Recent advances in endocrine therapy for postmenopausal women with early breast cancer: implications for treatment and prevention

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Background: In the treatment of advanced breast cancer, third-generation aromatase inhibitors (AIs) have shown superior efficacy and tolerability compared with tamoxifen and megestrol acetate, the previous standard endocrine therapies in the first- and second-line settings, respectively. AIs are now being assessed in the adjuvant and prevention settings.

Design: Literature review (PubMed search).

Results: Tamoxifen is currently the only endocrine option available for adjuvant therapy and chemoprevention in postmenopausal women. However, results from the ATAC (‘Arimidex’, Tamoxifen, Alone or in Combination) trial have shown anastrozole to be more effective than tamoxifen as adjuvant therapy for postmenopausal women with hormone-responsive early breast cancer. Other third-generation AIs, including letrozole and exemestane, are also being investigated as adjuvant therapies. In the chemoprevention setting, tamoxifen is the only available endocrine option for women at high risk of breast cancer but, given that these are healthy subjects, is associated with an unacceptable rate of adverse events. Raloxifene is being further assessed in the STAR (Study of Tamoxifen and Raloxifene) trial, while anastrozole is being evaluated in the second IBIS-II (International Breast Intervention Study II).

Conclusions: AIs, in particular anastrozole, are set to change the way that early breast cancer is treated. Effective and better-tolerated endocrine alternatives for breast cancer prevention may become available in the future.

Key words: adjuvant, advanced breast cancer, aromatase inhibitor, endocrine, prevention

Introduction

Endocrine therapy is an important systemic treatment for all stages of hormone receptor-positive breast cancer and has seen significant advances since Beatson first made the link between the endocrine system and breast cancer more than 100 years ago [1]. In the past few decades, modern endocrine therapies, such as the orally administered selective estrogen receptor modulator (SERM) tamoxifen, have revolutionised early breast cancer therapy, offering a real improvement in terms of both disease-free (DFS) and overall survival. Treatment guidelines now call for the determination of estrogen and progesterone receptor status in all primary breast tumours, and endocrine therapies are only recommended for women with known hormone receptor-positive disease [2].

Unlike advanced disease, early breast cancer is potentially curable [3]. Treatment of early breast cancer may involve adjuvant therapy consisting of systemic endocrine therapy, chemotherapy or both, after initial surgery to remove the tumour to prevent or delay tumour recurrence. The ultimate goal of adjuvant endocrine therapy is to increase the chances of curing invasive early breast cancer, with as low a level of adverse side-effects as possible.

Historically, tamoxifen was the first successful hormonal treatment and became the ‘gold standard’ adjuvant endocrine therapy in postmenopausal women. It has been shown to be more effective than chemotherapy in women >50 years of age with hormone receptor-positive early breast cancer [4, 5], and these findings have prompted its investigation as a chemopreventive agent in women at risk of breast cancer [6]. Bearing in mind that this study had a short follow-up, tamoxifen was found to be associated with an almost 50% reduction in new tumours compared with placebo [6]. As a result, Nolvadex™ (tamoxifen citrate) was approved by the US Food and Drug Administration (FDA) in 1998 for reducing the incidence of...
breast cancer in women at high risk of developing the disease. However, despite its proven effectiveness, tamoxifen therapy is associated with a number of serious side-effects, including an increased risk of endometrial cancer and sarcoma, and thromboembolic disorders [5, 7–10], all of which are potentially life-threatening. This clearly limits its use both as adjuvant therapy (where it is usually recommended for up to 5 years) and, in particular, as a preventative therapy. This shortcoming has prompted the search for, and development of, new agents with equal or improved efficacy and fewer side-effects. This review presents the recent advances that have been made in endocrine therapy and their subsequent impact on treatment strategies.

**Search strategy and selection criteria**

Data for this review were identified by searches of PubMed, the Internet and references from relevant articles. Abstracts were included only when the relevant information had not been published in full elsewhere. Only papers published in English were included.

