Review

Advances in Aromatase Inhibition: Clinical Efficacy and Tolerability in the Treatment of Breast Cancer

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Introduction

The successful management of breast cancer remains a major challenge to surgeons and oncologists in the 21st century. Although the incidence of breast cancer varies throughout the world, the disease is universally perceived to be a major cause of morbidity and mortality in both pre- and postmenopausal women.

It has long been established that estrogen is the major hormone involved in the biology of breast cancer (1). Endocrine agents have therefore been designed to affect the supply of estrogens to the breast tumor, principally by blockade of estrogen activity at the receptor level or by inhibition of estrogen production (although the widely used antiestrogen, tamoxifen, is known to have additional modes of action, such as via production of the inhibitory growth factor transforming growth factor β (2, 3) and suppression of insulin-like growth factor 1 (4), a potent mitogen for breast cancer). Drug resistance, however, remains a significant problem in breast cancer treatment, and this has led to the development of a variety of endocrine agents to extend the treatment options for breast cancer patients with hormone-sensitive disease. The success of the approach to use different endocrine therapies sequentially is made evident by the fact that 25% of patients with advanced breast cancer who eventually progress after an initial response on primary treatment are known to respond to second-line therapy with another endocrine agent (5). In a recent study, ~40% of patients with advanced breast cancer failing after an initial response to tamoxifen gained clinical benefit (clinical benefit = CR2 + PR + SD ≥ 24 weeks) from the second-line use of a second endocrine therapy (6).

Over the past 30 years, the antiestrogen, tamoxifen, has been the most widely used endocrine drug for the management of all stages of breast cancer in women with estrogen-dependent tumors, irrespective of their age and menopausal status (7–9), and, until recently, it has maintained an unrivalled position as the standard first-line endocrine therapy for postmenopausal women with advanced breast cancer.

Aromatase inhibitors are endocrine agents which have a different mode of action against breast tumor in postmenopausal women from that of tamoxifen. The first clinically available aromatase inhibitor, aminoglutethimide, was introduced for the second-line treatment of advanced breast cancer in the late 1970s (10). But despite proven efficacy in this setting, its widespread use was limited by its overall toxicity and its lack of selectivity for the aromatase enzyme, which necessitated concomitant corticosteroid supplementation (11). This led to the search for novel, more effective, and less toxic aromatase inhibitors. As a result, several aromatase inhibitors with a high degree of selectivity for aromatase and improved tolerability have become clinically available for the treatment of postmenopausal women with advanced breast cancer: anastrozole (1 mg once daily); letrozole (2.5 mg once daily); and exemestane (25 mg once daily; Fig. 1; Refs. 12–22).

It is the aim of this review to evaluate the clinical efficacy and tolerability of these latest additions to this class of drugs in the management of advanced breast cancer in postmenopausal women and to discuss their potential for use in the adjuvant treatment of early disease.

Pharmacology of Aromatase Inhibitors

In postmenopausal women, ovarian estrogen production diminishes with age. In these women, estrogen concentrations are maintained primarily via aromatase, a cytochrome-p450 enzyme complex which acts at the final step in the estrogen-synthesis pathway and catalyzes the production of the estrogens, estrone and estradiol, by extraglandular conversion from the androgens, androstenedione, and testosterone, respectively (Fig. 2).

It is knowledge of this peripheral route of estrogen supply in postmenopausal women that has led to the development of the aromatase inhibitors. These drugs act by suppression of the supply of endogenous estrogens in fat, liver, and muscle cells and in breast tumor tissue itself. They can be divided into two classes: steroidal and nonsteroidal drugs (23). The steroidal class (type I) comprises primarily formestane and exemestane, and the nonsteroidal class (type II) comprises primarily the imide, aminoglutethimide; the imidazole, fadrozole; and the triazoles, anastrozole and letrozole. A third nonsteroidal triazole, vorozole, has recently been withdrawn from clinical development.

