<td>29 (0.43–0.75)</td>
<td>0.57</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ABCSG 6a‖</td>
<td>LET</td>
<td>856</td>
<td>60 (0.41–0.99)</td>
<td>0.64</td>
<td>—</td>
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* Patients with hormone-receptor–positive tumors; † Based on similar disease-free survival time (hazard ratios 0.84 vs 0.83); ‡ Based on disease-free survival time hazard ratios of 0.66 vs 0.58 in the earlier analysis.

ABCSG 6a = Austrian Breast and Colorectal Cancer Study Group trial 6a; ABCSG 8 = Austrian Breast and Colorectal Cancer Study Group trial 8; AI = aromatase inhibitor; ANA = anastrozole; ARNO = Arimidex-Nolvadex trial; ATAC = Arimidex, Tamoxifen, Alone or in Combination trial; BIG 1-98 = Breast International Group 1-98 trial; CIs = confidence intervals; ER+ = estrogen-receptor positive; EXE = exemestane; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole trial; LET = letrozole; PgR- = progesterone-receptor negative; PgR+ = progesterone-receptor positive; – = data unavailable.

use of the oral bisphosphonates alendronate and risedronate is complicated by the need for daily administration, gastrointestinal intolerance that limits their optimal dosing, and their poor and variable gastrointestinal absorption. Other preparations include oral weekly alendronate or monthly ibandronate. Using a single 4-mg dose of zoledronic acid (Zometa; Novartis, East Hanover, NJ), a recent trial showed an increase in bone mineral density 12 months postdose in postmenopausal women with low bone mineral density. On the basis of these encouraging results, the Zometa/Femara Adjuvant Synergy Trial (Z-FAST) was initiated.

Z-FAST is a randomized, open-label trial that is comparing the efficacy and safety of early versus delayed zoledronic acid therapy in preventing cancer-treatment-induced bone loss. Postmenopausal women with stage I-IIIA, estrogen-receptor–positive and/or progesterone-receptor–positive BC who were starting letrozole therapy were randomized to receive early or delayed treatment with zoledronic acid, 4 mg intravenously every 6 months. Preliminary trial data showed that early zoledronic acid therapy increased bone mineral density in the lumbar spine by 1.55% and in the hip by 1.02%, whereas delayed zoledronic acid therapy resulted in decreases in bone mineral density of 1.78% in the lumbar spine and of 1.4% in the hip. However, zoledronic acid is not US Food and Drug Administration approved for the treatment of bone loss or osteoporosis.

In addition to bisphosphonate therapy, vitamin D supplementation may be helpful in preventing osteoporosis in patients with BC who are receiving adjuvant AI therapy. When 25-hydroxyvitamin D levels were analyzed in 147 postmenopausal women with early BC who had been randomized to receive exemestane or placebo, most were found to be deficient in vitamin D regardless of treatment group.

CARDIOVASCULAR EVENTS

The results of the clinical trials to date suggest that no difference exists in the risk of a cardiovascular event with anastrozole or exemestane compared with tamoxifen. The data regarding letrozole are conflicting and involve a shorter duration of follow-up than the anastrozole and exemestane trials. Because coronary heart disease was not an exclusion criterion in the adjuvant AI trials, it is likely that a difference in cardiovascular risk between AIs and tamoxifen would have been observed if one existed. Consequently, it seems reasonable to conclude that cardiovascular risk should not influence the decision to use an AI in the treatment of postmenopausal early BC.

LIFESTYLE ADVICE

Although weight gain is a common consequence of tamoxifen therapy, it does not seem to be a side effect of AI therapy. In a study of 96 outpatients with BC who were receiving adjuvant therapy, in the anastrozole therapy group (n = 26), the mean weight gain was not found to be clinically significant at any point during 12 months of therapy. Nonetheless, reducing dietary fat intake seems to be beneficial in postmenopausal women with primary BC. The Women’s Intervention in Nutrition Study found that reducing dietary fat intake by one third improves the relapse-free survival of patients with estrogen-receptor–negative BC, but such improvement was not found in patients with estrogen-receptor–positive BC.

CONCLUSIONS

The important role of AIs in the adjuvant treatment of postmenopausal women with early BC is sup-

![Figure. Model Comparing Initial Use of an Aromatase Inhibitor with Sequencing After Tamoxifen in Postmenopausal Women with Estrogen-Receptor–Positive Breast Cancer](image-url)
ported by a large body of efficacy and safety data. Consequently, an AI should be used in adjuvant therapy initially or after 2 to 3 years of tamoxifen in postmenopausal women with hormone-receptor–positive BC. However, questions regarding the appropriate duration of AI therapy remain unanswered. In addition, the differences between the AIs are unclear. Although AIs are safe and generally well tolerated, their use has been associated with a reduction in bone mineral density, which often leads to a fracture. However, bisphosphonate therapy appears to substantially decrease this risk. Although no difference has been found in the rate of cardiovascular events in patients who received AIs compared with those who received tamoxifen, AIs seem to be less likely to cause a thromboembolic event than tamoxifen. Ongoing research may provide even greater clarity regarding the role of AIs as adjuvant therapy in postmenopausal women with early BC.

REFERENCES