**Advanced breast cancer**

**Aromatase inhibitors**

Aromatase inhibitors (AIs) have had a major impact on the treatment of breast cancer. These agents were developed for the treatment of women in whom ovarian function has ceased (naturally due to the menopause or artificially, because of surgery or chemotherapy). They inhibit aromatase, a cytochrome P450 enzyme that catalyses the conversion of androgens to estrogens in ‘peripheral tissues’ such as body fat, liver, breast and muscle cells [11, 12], and in the breast tumour tissue itself [13, 14], thus reducing synthesis and output of estrogen in postmenopausal women. In premenopausal women, the ovaries are the primary sites of estrogen production and AIs are not able to block completely ovarian estrogen production. As a result, initial endocrine options for premenopausal women with advanced disease consist of tamoxifen, either alone or in combination with a luteinising hormone-releasing hormone agonist such as goserelin. If required, further endocrine therapy in the premenopausal setting may include surgical/radiological oophorectomy or megestrol acetate [2].

Aminoglutethimide, the first AI to be used to treat breast cancer [15], was an effective therapy that was used widely and successfully. However, its overall toxicity and lack of selectivity for the aromatase enzyme prevented it from being more generally adopted, and also meant that concurrent corticosteroid supplementation was necessary. Foremostane, a second-generation AI, has increased selectivity and fewer side-effects compared with aminoglutethimide or megestrol acetate [16, 17]; however, it is administered by injection every 2 weeks, possibly limiting patient acceptability. The third-generation AIs, which include the non-steroidal agents anastrozole (Arimidex) and letrozole, and the steroidal compound exemestane, are the most recent AIs to become available for use in postmenopausal women with metastatic hormone-responsive breast tumours. These drugs are administered orally and are highly selective for the aromatase enzyme. Results from clinical studies to date have indicated that anastrozole is highly selective for aromatase, having no effect on cortisol and aldosterone levels at up to 10 times the clinical dose when administered for up to 115 days [18], while a short-term study with exemestane (up to 800 mg) suggested that it has no effect on adrenal steroidogenesis [19]. In contrast, there is some evidence that treatment with letrozole (0.5–2.5 mg) for up to 84 days alters cortisol and aldosterone levels [20, 21].

In the second-line setting, anastrozole, letrozole and exemestane have all been shown to offer efficacy and tolerability advantages over megestrol acetate, the previous standard second-line endocrine therapy, in tamoxifen-resistant patients with hormone-dependent advanced breast cancer. In the combined analysis of two phase III trials, anastrozole (1 mg once daily) was associated with a significant survival advantage over megestrol acetate. It had a lower death rate (57.4% versus 67.6%; P<0.025) and a longer median time to death (26.7 versus 22.5 months) at a median follow-up of 31 months [22]. Patients in a phase III trial receiving exemestane experienced significantly longer survival compared with those receiving megestrol acetate (median survival with exemestane had not yet been reached, while median survival with megestrol acetate was 29 months; P=0.039) at a relatively short median follow-up of 11 months [23]. The final, mature result from this trial is not yet available in the current literature.

Conflicting results were obtained in two phase III trials comparing letrozole (0.5 mg once daily and 2.5 mg once daily) with megestrol acetate [24, 25]. In the European study [24], neither dose of letrozole showed a significant difference in terms of survival compared with megestrol acetate, but letrozole 2.5 mg showed significantly longer survival compared with letrozole 0.5 mg (P=0.03). By contrast, in the second study [25] there were no significant differences in survival between any of the three treatment groups. However, it should be borne in mind that survival analyses in clinical trials of patients with advanced disease require careful consideration, and may be problematical due to trial design factors and the need for sufficient statistical power. Overall, the letrozole studies emphasise that the superiority of the third-generation AIs over megestrol acetate is based not only on a simple efficacy advantage, but also on their favourable overall efficacy/tolerability profile.

Results of phase III studies (Figure 1) have demonstrated the superiority of both anastrozole and letrozole versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer. The efficacy of anastrozole versus tamoxifen was assessed in two phase III trials, one European [the TARGET (Tamoxifen and Arimidex Randomized Group Efficacy and Tolerability) trial] [26] and one North American [27]. These trials were similar in design and prospectively planned for combined analysis [28]. Anastrozole showed superior efficacy to tamoxifen in terms of time to progression...
(TTP) in patients with hormone receptor-positive tumours (North American study, \( P = 0.005 \); combined analysis, \( P = 0.022 \)) in addition to a number of tolerability benefits [27, 28]. A single phase III study has assessed the efficacy of letrozole in postmenopausal women with advanced breast cancer [29]. Letrozole also showed superiority to tamoxifen in terms of a number of end points, including TTP (\( P = 0.0001 \)) (Figure 1). This analysis was performed in the total (overall) population, where only 66% of patients had hormone receptor-positive tumours. However, when the treatment comparisons were adjusted for receptor status, TTP was not significantly affected. There are no phase III data available for exemestane versus tamoxifen, and it is not approved for first-line use. However, the results of a limited phase II trial were encouraging and preliminary data from a phase III trial indicated the beneficial activity and tolerability of exemestane compared with tamoxifen [30].

