Anastrozole as an Adjuvant Endocrine Treatment for Postmenopausal Patients with Breast Cancer: Emerging Data

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Abstract

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared the efficacy and safety of anastrozole versus tamoxifen versus the combination as initial adjuvant treatment for early breast cancer in over 9,000 postmenopausal women. Analyses at 33 and 47 months median follow-up showed that anastrozole significantly prolonged disease-free survival and time to recurrence and reduced the incidence of contralateral breast cancer compared with tamoxifen. Results of the completed treatment analysis at 68 months median follow-up confirmed the earlier findings, showing that the absolute difference in disease-free survival continued to increase beyond completion of treatment. Mature safety data from the ATAC trial show that, overall, anastrozole has a favorable safety profile compared with tamoxifen. In the absence of current data on further follow-up or the outcome of trials investigating proactive sequencing of endocrine therapies, we present a model based on several trials, including ATAC. This model suggests that using an aromatase inhibitor as initial adjuvant therapy is a better option than switching to an aromatase inhibitor after ≥2 years of tamoxifen. The relative toxicities of the three approved third-generation aromatase inhibitors, anastrozole, letrozole, and exemestane, are discussed. These data suggest that long-term safety profiles may differ between aromatase inhibitors, although comprehensive comparative data for letrozole and exemestane versus tamoxifen are lacking.

Until recently, 5 years of tamoxifen treatment was the standard initial adjuvant endocrine treatment for early-stage breast cancer (1). However, despite the clear benefits of adjuvant tamoxifen therapy, many patients still develop recurrent disease. In addition, tamoxifen is associated with some serious adverse effects, including an increased incidence of thromboembolic and cerebrovascular events and of endometrial cancer (2–5). Data from recent and ongoing trials of third-generation aromatase inhibitors as adjuvant therapy for postmenopausal women have challenged the position of tamoxifen by showing superior efficacy in terms of reduction of recurrence rate and a different and probably better safety profile when starting with, or switching to, an aromatase inhibitor. In some of these trials, an aromatase inhibitor has been used as initial therapy (6); in others, a switch was made to an aromatase inhibitor after several years of tamoxifen treatment (7–12).

The American Society of Clinical Oncology Technology Assessment Panel recently recommended that the optimal treatment for hormone-sensitive early breast cancer in postmenopausal women should include an aromatase inhibitor (13). Subsequently, further data relating to the long-term efficacy and adverse-effect profile of anastrozole (Arimidex) have emerged, with follow-up now extending beyond the planned 5 years of adjuvant treatment. Here, we review the efficacy, safety, and tolerability of anastrozole versus tamoxifen, and also discuss the relative safety of the third-generation aromatase inhibitors anastrozole, letrozole, and exemestane. We also use data from trials of these compounds to model the likely effect in the treatment population of using an aromatase inhibitor as initial adjuvant therapy versus switching to an aromatase inhibitor after initial use of tamoxifen for ≥2 years.

Materials and Methods: Arimidex, Tamoxifen, Alone or in Combination Trial

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, a randomized, double-blind study, was designed to compare the efficacy and safety of tamoxifen with anastrozole alone and in combination with tamoxifen, as initial adjuvant therapy in postmenopausal women with early breast cancer. The combination arm was discontinued following the first analysis (median follow-up 33 months) because it showed no benefit compared with tamoxifen alone in terms of either efficacy or tolerability (14); therefore, the data reported here refer only to the monotherapy arms.

All analyses were based on the intent-to-treat population or the hormone receptor-positive population (84% of the intent-to-treat population) and all P values were two sided. Analyses
for predefined adverse effects were carried out using methodology previously described (14) and were based on treatment first received (safety population). In addition, exploratory analyses of additional adverse events were carried out for the safety population. Events were categorized according to Coding Symbols for thesaurus of adverse reaction terms (15). Investigators indicated whether or not any adverse event was considered drug related.

**Modeling initial adjuvant treatment with an aromatase inhibitor versus tamoxifen.** Hazard ratios (HR) for recurrence based on treatment type and hormone receptor status were derived from published data and are shown in Table 1 (6-12, 16). Recurrence rates were extrapolated to the 10 years follow-up point for a range of efficacy variables (16). A "surface model" was developed that used only observed HRs, baseline data on tamoxifen from ATAC (12) and the Oxford overview (1), and made no mechanistic assumptions. The main end point was time lost to recurrence, which is a cumulative measure of the area under the time-to-recurrence curve, and weighs early recurrences more heavily than later ones.

**Results: ATAC trial**

**Study population**

Recruitment took place between July 1996 and March 2000. Of the 9,366 patients in the study, 6,241 were randomized between the two monotherapy arms (intent-to-treat population). Patient characteristics were well balanced across treatment groups. The mean age at entry was 64 years; 61% of patients were known to be lymph node negative, 84% were hormone receptor positive, and 64% had a tumor ≤2 cm in maximum diameter (14). At the time of data cutoff, median follow-up was 68 months and only 8% of patients remained on trial therapy, each with <1 year of scheduled treatment remaining.