Method of Administration. The newer nonsteroidal drugs, anastrozole and letrozole, are well absorbed after oral administration, with long terminal half-lives, allowing for once-daily dosing (14–16). In contrast, the first steroidal drug to...
become clinically available, formestane (250 mg i.m. every 2 weeks), is subject to high first-pass metabolism when given p.o., and has a relatively short terminal half-life (~2 h), and consequently has to be administered by i.m. injection every 2 weeks (18, 24). Exemestane, the other steroidal drug, is p.o. bioavailable and has a terminal half-life of ~24 h during chronic treatment (21), allowing once-daily therapy at a dose of 25 mg of drug (25, 26).

**Mechanism of Action.** Steroidal and nonsteroidal aromatase inhibitors differ in their modes of interaction with, and their inactivation of, the aromatase enzyme. Steroidal inhibitors compete with the endogenous substrates, androstenedione and testosterone, for the active site of the enzyme, where they act as false substrates and are processed to intermediates that bind irreversibly to the active site, causing irreversible enzyme inhibition. Nonsteroidal inhibitors also compete with the endogenous substrates for access to the active site, where they then form a coordinate bond to the heme iron atom. Therefore, they effectively exclude both the natural substrate and oxygen from the enzyme. The coordinate bonding is strong but reversible, so that enzyme activity can recover if the inhibitor is removed; but inhibition is sustained whenever the inhibitor is present. Al-
though both classes of aromatase inhibitor lead to potent suppression of aromatase, the enzyme is capable of rapid regeneration, and so it is doubtful whether or not the type of inhibition (i.e., reversible or irreversible) is of any clinical relevance. There are currently no clinical data that compare the relative efficacy of each type of agent. Their different modes of action, however, allow for sequential use in patients with advanced breast cancer, as described later.

**Selectivity.** The degree of selectivity of an aromatase inhibitor for the aromatase enzyme has a bearing on both the ease of use and the tolerability profile of the drug. For instance, the lack of selectivity of the first-generation aromatase inhibitor for aromatase, aminoglutethimide, led to concomitant suppression of the important corticosteroids, aldosterone and cortisol. As a result, in clinical use, it became necessary to coadminister a corticosteroid, such as hydrocortisone, as replacement therapy (11). Although the second-generation aromatase inhibitor, fadrozole, was shown to be more potent and selective (23) than aminoglutethimide, it nevertheless demonstrated a lack of selectivity through its effect on 11-deoxycorticosterone and aldosterone concentrations as well as on sodium and potassium levels in animals (11, 27–30).

The third-generation aromatase inhibitor, anastrozole, has a high degree of selectivity for aromatase in clinical pharmacology studies, with no significant effects being observed on either cortisol or aldosterone secretion at up to 10 times the daily recommended dose after 28 days of exposure (31, 32) and also when given for up to 3 months (33). Letrozole showed a similar degree of enzyme selectivity after an exposure period of 28 days, (34, 35) although in a study evaluating the dosing of letrozole 0.5 mg over a period of 12 weeks, cortisol levels were reduced significantly at this dose after 2 months (36) while remaining within the limits of normality (37, 38). Additionally, a more recent study has shown significant reductions in adrenocorticotropin hormone-stimulated cortisol ($P = 0.015$) and aldosterone ($P = 0.04$) concentrations after a 3-month exposure to letrozole at the clinical dose of 2.5 mg daily (39).

Vorozole is also selective for the aromatase enzyme, as seen from studies of 2.5 and 5 mg doses once daily, which reported no effect on adrenal steroidogenesis (40, 41). However, in one study at the 5-mg daily dose, vorozole led to a reduction in cortisol, the clinical relevance of which was uncertain (42). The higher selectivity of anastrozole, letrozole, and vorozole for aromatase leads to improved tolerability, compared with earlier drugs of this class, through an overall lack of adverse effect on steroidogenesis.