**Estrogen receptor antagonists**

A more recent addition to the armamentarium of endocrine therapies is the estrogen receptor antagonist fulvestrant, which competively binds to the estrogen receptor with a much greater affinity than tamoxifen [31], preventing estrogen receptor dimerisation, inhibiting estrogen receptor DNA binding and leading to down-regulation of estrogen-regulated genes [32]. The activity of fulvestrant has been established in phase I and II clinical trials that have demonstrated a lack of cross-resistance between fulvestrant and tamoxifen [33]. It has also been shown to be as effective as anastrozole in patients progressing on a prior anti-estrogen in two phase III trials [34, 35]. A prospective combined analysis of these two multicentre trials (\( n = 851 \)) has been performed. The initial combined efficacy analysis at 15.1 months median follow-up showed that fulvestrant was at least as effective as anastrozole in terms of TTP (5.5 versus 4.1 months, respectively; \( P = 0.48 \)). At a survival analysis at a later time point (median follow-up of 27.2 months), 74.5% and 76.1% of patients had died in the fulvestrant and anastrozole group, respectively. The median time to death (TTD) was 27.4 months (fulvestrant) and 27.7 months (anastrozole); statistical analysis confirmed that the two groups were not different in terms of TTD (\( P = 0.81 \)). Therefore, the combined TTD from these phase III trials show that fulvestrant is at least as effective as anastrozole in terms of overall survival, with a similar adverse event profile. Fulvestrant therefore appears to be an additional treatment option for hormone receptor-positive women with advanced breast cancer following prior anti-estrogen therapy [36].

As first-line therapy, fulvestrant has been shown to be of similar efficacy to tamoxifen in patients with hormone receptor-positive tumours [37], although which patient population is the most appropriate for its use in the first-line setting has yet to be determined. After a median follow-up of 14.5 months, there was no significant difference between the fulvestrant
(250 mg monthly intramuscular injection) and tamoxifen (20 mg once daily) groups in the hormone receptor-positive population for TTP, clinical benefit or objective response.

The efficacy of fulvestrant in the first- and second-line treatment of postmenopausal women with advanced disease leads to the important issue of the efficacy of further endocrine treatments after progression on fulvestrant. Ongoing studies are beginning to deliver promising results, with early data showing good efficacy of fulvestrant in patients with metastatic disease, with those patients receiving fulvestrant earlier in the treatment sequence achieving better responses [38].

**Adjuvant therapy**

Based on their proven efficacy and safety as first- and second-line therapies in the advanced disease setting, the third-generation AIs are currently being evaluated in the adjuvant setting. Several ongoing trials are investigating the use of third-generation AIs as adjuvant therapy for early breast cancer (Table 1) [39–41]. Of these trials, the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial is the only one to compare an AI versus tamoxifen as first-line adjuvant therapy. Other studies have involved treatment switches where patients are initially given tamoxifen and then switched to an AI, or have examined extending therapy beyond 5 years. The ATAC trial is the first of these trials to publish results for anastrozole and is the largest single cancer treatment trial reported to date [39].

**Table 1.** Design of ongoing adjuvant clinical trials involving aromatase inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>9366</td>
<td>Tamoxifen × 5 years&lt;br&gt; Anastrozole × 5 years&lt;br&gt; Tamoxifen+anastrozole × 5 years</td>
</tr>
<tr>
<td>BIG 01-98</td>
<td>8028</td>
<td>Tamoxifen × 5 years&lt;br&gt; Letrozole × 5 years&lt;br&gt; Tamoxifen × 2 years → letrozole × 3 years&lt;br&gt; Letrozole × 2 years → TAM × 3 years</td>
</tr>
<tr>
<td>NCIC MA.17</td>
<td>5187</td>
<td>Tamoxifen × 4.5–6 years → letrozole × 5 years versus placebo</td>
</tr>
<tr>
<td>NCIC MA.17R</td>
<td>1800</td>
<td>Letrozole × 5 year (MA.17) → letrozole × 5 years versus placebo</td>
</tr>
<tr>
<td>TEAM</td>
<td>4400</td>
<td>Tamoxifen × 5 years&lt;br&gt; Exemestane × 5 years</td>
</tr>
<tr>
<td>ABCSG 8</td>
<td>3500</td>
<td>Tamoxifen × 2 years → anastrozole versus tamoxifen × 3 years</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>3000</td>
<td>Tamoxifen × 57–66 months → exemestane × 2 years versus placebo</td>
</tr>
<tr>
<td>ABCSG 6</td>
<td>2021</td>
<td>Tamoxifen × 5 years&lt;br&gt; Tamoxifen × 5 years+ aminoglutethimide × 2 years</td>
</tr>
<tr>
<td>GABG IV-C ARNO-95</td>
<td>1059</td>
<td>Tamoxifen × 2 years → anastrozole versus tamoxifen × 3 years</td>
</tr>
</tbody>
</table>