**Efficacy**

Data for all primary efficacy measures in intent-to-treat and hormone receptor- positive patients are summarized in Fig. 1. Disease-free survival was significantly greater in the anastrozole group compared with the tamoxifen group in the intent-to-treat population [HR, 0.87; 95% confidence intervals (95% CI), 0.78-0.97; \(P = 0.01\)] and in the hormone receptor–positive population (HR, 0.83; 95% CI, 0.73-0.94; \(P = 0.005\)), with a 17% lesser risk of recurrence and an absolute difference of 3.3% between treatment arms in hormone receptor–positive patients at a median follow-up of 68 months.

Time to recurrence was significantly improved with anastrozole compared with tamoxifen in both the intent-to-treat population (HR, 0.79; 95% CI, 0.70-0.90; \(P = 0.0005\)) and the hormone receptor–positive population (HR, 0.74; 95% CI, 0.64-0.87; \(P = 0.0002\); ref. 12). In patients known to be hormone receptor positive, the absolute difference in recurrence rates diverged between the anastrozole group and the tamoxifen group, from 1.7% at 2 years to 3.7% at 6 years (i.e., continuing to diverge after treatment discontinuation; Fig. 1A). This carry-over effect beyond treatment cessation seems greater in the anastrozole group than in the tamoxifen group and was greater in the hormone receptor–positive population.

As shown by annual hazard rates (Fig. 1B), the benefits with anastrozole were seen throughout the follow-up period. In terms of the benefit conferred by anastrozole in reducing risk of recurrence at 5 years, this amounts to an additional reduction of 26% on top of that conferred by tamoxifen (1). Time to distant recurrence was also greater in the anastrozole group; this was marginally significant in the intent-to-treat population (HR, 0.86; 95% CI, 0.74-0.99; \(P = 0.04\)) and not significant in the hormone receptor–positive population (HR, 0.84; 95% CI, 0.70-1.00; \(P = 0.06\)). In the hormone receptor–positive population, there was a 53% reduction in all contralateral breast cancers in the anastrozole group (n = 21.80%) compared with the tamoxifen group (n = 48.1.85%; HR, 0.47; 95% CI, 0.29-0.75; \(P = 0.001\)); a similar 57% reduction in invasive contralateral breast cancer was seen. Although there was no material difference for overall survival (\(P = 0.7\) in both the intent-to-treat and hormone receptor–positive populations; HR, 0.97; 95% CI, 0.85-1.12 and HR, 0.97; 95% CI, 0.83-1.14, respectively), there was a nonsignificant trend in favor of anastrozole for time to breast cancer death (\(P = 0.2\) in both the intent-to-treat and hormone receptor–positive populations; HR, 0.88; 95% CI, 0.74-1.05 and HR, 0.87; 95% CI, 0.70-1.09, respectively).

**Subgroup analyses**

A benefit for anastrozole compared with tamoxifen with respect to time to recurrence was apparent for all subgroups examined in the intent-to-treat population (Fig. 2A). There was no significant interaction at the 1% level for any predefined baseline prognostic factor, although an apparent significant difference has been seen based on progesterone receptor (PR) status (17). A retrospective, unplanned, hypothesis-generating analysis showed that among hormone receptor–positive patients, the advantage of anastrozole in reducing the risk of recurrence was more heavily than later ones.

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**Table 1. HRs for recurrence of breast cancer in the model used to compare initial use of an aromatase inhibitor with sequencing in hormone receptor–positive postmenopausal women (16)**

<table>
<thead>
<tr>
<th>Trial (AI)</th>
<th>HR</th>
<th>ER+/PR+</th>
<th>ER+/PR-</th>
<th>All ER+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial AI vs tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC (anastrozole)</td>
<td>0.84</td>
<td>0.43</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>BIG-198 (letrozole)</td>
<td>0.72*</td>
<td>0.72*</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Sequencing AI vs tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARNO 95/ABC SG 8 (anastrozole)</td>
<td>0.65</td>
<td>0.42</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>ITA (anastrozole)</td>
<td>—</td>
<td>—</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>IES ( exemestane)</td>
<td>0.72†</td>
<td>0.63†</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Extended AI vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-17 (letrozole)</td>
<td>—</td>
<td>—</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>ABC SG 6a</td>
<td>—</td>
<td>—</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IA, aromatase inhibitor; ITA, Italian Tamoxifen Arimidex trial; ARNO, Arimidex-Nolvadex; ABC SG, Austrian Breast and Colorectal Cancer Study Group.

*Approximate value based on similar disease-free survival.

†Approximate based on disease-free survival values of 0.66 versus 0.58 in an earlier analysis.
recurrence was more pronounced in the estrogen receptor–positive (ER+)/PR-negative (PR−) group (HR, 0.43; 95% CI, 0.31-0.61) than in the ER+/PR+ group (HR, 0.43; 95% CI, 0.69-1.02; Fig. 2B; ref. 17). In addition, the benefit of anastrozole was seen whether or not the patient had received prior chemotherapy and was independent of the type of chemotherapy given (18).

**Adverse events**

Adverse events judged by the investigator to be treatment related were significantly less common with anastrozole than with tamoxifen, as were treatment-related serious adverse events. Withdrawals due to adverse events were significantly less frequent for anastrozole than tamoxifen (Table 2). Treatment-related adverse events leading to death that occurred while receiving study treatment numbered 6 (0.2%) in the anastrozole group and 10 (0.3%) in the tamoxifen group (difference between groups not significant, \( P = 0.5 \)).