In the case of the steroidal aromatase inhibitors, both formestane (43–45) and exemestane (26, 46) are selective for aromatase and do not affect either cortisol or aldosterone concentrations adversely.

The available data on selectivity confirm that all of the aromatase inhibitors developed since aminoglutethimide first became clinically available are far more selective than the prototype compound. More recent data from indirect clinical pharmacology studies, however, do show variations between the different aromatase inhibitors. For anastrozole and letrozole, there seem to be differences in overall selectivity that, although not seen after short-term administration, do become apparent after longer-term exposure, *i.e.*, up to 3 months. The clinical relevance of such changes is not yet clear; however, although there may not be any clinical detriment in the metastatic setting, it would be important to monitor closely for the potential impact in the adjuvant setting, where these compounds are likely to be administered for up to 5 years, and where tolerability assumes greater importance in a patient who otherwise may be “cured” of disease.

**Estrogen Suppression and Aromatase Inhibition.** Both steroidal and nonsteroidal aromatase inhibitors result in a significant decrease in serum estrogen concentrations. Aminoglutethimide was the first nonsteroidal aromatase inhibitor to demonstrate a high level of aromatase inhibition, but this was not accompanied by a reduction in estrogen concentrations comparable with that now seen with the third-generation nonsteroidal aromatase inhibitors (23). An increase in potency was found with the second-generation drug, fadrozole (22), but, again in comparison, the newer-generation triazole drugs, anastrozole and letrozole, both produce a much greater suppression of estrogens, to the limits of detection of current assays, and have demonstrated a high degree of consistency between the inhibition of whole-body aromatase activity and estrogen suppression (16, 18, 23, 47).

Recent data have been reported from a small, double-blind, randomized, cross-over study in 12 postmenopausal women with advanced breast cancer, comparing plasma estrogen suppression by letrozole (2.5 mg daily) and anastrozole (1 mg daily; 48). This study showed that letrozole led to significantly greater suppression of $E_1$ ($P = 0.019$) and $E_2S$ ($P = 0.0037$), but not of $E_2$, which is widely considered to be the most important estrogen in the etiology of breast cancer. When inhibition of whole-body aromatase was examined (49), it was shown that letrozole (>99.1%) achieved a greater inhibition of aromatase than did anastrozole (mean, 96.9%). No statistical analyses of these data have been presented to date, and the clinical relevance of such differences between drugs of this class in their effect upon aromatase remains questionable.

The injectable steroidal aromatase inhibitor, formestane, also suppresses estrogen concentrations significantly, but to a lesser extent than anastrozole (50). Formestane is associated with inconsistent suppression of serum estradiol suppression by letrozole (2.5 mg daily) and anastrozole (1 mg daily; 48). This study showed that letrozole led to significantly greater suppression of $E_1$ ($P = 0.019$) and $E_2S$ ($P = 0.0037$), but not of $E_2$, which is widely considered to be the most important estrogen in the etiology of breast cancer. When inhibition of whole-body aromatase was examined (49), it was shown that letrozole (>99.1%) achieved a greater inhibition of aromatase than did anastrozole (mean, 96.9%). No statistical analyses of these data have been presented to date, and the clinical relevance of such differences between drugs of this class in their effect upon aromatase remains questionable.

The injectable steroidal aromatase inhibitor, formestane, also suppresses estrogen concentrations significantly, but to a lesser extent than anastrozole (50). Formestane is associated with inconsistent suppression of serum estradiol levels, whereby estradiol levels begin to rise between the twice-weekly i.m. doses. This was shown in a small, randomized, comparative study, in which formestane (250 mg i.m. every 2 weeks; $n = 31$) was compared with the nonsteroidal aromatase inhibitor, anastrozole (1 mg once daily; $n = 29$), over 4 weeks in postmenopausal women with advanced breast cancer (50). More effective, reliable and consistent estradiol suppression was found with anastrozole than with formestane at the usual therapeutic doses (79% versus 58% reduction in estradiol levels, respectively; $P = 0.0001$). Estrone and estrone sulfate levels were also significantly suppressed to a greater extent by anastrozole compared with formestane (estrone, 85% versus 67%, $P = 0.0043$; estrone sulfate, 92% versus 67%, $P = 0.0007$; respectively; Ref. 50).