Results have recently been published for the MA.17 extended adjuvant trial, assessing whether patients who have received 5 years of adjuvant tamoxifen therapy would benefit from receiving an additional 5-year period of letrozole [42]. Preliminary results have also been published for the ITA (Italian Tamoxifen Arimidex) adjuvant trial in which patients receiving 2–3 years of adjuvant tamoxifen are continued on tamoxifen or switched to anastrozole for the remainder of the 5-year period [43]. The results of ongoing clinical trials evaluating the efficacy and safety of adjuvant exemestane are expected to be reported over the next 1–3 years.

**The ATAC trial**

The ATAC trial is a randomised, double-blind, multicentre study in postmenopausal women (n = 9366) with invasive operable early breast cancer [39, 44]. Patients who had completed primary therapy and were eligible for adjuvant therapy received anastrozole alone (1 mg once daily), tamoxifen alone (20 mg once daily) or a combination of the two. Primary end points were DFS (time to earliest local or distant recurrence, new primary breast cancer or death from any cause) and safety/tolerability.

Results from the first analysis (at a median follow-up for DFS of 33.3 months) showed anastrozole to be significantly more effective than tamoxifen. Anastrozole was associated with an improvement in DFS and time to a recurrence (TTR; defined similar to DFS, but censoring non-breast cancer-related deaths occurring prior to disease recurrence), and a reduced incidence of contralateral breast cancer. It also showed a number of important tolerability benefits [39]. The key benefits for anastrozole were as follows: DFS was significantly longer in patients receiving anastrozole alone compared with those receiving tamoxifen alone [hazard ratio (HR) 0.83; 95% confidence interval (CI) 0.71–0.96; P = 0.013] or the combination (P = 0.006); anastrozole was also superior to tamoxifen for TTR (HR 0.79; 95% CI 0.67–0.94; P = 0.008) and significantly reduced the odds of contralateral breast cancer by 58% [odds ratio (OR) 0.42; 95% CI 0.22–0.79; P = 0.007] compared with tamoxifen.

An efficacy update was carried out after a median follow-up of 47 months [44]. This confirmed that the benefit seen with DFS in the anastrozole-treated group was sustained in the overall population, and was accentuated in the known hormone receptor-positive population (Table 2). The number of first events (mostly relapses) was 413 and 472 for anastrozole (n = 3125) and tamoxifen (n = 3116), respectively. DFS estimates at 4 years were 86.9% and 84.5% for anastrozole and tamoxifen, respectively. The absolute difference increased from 1.5% at year 3 in the first analysis to 2.4% at year 4 in the updated analysis for the overall population, and increased further in the hormone receptor-positive subgroup from 1.7% (year 3) to 2.9% (year 4) (89% versus 86.1% for anastrozole and tamoxifen, respectively) [44]. TTR was also significantly longer for the anastrozole group versus the tamoxifen group in the overall population, with a larger benefit seen in the hormone receptor-positive population (Table 2). The overlap of
HRs for DFS and TTR for the first and updated efficacy analyses confirm the robustness and consistency of these 2 sets of results. The number of deaths without recurrence was 109 in both the anastrozole- and tamoxifen-treated groups. A reduction in contralateral breast cancer continued to be seen with anastrozole (OR 0.62; 95% CI 0.38–1.02; P = 0.062), which was significant in the hormone receptor-positive group (OR 0.56; 95% CI 0.32–0.98; P = 0.042) [44]. There were 25 and 40 contralateral breast cancer events for anastrozole versus tamoxifen, respectively.