Predefined adverse events have been reported more fully elsewhere (12) and occurred with similar relative frequency to previous reports (14, 19). As expected, the absolute rates at trial maturity were higher as a result of longer follow-up. Important prespecified adverse events are listed in Table 3. The table includes the majority of important adverse event categories for which a statistically significant difference between treatments was found; these findings were consistent with those of the previous 47-month analysis (19) with no new safety concerns arising. Importantly, the incidence of endometrial cancer remained significantly lower in the anastrozole group (0.22% versus 0.76%; \( P = 0.02 \)). In addition, the incidences of all venous thromboembolic events, including superficial thrombophlebitis, continued to be significantly lower in the anastrozole group (2.8% versus 4.5%; \( P = 0.0004 \); Table 3).

Overall, fractures occurred more frequently in the anastrozole group than in the tamoxifen group (11% versus 7.7%; \( P < 0.0001 \); Table 3). Average annual fracture rates were 2.26% for anastrozole and 1.56% for tamoxifen (HR, 1.44; 95% CI, 1.21-1.68; \( P < 0.0001 \)), and the relative risk of fracture remained roughly constant over the treatment period, although rates seemed to converge after ~4.5 years. Relatively higher fracture
rates for anastrozole versus tamoxifen were seen in sites such as the foot (1.4% versus 0.5%), humerus/arm (1.1% versus 0.6%), and spine (1.5% versus 0.9%). However, the difference in number of fractures was less pronounced in the hip [37 (1.2%) for anastrozole versus 31 (1.0%) for tamoxifen].

There were significantly fewer cerebrovascular events with anastrozole than with tamoxifen (2.0% versus 2.8%; \(P = 0.03\); Table 3); these differences were most apparent in the first 18 months of treatment. There was no significant difference in the incidence of ischemic cardiovascular events (4.1% for anastrozole versus 3.4% for tamoxifen; \(P = 0.1\)). Angina was the most frequent [71 (2.3%) versus 51 (1.6%)] cardiovascular event and the incidence of myocardial infarction was similar in the two treatment groups [37 (1.2%) in anastrozole-treated patients versus 34 (1.1%) for tamoxifen].

The incidences of nausea and vomiting, fatigue, and mood disturbances were similar between the treatment arms. Anastrozole was associated with significantly lower incidences of hot flashes and vaginal discharge, whereas tamoxifen was associated with fewer joint symptoms (Table 3). In total, 831 deaths occurred among patients randomized to the monotherapy arms (411 in the anastrozole arm; 420 in the tamoxifen arm), of which 500 (60%) followed local or distant breast cancer recurrence. More deaths from cerebrovascular events were seen in the tamoxifen group than in the anastrozole group (22 versus 14; not significant), although cardiovascular
deaths occurred with similar frequency in both the tamoxifen and the anastrozole group (46 and 49, respectively).

**Reducing recurrence: rationale for the initial use of an aromatase inhibitor**

Analysis of the data from the ATAC trial for recurrence (censoring for prior non-breast cancer deaths) at 2.5 years (Fig. 1A) gives an HR of 0.78 (95% CI, 0.65-0.93) in favor of anastrozole ($P = 0.007$). This is reflected in annual hazard rates, where the benefits with anastrozole were seen throughout the follow-up period (Fig. 1B). Data from 1,226 first events in the completed treatment analysis of the ATAC trial, of which 651 occurred in the tamoxifen arm and 575 in the anastrozole arm (HR, 0.87; 95% CI, 0.78-0.97), show that the frequency at 2.5 years of recurrence, distant recurrence, and deaths following recurrence was greater for tamoxifen than anastrozole (Table 4). In addition, overall numbers of most predefined adverse events were greater for tamoxifen than anastrozole at the 2.5-year time point, as were treatment-related withdrawals, although joint disorders and fractures were more frequent with anastrozole than tamoxifen (Table 4).

**Modeling the initial use of an aromatase inhibitor versus switching from tamoxifen.** Data from two trials, ATAC and Breast International Group (BIG) 1-98, support the initial use of aromatase inhibitors rather than tamoxifen as adjuvant therapy. Long-term data from trials investigating switching between therapies after 2 to 3 years are also now beginning to emerge. The Austrian Breast and Colorectal Cancer Study Group 8 and the Arimidex-Nolvadex 95 trial and the Intergroup Exemestane Study (IES) have shown a benefit for switching

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**Table 2. Adverse events or serious adverse events on treatment or within 14 days of discontinuation in the ATAC trial**

<table>
<thead>
<tr>
<th>Event</th>
<th>Anastrozole (n = 3,092)</th>
<th>Tamoxifen (n = 3,094)</th>
<th>Relative risk* (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs</td>
<td>1,884 (60.9)</td>
<td>2,117 (68.4)</td>
<td>0.89 (0.86-0.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>146 (4.7)</td>
<td>277 (9.0)</td>
<td>0.53 (0.43-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>344 (11.1)</td>
<td>442 (14.3)</td>
<td>0.78 (0.68-0.89)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Treatment-related SAEs leading to death</td>
<td>6 (0.2)</td>
<td>10 (0.3)</td>
<td>0.60 (0.22-1.65)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse events; SAE, serious adverse events.

*Anastrozole versus tamoxifen.