At the first analysis, anastrozole was associated with a significantly lower incidence of a number of important side-effects (Table 2), including hot flushes (P < 0.0001), vaginal discharge (P < 0.0001), vaginal bleeding (P < 0.0001), endometrial cancer (P = 0.02), cerebrovascular events (P = 0.0006) and thromboembolic events (P = 0.0006), including deep venous thromboses (P = 0.02). However, tamoxifen was associated with significantly fewer musculoskeletal disorders (P < 0.0001) and fractures (P < 0.0001) than anastrozole [39]. Furthermore, anastrozole was associated with significantly fewer withdrawals from treatment than tamoxifen (21.9% versus 26.0%, respectively; P = 0.0002), with fewer withdrawals due to drug-related adverse events (5.1% versus 7.2%, respectively).

An updated safety analysis was performed 7 months after the first analysis (median duration of therapy 36.9 months), in line with normal US FDA regulatory requirements [44]. Results for adverse events were consistent between the first analysis and the 7-month update (Table 3). The incidence of fractures was assessed every 6 months up to 48 months of treatment, while updated bone density data are available after 24 months of treatment [45, 46]. Anastrozole was associated with a modest loss in bone mineral density, but the risk of fractures associated with anastrozole did not increase from the first analysis to the updated analysis. At the first analysis, fracture incidence was 5.9% and 3.7% for anastrozole and tamoxifen, respectively (relative risk for anastrozole versus tamoxifen, 1.59); at the safety update the relative risk was very similar (1.60; P < 0.0001; fracture incidence 7.1% versus 4.4%, respectively). Fracture rates per 100 patients for each 6-month period, calculated from the proportion of patients with a first fracture, remained relatively stable for both anastrozole (range 0.93–1.57) and tamoxifen (range 0.58–1.37). Importantly, after an initial increase, fracture rates in the anastrozole group did not appear to increase over time with further treatment [46]. Anastrozole was still associated with fewer withdrawals overall (24.1% and 28.3% for anastrozole and tamoxifen, respectively), and less withdrawals due to drug-related adverse events (5.6% versus 8.1%, respectively) [44]. The anastrozole/tamoxifen combination was not significantly different from tamoxifen alone for all efficacy or tolerability end points. Because of these findings, the combination arm of the trial was discontinued after the first analysis.

### Switching adjuvant endocrine treatment trials

The preliminary results of the ITA trial, in which patients receiving 2–3 years of tamoxifen treatment were then randomised to tamoxifen or switched to anastrozole for a 5-year adjuvant treatment period, were recently presented by Boccardo et al. [43] at the San Antonio Breast Cancer Symposium, 2003. A total of 426 patients were enrolled in the study, of which 218 were randomised to continue on tamoxifen and 208 patients were switched to anastrozole. All patients were node- and estrogen receptor-positive. After a median follow-up of 24 months, switching to anastrozole appeared to decrease the risk of relapse (HR 0.36; 95% CI 0.17–0.75; P = 0.006) compared with remaining on tamoxifen, and was associated with fewer serious adverse events (14 versus 29) [43]. In terms of a lower risk of disease recurrence and fewer serious adverse events, these preliminary results suggest that patients can receive the benefits of anastrozole when already part way through their adjuvant tamoxifen treatment. Similarly, in the IES (Intergroup Exemestane Study), switching to exemestane after 2–3 years of tamoxifen therapy has been shown to be beneficial compared with continuing with tamoxifen therapy. Switching to exemestane was associated with a 32% reduction in risk of a first event, corresponding to an absolute benefit in DFS of 4.7% (range 2.6–6.8) [47].

### Extending adjuvant endocrine treatment trials

The results of the MA.17 trial have recently been published [42]. Unlike the ATAC trial, the double-blind, placebo-controlled MA.17 trial was designed to evaluate whether postmenopausal women with hormone receptor-positive early breast cancer who had already completed 5 years of adjuvant treatment with tamoxifen can benefit from receiving additional treatment with letrozole for a further 5 years.

A total of 5187 patients were enrolled with a median follow-up of 2.4 years. At the first analysis there was a significant difference in DFS (P < 0.001), with 75 recurrences or new primary contralateral breast cancers in the letrozole group (n = 2575) compared with 132 in the placebo group (n = 2582). The estimated 4-year DFS rates were significantly higher for letrozole (93% and 87% for letrozole and placebo, respectively; P ≤ 0.001). On the basis of these results the data and safety monitoring committee recommended that the trial should be terminated early and the results of this interim analysis be published. Updated results were recently presented at ASCO 2004, indicating that letrozole was associated with

### Table 2. Efficacy end points at the updated efficacy analysis of the ATAC trial [44]

<table>
<thead>
<tr>
<th>Efficacy end points</th>
<th>Hazard ratio (A/T)</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (overall population)</td>
<td>0.86</td>
<td>0.76–0.99</td>
<td>0.030</td>
</tr>
<tr>
<td>DFS (HR+)</td>
<td>0.82</td>
<td>0.70–0.96</td>
<td>0.014</td>
</tr>
<tr>
<td>TTR (overall population)</td>
<td>0.83</td>
<td>0.71–0.96</td>
<td>0.015</td>
</tr>
<tr>
<td>TTR (HR+)</td>
<td>0.78</td>
<td>0.65–0.93</td>
<td>0.007</td>
</tr>
</tbody>
</table>

A, anastrozole; T, tamoxifen; DFS, disease-free survival; TTR, time to a recurrence; HR+, hormone receptor-positive.
a 43% reduction in risk, producing an absolute improvement in 3-year DFS of 3% and 7% in patients with node-negative and node-positive disease, respectively [48]. Although the results of this study demonstrate a clear therapeutic effect of letrozole therapy after tamoxifen therapy, only 20 patients would have been eligible for analysis at 4 years, and therefore the data are not as robust as those obtained from the ATAC trial [42].

Owing to the early discontinuation of the trial, the study did not achieve its main aim of determining DFS and overall survival in women switching from tamoxifen to letrozole or placebo for 5 years, thus weakening the overall clinical usefulness of the data. Since no statistically significant survival benefit was observed, the optimal duration of letrozole therapy in this context remains undefined and, at present, it is not possible to recommend 5 years of letrozole as standard treatment post-tamoxifen.

**Impact on current treatment strategies**

Over the past 5 years, results from several large-scale major clinical trials have influenced the sequence in which hormonal therapies are used to treat advanced breast cancer.

As previously mentioned, while other AIs have shown activity, anastrozole is currently the only form of primary or initial endocrine therapy, other than tamoxifen, that has been shown to be an effective adjuvant therapy for postmenopausal women with early breast cancer [39, 44]. Since results from the first and updated analyses of the ATAC trial indicate that anastrozole is more effective than tamoxifen as adjuvant therapy, with a number of important tolerability benefits, it may ultimately become the preferred choice for early-stage breast cancer. In this circumstance, patients in whom treatment with adjuvant anastrozole is successful, but who recur, are unlikely to respond to other non-steroidal AIs such as letrozole. Alternative treatments for advanced breast cancer need to be determined. Only very limited data are available investigating the optimal sequence of therapies following recurrence on adjuvant anastrozole [49]. Treatment decisions must therefore be based on limited data in the advanced disease setting and on sound theoretical arguments. In addition, treatment choices will have to consider the impact of molecular factors that may influence tumour response to endocrine therapy. These factors include members of the epidermal growth factor receptor family, such as human epidermal growth factor receptor 2 (HER2), the expression of which may influence the response of tumours to endocrine therapies, including AIs [50, 51].

Fulvestrant, exemestane or tamoxifen may be valid treatment options for postmenopausal women who have progressed on anastrozole. In advanced breast cancer, tamoxifen has been shown to be as effective second-line after anastrozole [52]. Indeed, this study demonstrated prolonged time to second progression in patients treated with anastrozole then tamoxifen compared with those treated with tamoxifen then anastrozole. Exemestane, a steroidal AI, has also been shown to be effective in patients progressing on a non-steroidal AI, indicating incomplete cross-resistance between these treatment options [53]. As mentioned earlier, limited sequencing data from all the phase III trials investigating fulvestrant as first- and second-line therapy indicate that following progression on fulvestrant, responses to other endocrine therapies, including AIs and tamoxifen, are sometimes observed [38, 54]. In addition, there are preliminary data showing that fulvestrant produces clinical benefit following progression on a non-steroidal AI [55]. In theory, the low-estrogen environment resulting from treatment with anastrozole may result in an up-regulation of estrogen receptors. In this situation, the partial agonist action of tamoxifen may predominate; an estrogen receptor antagonist with no agonist activity, such as fulvestrant, may therefore be a more effective option in patients recurring on or after adjuvant anastrozole.