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**Table 3. ATAC trial: Predefined adverse events (for which a significant difference was found between treatment groups) on treatment or within 14 days of discontinuation, with the exception of fractures of hip, spine, or wrist/Colles (combined), deep vein thromboembolic events, and endometrial cancer, which are recorded until recurrence, and hysterectomy details**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. patients (%)</th>
<th>Anastrozole (n = 3,092)</th>
<th>Tamoxifen (n = 3,094)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>1,104 (35.7)</td>
<td>1,264 (40.9)</td>
<td>0.89 (0.86-0.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>167 (5.4)</td>
<td>317 (10.2)</td>
<td>0.53 (0.43-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>109 (3.5)</td>
<td>408 (13.2)</td>
<td>0.78 (0.68-0.89)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Endometrial cancer*</td>
<td>5 (0.22)</td>
<td>17 (0.76)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Ischemic cerebrovascular events</td>
<td>62 (2.0)</td>
<td>88 (2.8)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>87 (2.8)</td>
<td>140 (4.5)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Joint symptoms</td>
<td>1,100 (35.6)</td>
<td>911 (29.4)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>340 (11)</td>
<td>237 (7.7)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>37 (1.2)</td>
<td>31 (1.0)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>45 (1.5)</td>
<td>27 (0.9)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Wrist/Colles</td>
<td>72 (2.3)</td>
<td>63 (2.0)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>All other sites†</td>
<td>220 (7.1)</td>
<td>142 (4.6)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>(1.3)</td>
<td>(5.1)</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; SAEs, serious adverse events.

*Anastrozole versus tamoxifen.

†Predefined adverse events were identified as those events that were significant in the predefined list of events identified a priori and were thought to be related to the treatment being evaluated. The predefined list of events was based on the types of events that were reported in clinical trials of tamoxifen and anastrozole and on the adverse events that were expected to be related to aromatase inhibition. The predefined adverse events were identified prior to unblinding of the study and before knowledge of the results of the study.

‡Patients with $>1$ fractures occurring at any time before recurrence (includes patients no longer receiving treatment).

§Patients may have had $>1$ fracture at different sites.

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*$n = 2,229$ for anastrozole and 2,236 for tamoxifen (excluding patients with hysterectomy at baseline), recorded at any time.

†Including thrombophlebitis.

‡In favor of tamoxifen.
postmenopausal women with hormone-sensitive early breast cancer to an aromatase inhibitor after 2 to 3 years of adjuvant tamoxifen, although data are only available for a median follow-up of 28 months for Austrian Breast and Colorectal Cancer Study Group 8/Arimidex-Nolvadex 95 and 37 months for the IES (8–10, 20). However, HRs between treatments are available from published data, including for extended adjuvant therapy (>5 years) versus placebo (6–12) and are shown in Table 1. These data have been used to model the likely effect in the treatment population of using an initial aromatase inhibitor versus switching to an aromatase inhibitor after initial use of tamoxifen (16). For these switching strategies, a change in the HR, according to the relevant published data, was introduced to the model at the time an aromatase inhibitor was introduced. Figure 3 shows the model for the percentage of years of life lost to recurrence in ER+ patients (5-year carry-over). At 10 years follow-up, 12.1% of years are lost when the adjuvant therapy regimen is 5 years of tamoxifen. This falls to 10.9% of years with 5 years of tamoxifen followed by 5 years of aromatase inhibitor. However, 2 years of tamoxifen plus 3 years of aromatase inhibitor is superior still, despite the total duration of endocrine treatment being only 5 years, with 9.6% of years lost. Aromatase inhibitor treatment for 5 years gives the best result, with 9.0% of years lost to recurrence. Moreover, the superiority of this regimen is seen at all time points up to 10 years (Fig. 3).

**Comparative toxicities of the available aromatase inhibitors**

Some differences in the adverse-effect profiles of the different aromatase inhibitors have been suggested by the available data. Relatively small differences between the properties of the aromatase inhibitors may translate, with long-term use in increasing numbers of patients, into significant clinical concerns. Therefore, it is important to consider the structural, pharmacologic, and pharmacokinetic differences between the aromatase inhibitors that may influence their androgenic adverse effect profiles, selectivity, potency in estrogen suppression, and lipid and bone effects. Although no long-term data are available that directly compare the adverse effects of the currently available agents (anastrozole, letrozole, and exemestane), there are data available from studies that compare these agents individually with tamoxifen or with placebo.

In the MA-17 trial, which compared 5 years of letrozole therapy with placebo in women who had already received 5 years of tamoxifen therapy, no significant differences in the incidence of cardiovascular events were seen (21, 22). Differences in cardiovascular and cerebrovascular adverse event rates in trials comparing an aromatase inhibitor with tamoxifen may be emerging, although much of the data are still immature. Data from the BIG 1-98 trial, a prospective, randomized, double-blind trial that is comparing letrozole with tamoxifen in 8,028 postmenopausal women in the adjuvant setting, are currently only available for a median follow-up of 25.8 months (6). No difference was seen between letrozole and tamoxifen in the incidence of cerebrovascular adverse events (Table 5), contrasting with ATAC, where the incidence of ischemic cerebrovascular events was significantly lower with anastrozole. In BIG 1-98, letrozole gave rise to a significantly higher incidence of grades 3 to 5 cardiac events than tamoxifen (Table 5). However, similar to anastrozole in ATAC, the number of thromboembolic events was significantly lower with letrozole compared with tamoxifen in BIG 1-98. The number of thromboembolic deaths in BIG 1-98, however, was the same for both letrozole and tamoxifen. In the patients treated with letrozole, compared with tamoxifen, 13 versus 6 cardiac deaths and 7 versus 1 cerebrovascular deaths occurred (Table 5). The majority of cardiac deaths with letrozole occurred while on study treatment. In both BIG 1-98 and ATAC, the bone fracture rate was significantly higher with the aromatase inhibitor compared with tamoxifen (Table 5), and the endometrial cancer rate was lower with the aromatase inhibitor, although the difference was not significant in the BIG 1-98 analysis.

The IES is a double-blind, randomized, study evaluating the efficacy of switching to exemestane after 2 to 3 years of tamoxifen in 4,742 postmenopausal women (9). The IES differs from ATAC and BIG 1-98 in that it is not comparing an aromatase inhibitor to tamoxifen in the primary adjuvant setting. Data are available from an interim analysis conducted...
at a median follow-up of 30.7 months and an updated analysis at 37.4 months of median follow-up (9, 10). At 37 months, the incidence of myocardial infarction was significantly greater in patients who switched to exemestane compared with those who continued on tamoxifen (20 versus 8 events, respectively; \( P = 0.02 \); Table 6); this result has not been observed for anastrozole in the ATAC trial. Thromboembolic events in IES were significantly lower with exemestane (9), in agreement with data reported for anastrozole and letrozole in ATAC and BIG 1-98, respectively. This suggests an increased association between tamoxifen use and thromboembolic events, which has been documented previously (1). In IES, the number of deaths due to cardiac or vascular causes was comparatively high with exemestane and there were also a comparable number of thromboembolic deaths with exemestane and tamoxifen (9).

In summary, although the respective safety profiles of the aromatase inhibitors share several features, some differences may exist, including potentially a higher incidence of cardiovascular events with letrozole and exemestane, and of ischemic cerebrovascular events with letrozole and exemestane, when compared indirectly with anastrozole. However, as noted above, in the MA-17 trial, there were no significant differences in the incidence of cardiovascular events in the letrozole and placebo groups.

**Differences in selectivity and potency between the aromatase inhibitors**

It is reasonable to assume that molecular differences between the aromatase inhibitors may affect their activity. For example, the nonsteroidal aromatase inhibitors anastrozole and letrozole have inhibitory effects on cytochrome P450 enzymes, including CYP1A2 and CYP2A6, respectively, whereas the steroidal aromatase inhibitor exemestane is metabolized by CYP3A4 (23). Therefore, concomitant use of aromatase inhibitors with other drugs that are metabolized by these CYP classes may lead to specific drug interactions that do not extend to the aromatase inhibitor class in general, and the different aromatase inhibitors

<table>
<thead>
<tr>
<th>Event</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Letrozole ((n = 3,975))</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>1.0</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1.5</td>
</tr>
<tr>
<td>Grades 3-5</td>
<td>0.8*</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4.1</td>
</tr>
<tr>
<td>Grades 3-5</td>
<td>2.1*</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>5.7</td>
</tr>
<tr>
<td>Bone fracture rate (per 100 patient-years)</td>
<td>2.2</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>3.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>43.5</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>33.5</td>
</tr>
<tr>
<td>Night sweats</td>
<td>13.9</td>
</tr>
<tr>
<td>Invasive endometrial cancer (excludes patients with hysterectomy at baseline)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Death on study</td>
<td>166</td>
</tr>
<tr>
<td>Death following cancer event</td>
<td>111</td>
</tr>
<tr>
<td>Death without prior cancer event</td>
<td>55</td>
</tr>
<tr>
<td>CVA</td>
<td>7</td>
</tr>
<tr>
<td>Venous thromboembolic</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac</td>
<td>13</td>
</tr>
<tr>
<td>Sudden death (cause unknown)</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack.
* \( P < 0.0005 \).
* Risk ratio, 1.42; \( P < 0.0006 \).
* Risk ratio, 0.40; \( P < 0.087 \).
cannot be assumed to be interchangeable. Structural differences between aromatase inhibitors may play a role in their specificity; for example, letrozole is similar to 11-β-hydroxysteroidase, which may cause letrozole to interfere with the adrenal steroidogenesis pathway (24, 25). Anastrozole is specific to aromatase and has no significant interactions with other enzymes. Pharmacokinetics of each drug account for the difference in reaching steady-state and plasma levels: Letrozole has a longer half-life and consequently takes almost eight times longer to reach steady-state at relatively higher plasma levels.