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**Table 3. Incidence of predefined adverse events at the first and updated analyses of the ATAC trial for which there were significant differences between anastrozole and tamoxifen at the first analysis [39, 44]**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>At first analysis [n (%)]</th>
<th>At updated analysis [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (n = 3092)</td>
<td>T (n = 3094)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Endometrial cancerb</td>
<td>3 (0.1)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>138 (4.5)</td>
<td>253 (8.2)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>86 (2.8)</td>
<td>354 (11.4)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>31 (1.0)</td>
<td>65 (2.1)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>64 (2.1)</td>
<td>109 (3.5)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>1060 (34.3)</td>
<td>1229 (39.7)</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>860 (27.8)</td>
<td>660 (21.3)</td>
</tr>
<tr>
<td>Fractures</td>
<td>183 (5.9)</td>
<td>115 (3.7)</td>
</tr>
</tbody>
</table>

*Relative risk (RR): <1 favours anastrozole, RR >1 favours tamoxifen.
Excluding patients with hysterectomy.
A, anastrozole; T, tamoxifen.
Chemoprevention

Tamoxifen

The efficacy of tamoxifen as a preventative therapy for women at high risk of developing breast cancer has been assessed in several studies. Indicators of women at high risk of invasive carcinoma include a previous diagnosis of in situ (non-invasive) tumour(s) confined to the breast ducts (ductal carcinoma in situ, DCIS) or lobules (lobular carcinoma in situ). A recent NSABP (National Surgical Adjuvant Breast and bowel Project) trial, NSABP B-24, involving subjects with small, localised DCIS, demonstrated that tamoxifen after lumpectomy and radiation therapy decreases the rate of all subsequent breast cancer events, particularly invasive breast cancer, compared with placebo [56].

In the NSABP-P1 prevention trial [6], 5 years of treatment with tamoxifen was shown to reduce the risk of invasive breast cancer by 49% compared with placebo in women at high risk of developing invasive breast cancer (P < 0.00001). However, two other studies published in the same year, one based at the Royal Marsden Hospital, London, UK [57], and one based in Italy involving 5408 women [58] found that the frequency of breast cancer did not vary significantly between women on tamoxifen compared with placebo (34 cases in the tamoxifen group versus 36 in the placebo group; 19 cases in the tamoxifen group versus 22 cases in the placebo group, respectively) [57, 58]. These conflicting results may be due to differences within the population characteristics of these trials. However, all three trials and the results of an overview by the Early Breast Cancer Trialists’ Collaborative Group [4], jointly comprising approximately 22 000 women, showed an increase in the incidence of a number of adverse events with tamoxifen compared with placebo including endometrial cancer (OR 2.41) and thromboembolic events (OR 1.94).

In the most recent placebo-controlled tamoxifen breast cancer prevention trial, IBIS-I (International Breast Intervention Study I) [59], tamoxifen significantly reduced the incidence of breast cancer over 10 years; there were 69 cases in the tamoxifen group compared with 101 cases in the placebo group (risk reduction 32%; P = 0.013). In this study, the incidence of endometrial cancer was not significantly different with tamoxifen compared with placebo (11 versus five cases, respectively), while thromboembolic events were significantly increased (43 versus 17 cases, respectively; P = 0.001) in the tamoxifen group, particularly following surgery [59]. The number of deaths from all causes was also significantly higher in the tamoxifen group compared with the placebo group (25 versus 11, respectively; P = 0.028). These findings led the IBIS Study Chairman to recommend that women should no longer be given tamoxifen for the prevention of breast cancer and the UK Committee on Safety of Medicines to provide specific recommendations for initiating and discontinuing tamoxifen, and for the management of patients in the event of surgery or immobility, both of which increase the risk of venous thromboembolism [60].

While these trials have compared the effects of tamoxifen versus placebo, the recently published trial by the UK Coordinating Committee on Cancer Research (UKCCCR) Ductal Carcinoma In S itu Working Party used radiotherapy as an active comparison [61]. In this study of 1701 patients with completely excised DCIS (median follow-up of 52.6 months), tamoxifen was not found to reduce the incidence of ipsilateral invasive disease but did reduce the recurrence of overall DCIS. By contrast, radiotherapy significantly reduced the incidence of ipsilateral invasive disease (0.45; P = 0.01) and ipsilateral DCIS (0.36; P = 0.0004), but there was no apparent effect on the occurrence of contralateral disease. The authors concluded that whereas radiotherapy can be recommended for patients with DCIS treated by complete excision, there is little support for the use of tamoxifen in these women [61].