**Effects on estrogen and serum lipids.** Differential effects on estrogen plasma levels may be important in understanding the cardiovascular effects of the aromatase inhibitors. Studies have shown that changing levels of low-density lipoprotein and high-density lipoprotein cholesterol are important risk factors for cardiovascular disease (26). Lipid cholesterol levels are lowered by tamoxifen (27) and although initial indications of an effect on myocardial infarction (28–31) have not been borne out in most subsequent studies (32), indications are that lipid cholesterol levels are not affected in the same way by the different aromatase inhibitors. The effects of anastrozole, exemestane, and tamoxifen on serum lipids in postmenopausal women with breast cancer (30 patients per treatment group randomized to 3 months of adjuvant therapy) have been evaluated (33). It was found that tamoxifen was strongly associated with reduced total cholesterol (−14.8% change, \( P < 0.005 \)) and low-density lipoprotein cholesterol (−22.6% change, \( P = 0.001 \)). No significant effects for anastrozole or exemestane were seen. A similar result for anastrozole has been reported in another study with longer exposure periods of up to 2 to 3 years before switching from tamoxifen to anastrozole will result in some patients developing recurrences that could have been prevented by initial adjuvant treatment with anastrozole (12). Treatment with anastrozole showed superior disease-free survival, time to recurrence, and time to distant recurrence, as well as contralateral recurrence benefits, compared with tamoxifen. Without adjuvant treatment, the recurrence rate observed over 5 years is 26.5% in women with ER+ disease, a rate that is reduced to 15.1% with tamoxifen (1). The efficacy benefits shown in the ATAC trial for anastrozole are over and above the benefits seen with tamoxifen and lead to a further 3.3% absolute reduction in the risk of recurrence at 5 years for patients receiving anastrozole compared with those receiving tamoxifen.

The benefits with anastrozole were seen throughout the follow-up period and extended beyond the completion of treatment. In particular, the differences seen in year 6 were as large as those seen in the first 5 years on active treatment (Fig. 4). However, a particularly important benefit is seen during years 1 to 3, when the well-documented peak of recurrence, characteristic of tamoxifen, occurs (2). During the first 2.5 years of adjuvant treatment, patients treated with anastrozole experienced almost half the rate of first events of recurrence, and of deaths following recurrence, than patients treated with tamoxifen (Table 4; ref. 39). With respect to hazard rates by year, care must be taken not to over interpret minor fluctuations in the hazard curves. However, the main features are suppression by anastrozole of the early peak of recurrence observed with tamoxifen treatment and continued hazard reduction throughout the entire treatment period, which seems to extend beyond the end of treatment. Therefore, waiting for 2 to 3 years before switching from tamoxifen to anastrozole will result in some patients developing recurrences that could have been prevented by initial adjuvant treatment with anastrozole (16). Modeling of data for aromatase inhibitors versus tamoxifen in ER+ tumors shows that initial or early treatment occurred in only 3 of 20 data points: in high-density lipoprotein cholesterol at 6 months (\( P = 0.049 \)) in the placebo group and in low-density lipoprotein cholesterol at 12 months (\( P = 0.033 \)) and triglycerides at 24 months (\( P = 0.036 \)) in the letrozole group (36). Overall, results suggested that letrozole does not significantly alter serum cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, or lipoprotein (a) up to 36 months of treatment.

The effects on serum lipids may be due to selectivity differences between the aromatase inhibitors, leading to significant differences in their inhibitory effect on total body aromatization but important differences in their interaction with other metabolic pathways. Plasma estrogen levels have been compared in a randomized, crossover study in which postmenopausal women (\( n = 12 \)) with ER+ metastatic breast cancer received anastrozole 1 mg orally or letrozole 2.5 mg orally for 6 weeks (37, 38). On treatment, plasma estradiol fell to similar levels (from 17.2 to 2.6 pmol/L with anastrozole and to 2.1 pmol/L with letrozole; no significant difference). However, estrone and estrone sulfate levels were lowered to a greater extent with letrozole compared with anastrozole (\( P = 0.019 \) and \( P = 0.0037 \), respectively; ref. 38).

### Discussion

The 68-month follow-up analysis of the ATAC trial, in which almost all patients had completed treatment, provides the only long-term data comparing an aromatase inhibitor with tamoxifen as initial adjuvant endocrine treatment (12). Treatment with anastrozole showed superior disease-free survival, time to recurrence, and time to distant recurrence, as well as contralateral recurrence benefits, compared with tamoxifen. Without adjuvant treatment, the recurrence rate observed over 5 years is 26.5% in women with ER+ disease, a rate that is reduced to 15.1% with tamoxifen (1). The efficacy benefits shown in the ATAC trial for anastrozole are over and above the benefits seen with tamoxifen and lead to a further 3.3% absolute reduction in the risk of recurrence at 5 years for patients receiving anastrozole compared with those receiving tamoxifen.

**Table 6. Data from the ongoing IES study of adjuvant exemestane at a median follow-up of 37.4 months**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Percentage of patients</th>
<th>Exemestane</th>
<th>Tamoxifen</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td></td>
<td>8.3</td>
<td>6.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Anthralgia</td>
<td></td>
<td>19.8</td>
<td>13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td>2.4</td>
<td>1.5</td>
<td>0.0004</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td></td>
<td>1.9</td>
<td>3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gynecologic symptoms</td>
<td></td>
<td>14.3</td>
<td>17.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>5.3</td>
<td>3.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction (all)</td>
<td></td>
<td>0.9</td>
<td>0.4</td>
<td>0.023</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>22.5</td>
<td>20.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE: Data are from ref. (10).Abbreviation: NS, not significant.
with an aromatase inhibitor dominates a strategy of switching after ≥2 years of tamoxifen to an aromatase inhibitor for a period extending to at least 10 years. However, results from models depend on assumptions and end points and conclusions may therefore differ. The model of Burstein et al. (40) found that switching from tamoxifen to an aromatase inhibitor at 2.5 years yielded superior 10-year disease-free survival than treatment with either tamoxifen or aromatase inhibitor treatment alone, and a further analysis suggested that switching from tamoxifen to an aromatase inhibitor after 2 years seems superior for ER+/PR+ tumors, whereas 5-year treatment with an aromatase inhibitor may yield superior outcomes for ER+/PR− tumors (40). A further model is discussed by Hilsenbeck and Osborne (41) in this issue.

In terms of time to distant recurrence, there was a trend favoring anastrozole compared with tamoxifen in patients with hormone receptor–positive disease that was significant in the larger intent-to-treat population. Overall survival showed a nonsignificant trend for superiority with anastrozole, a benefit that was more apparent when non–breast cancer deaths were excluded. Large adjuvant studies in populations of patients with good prognoses take a substantial time for overall benefits to become apparent, although as time elapses to allow a fuller analysis of long-term efficacy measures, these data may reveal a more significant trend. Furthermore, anastrozole was superior to tamoxifen with regard to time to recurrence irrespective of baseline prognostic factors or whether or not patients had received prior chemotherapy (42). Retrospective evidence suggests that PR status may influence the effect of anastrozole on risk of recurrence; however, this remains to be confirmed prospectively (17).

In addition to the established efficacy benefits of anastrozole, a lower incidence of serious adverse events and significantly fewer withdrawals from treatment were also seen compared with tamoxifen. The major gains with anastrozole were fewer vasomotor and gynecologic symptoms (except for vaginal dryness, which was increased) and procedures, fewer endometrial cancers, and fewer thromboembolic and cerebrovascular events. No new safety concerns emerged with longer follow-up. However, bone fractures and joint symptoms were increased. The partial estrogen agonist activity of tamoxifen is associated with a protective effect on bone in postmenopausal women; in contrast, aromatase inhibitors reduce estrogen levels and lead to losses in bone density that increase the risk of fracture (43, 44). In the ATAC trial, the relative increase in fractures on anastrozole relative to tamoxifen remained constant over the 5-year treatment period, equating to a risk of 2.2 fractures per 100 patient-years, compared with 1.5 fractures per 100 patient-years with tamoxifen. In year 6, after completion of anastrozole treatment, the fracture rate on anastrozole fell to 1.0 per 100 patient-years. At the end of 6 years, the cumulative fracture rates for both anastrozole (11.0%) and tamoxifen (7.7%) are substantial enough to be of concern in this patient group comprising older women.

Differences in the adverse effect profiles of the aromatase inhibitors seem to be emerging from trial data, although some data are still immature so conclusions drawn at this stage are only tentative. The numbers of cerebrovascular events seen with letrozole in BIG 1-98 were similar to those in the tamoxifen arm (6). However, in ATAC, the rate of these events was significantly reduced by anastrozole compared with tamoxifen, suggesting that aromatase inhibitors may differ in their adverse effect profiles in this respect.

In BIG 1-98, letrozole was associated with an increased rate of cardiovascular deaths; however, in the MA-17 trial comparing letrozole with placebo, no significant difference in cardiac events was seen. It has been previously documented that tamoxifen has a cardioprotective effect (1, 45), which may go some way to explain the differences in findings from the BIG 1-98 and MA-17 trials. In ATAC, there was little difference in cardiovascular event rates between treatment groups, except for

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**Fig. 4.** Summary of efficacy endpoints in the ATAC trial: HRs (anastrozole/tamoxifen) and 95% CI, in the intent-to-treat (ITT) population and the hormone receptor–positive (HR+ve) population. Reprinted from ref (12). ©2005 with permission from Elsevier.
an increase in mild to moderate angina and hypertension with anastrozole and a lack of difference in serious cardiovascular adverse effects or deaths between anastrozole and tamoxifen.

The cholesterol-reducing properties of tamoxifen have been well characterized (46). Although lipid profiles were not systemically measured as part of the ATAC trial, results from other recent studies designed to specifically evaluate lipid levels in the adjuvant and neoadjuvant settings indicate that anastrozole is clinically lipid neutral (33, 34, 47–49). Data have shown little overall differences in lipid profile for letrozole versus placebo in a large trial (36), but data from comparative trials of letrozole and exemestane are not available. Lipid profile differences seen between the aromatase inhibitors may be due to the observed differences in plasma estrogen levels that result from exposure to different aromatase inhibitors (38). In BIG 1-98 (6, 12), this may have translated into the increased cardiovascular event and death rate seen for letrozole, although data are still too immature at this stage to draw definitive conclusions (9, 10). The mature data from the ATAC trial (12) indicate that cardiovascular adverse events do not pose a safety issue with anastrozole and thus this does not seem to be an aromatase inhibitor class effect.