Another trial, STAR (Study of Tamoxifen and Raloxifene), also conducted by the NSABP, will involve postmenopausal women who are at least 35 years old and at increased risk from developing breast cancer [62]. This study will further determine whether raloxifene, which, like tamoxifen, is a SERM, effectively reduces the risk of developing breast cancer in women who have not had the disease, and whether the drug has benefits over tamoxifen, including fewer side-effects. Results will be available by 2005 [63].

Aromatase inhibitors

Anastrozole has shown improved efficacy and tolerability benefits in terms of endometrial cancer and thromboembolic events compared with tamoxifen as therapy for women with early breast cancer [39, 44], providing justification and optimism about its potential role in chemoprevention. In particular, the low incidence of contralateral breast cancer with anastrozole compared with tamoxifen provides a good rationale for its use in the prevention setting. Therefore, the IBIS-II trial has been designed to investigate whether the superiority of anastrozole over tamoxifen in the ATAC trial will translate into the prevention setting [64]. IBIS-II is a large, multicentre, randomised, double-blind, controlled study in postmenopausal women with DCIS or an increased risk of breast cancer. Normal women at increased risk of breast cancer will receive anastrozole (1 mg once daily) or placebo for 5 years, while subjects with proven, completely excised DCIS will receive anastrozole (1 mg once daily) or tamoxifen (20 mg once daily) for 5 years. This comparison is justified by the results of the NSABP B-24 trial [56], which showed that tamoxifen decreased the rate of subsequent breast cancer events after DCIS lumpectomy. The primary end point for this trial is incidence of breast cancer (including DCIS), and recruitment began in February 2003.

Evaluation of other AIs as adjuvant therapy will help to determine their potential for use as chemopreventive agents. There are no clinical chemoprevention data currently available for letrozole and exemestane. However, for exemestane, chemoprevention is in early development. One preclinical study has investigated the chemopreventive effect of 19 weeks of treatment with a combination of exemestane and raloxifene.
in rats with dimethylbenzanthracene-induced mammary tumours [65]. The authors reported that the combination of exemestane and raloxifene was more effective than either treatment alone in increasing tumour latency and reducing tumour incidence and multiplicity, suggesting a possible role in breast cancer chemoprevention in high-risk women.

Conclusions

The third-generation AIs have become established treatments for advanced breast cancer based on their excellent activities as first- and second-line therapies compared with the previous standard endocrine treatments in these settings, tamoxifen and megestrol acetate, and are now being evaluated in the adjuvant setting.

Anastrozole is the only third-generation AI for which data on adjuvant treatment of early breast cancer in postmenopausal women has been published to date. Initial and updated results from the ATAC trial confirm it to be more effective than tamoxifen for postmenopausal women with hormone-responsive tumours, with several tolerability benefits; these advantages are likely to be maintained in the long term. Since there are several differences between AIs in terms of pharmacokinetics and effects on lipid profiles, bone absorption and steroidogenesis [66], differences in safety profiles between AIs may become apparent following long-term dosing. For this reason, the ATAC data should not be extrapolated to other AIs [67]. Therefore, for the first time, anastrozole provides a valid choice of endocrine adjuvant therapy for early breast cancer. This may prompt a change in treatment sequencing, with anastrozole replacing tamoxifen as adjuvant therapy for early breast cancer.

For patients who have received 2–3 years of tamoxifen as their initial treatment, preliminary data indicate that it is beneficial to switch to anastrozole or exemestane [47]. However, these data are currently preliminary, and further follow-up and additional studies will be required to establish fully the activity and tolerability advantages of these AIs in this setting.

Tamoxifen currently remains the only available endocrine option for use in the chemoprevention setting, and has been shown to reduce the risk of invasive cancer in patients with DCIS. However, its efficacy in high-risk women is uncertain, as data are conflicting, with a high risk of adverse events in this otherwise healthy population [60]. Other endocrine therapies may provide alternative chemopreventive options to tamoxifen with fewer side-effects, and are being investigated in ongoing trials. One such candidate is anastrozole, which, based on the results of the ATAC trial, is associated with a significantly lower incidence of contralateral breast cancer and a number of tolerability benefits compared with tamoxifen.

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