Conclusions

In summary, a wide body of data are available supporting the aromatase inhibitors as adjuvant treatment (7, 10–12, 20). In the initial adjuvant setting, trials support the efficacy of both anastrozole and letrozole compared with tamoxifen. For anastrozole, trial data are more mature (68 months) compared with the shorter follow-up period (26 months) in the letrozole study. Anastrozole is also supported by good tolerability data and has gained regulatory approval for initial adjuvant use. In the adjuvant switching setting (i.e., after completion of 2 to 3 years of tamoxifen), the use of anastrozole or exemestane is supported by studies showing good efficacy and tolerability versus continued tamoxifen treatment (7, 10–12, 20). Letrozole has gained regulatory approval in the postadjuvant setting as a result of a trial showing good efficacy and tolerability versus placebo following completion of 5 years of tamoxifen. Exemestane has received approval from the U.S. Food and Drug Administration for the adjuvant treatment of postmenopausal women with ER+ early breast cancer who have received 2 to 3 years of tamoxifen and are switched to exemestane for completion of a total of 5 consecutive years of adjuvant hormonal therapy.

The American Society of Clinical Oncology Technology Assessment recommendations state that optimal treatment for postmenopausal women with early breast cancer should include the use of an aromatase inhibitor to reduce the risk of tumor recurrence (13, 50). Based on currently available data, anastrozole is effective and has a well-studied and acceptable safety profile in the setting of initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer.

Open Discussion

Dr. Carlos Arteaga: Dr. Ingle showed cardiac data with exemestane and letrozole. I take it those cardiac data don’t exist for anastrozole?

Dr. Buzdar: I showed you the 49 deaths due to cardiac events. Nonfatal cardiac events are not statistically significantly different between the two groups. They are slightly higher in the anastrozole arm.

Dr. Stephen Johnston: I think a lot of this cardiac difference is about cholesterol, and here the favorable cardiovascular effects of tamoxifen have to be borne in mind rather than any differences between aromatase inhibitors as to what the drug does to absolute cholesterol values.

Dr. Kathleen Pritchard: Yes, and the place to see that is in the MA-17 study, where there was a placebo control. There was virtually no difference in cardiac events.

Dr. Johnston: Given the absolute HRs of around a 40% improvement for the three trials examining a switch strategy, and up to a 50% improvement in risk reduction for extended adjuvant therapy, I’m more convinced for a switch strategy than an upfront strategy. I know the arguments are being mounted to say we save every recurrence with an upfront strategy, but the contrary argument is very potent on the basis of adverse events. I’m more in the camp represented by Kent Osborne, thinking that there may be a whole group of patients who do better by having tamoxifen and then switching.

Dr. Buzdar: I think that is an interesting question, but we have no data to support that, right?

Dr. Eric Winer: In the IES, there are more myocardial infarctions; in the BIG 1-98 trial, there is an almost statistically significant increase in non–breast cancer deaths; and in the ATAC trial, there is a numerical increase in non–breast cancer deaths. I don’t think that will be a huge issue for a woman with multiple positive lymph nodes, but as we put women with a T3N2 lesion who are older and at risk for an MI on aromatase inhibitors, I worry that the risk/benefit ratio may be different than what we expect.

Dr. Buzdar: We need to keep in mind that when you are following an aging population with a median age of 64 years, and you are looking at outcomes at 6 years, when they are almost close to 70 years old, if you are keeping them free of recurrence, you are not making them immortal. They are going to die from other competing causes.

Dr. Johnston: Tamoxifen may help by addressing non–breast cancer mortality.

Dr. Buzdar: The total years lost of life is far more if you recur early, compared with recurrence 5 or 10 years later in a smaller group of patients. Some of these models don’t take this into account, whereas it is included in the Cuzick model. It is a dramatic difference regarding when you start with what therapy.

Dr. Steven Come: That’s only cancer-specific loss of life. If there is increased loss from noncancer deaths linked to the therapies that would compensate, wouldn’t it?

Dr. James Ingle: If you look at ATAC, there are more adverse events in that first 2.5 years also, so you have decreased recurrences. What is important may vary between individuals. I think we have to have a way to communicate properly what the reality is, as best we know it. That is where Jack Cuzick’s person-years of life lost is valuable; you can say over time what the results of the different models are.

Dr. Mitch Dowsett: In ATAC, when you measure PR– and PR+, tamoxifen and the combination perform very similarly, which is what you’d expect. The point that Dr. Buzdar was also making is that if you look at the survival
curves for anastrozole, it is also better to be PR+ than PR−, but the curves are fairly similar. They are not actually overlapping, but they’re very much closer than with tamoxifen or the combination.

Dr. Buzdar: People have been saying that if the patient is ER+, PR+, the gains are not there with aromatase inhibitors. That is not true.

Dr. Dowsett: The P is 0.09. Jack Cuzick keeps telling me that it doesn’t matter, if you just keep cutting into smaller groups, your P is going to be less significant anyway, so you shouldn’t take too much notice of that P. But the other thing you have to see is how rapid the recurrence is in that PR− group if the patient is on tamoxifen.

Dr. Myles Brown: Maybe this is where you need to have a patient-oriented strategy that bases the decision on PR and other yet-to-be-determined predictive factors that would actually tell you which cases do better on which therapy. The PR− definitely have to get an aromatase inhibitor first, whereas the PR+ may be not much different.

Dr. Ingle: Yes, the debate is over what to do with the PR− cases.

Acknowledgments

We thank Dr. John H Bull (Complete Medical Communications) who provided medical writing support on behalf of AstraZeneca.

References


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Clin Cancer Res 2006;12(3 Suppl) February 1, 2006
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Anastrozole as an Adjuvant Endocrine Treatment for Postmenopausal Patients with Breast Cancer: Emerging Data

Aman U. Buzdar and Jack Cuzick


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