Recently available results indicate that the oral steroidal aromatase inhibitor, exemestane, at daily doses of 10–25 mg, suppresses estrogen concentrations to 6–15% of pretreatment levels, showing more pronounced activity than formestane and comparable activity with that of the clinically available, nonsteroidal aromatase inhibitors, anastrozole and letrozole (52, 53).
In another report, exemestane exhibited potent aromatase inhibition \textit{in vivo} and suppressed plasma levels of estrogens to the limits of detection of current assays (25).

In conclusion, it appears that the most effective aromatase inhibitors can provide near maximal suppression of plasma estrogens, irrespective of their precise mode of inhibition of aromatase. It is clear that the newer-generation aromatase inhibitors, anastrozole, letrozole, and exemestane, provide greater suppression of estrogens than the earlier aromatase inhibitors, aminogluthimide, fadrozole, and formestane. The clinical data available for the newer aromatase inhibitors versus the previous standard therapies, megestrol acetate and tamoxifen (see below), indicate that step-changes in estrogen suppression are clinically important. However, the clinical relevance of the small differences in estrogen suppression between the newer aromatase inhibitors remains to be established. Ultimately, only direct head-to-head comparative clinical studies will provide the answers to these questions.

**Clinical Efficacy**

**Second- and Third-line Therapy in Advanced Breast Cancer with Nonsteroidal Aromatase Inhibitors**

\textbf{Anastrozole versus Megestrol Acetate.} In 1995, anastrozole was the first of the newer-generation aromatase inhibitors to become clinically available for second-line therapy in postmenopausal women with advanced breast cancer failing on an antiestrogen, usually tamoxifen. This came after the results of two large, Phase III studies, which were performed in parallel, comparing oral anastrozole (1 mg or 10 mg, once daily) with oral megestrol acetate (40 mg four times daily) in postmenopausal women with advanced breast cancer who had progressed on tamoxifen (54, 55). The designs of each trial [one conducted predominantly in Europe \((n = 378)\) and the other in North America \((n = 386)\)] were identical and prospectively intended to allow the data to be combined to strengthen the overall statistical reliability of the trial results (56). Each trial was a multicenter, randomized, controlled, parallel group, double-blind for each anastrozole arm and open-label for megestrol acetate. The primary objectives were to compare the three treatment groups in terms of TTP and OR (OR = CR + PR), and the secondary objectives were survival, time to TTF, and response duration. Rigorous criteria for assignment of objective response were applied on the basis of a strict interpretation of UICC guidelines (6, 57, 58).

At a median follow-up of \(~6\) months, a combined analysis of the above two trials showed that approximately one-third of patients who were treated with either anastrozole (1 mg or 10 mg, once daily) or megestrol acetate (160 mg daily) derived clinical benefit from their treatment (58). There were no statistically significant differences among the three treatment arms in terms of efficacy (tumor response or TTP) in either trial. The data were too immature for an analysis of survival to be performed at that time.

Intent-to-treat analyses were subsequently performed on the mature combined data from the two trials (62% of patients had died), when the median follow-up was 31.2 months (6). At the clinical dose of 1 mg daily, anastrozole demonstrated a statistically significant survival advantage over megestrol acetate, with a HR of 0.78 \((P < 0.025)\). The median duration of survival was 26.7 months for the anastrozole 1 mg group compared with 22.5 months for the megestrol acetate group. The HR indicated that patients treated with anastrozole 1 mg were 22% less likely to die over a given time period than patients treated with megestrol acetate. Patients receiving anastrozole 10 mg daily also showed a survival benefit compared with the patients receiving megestrol acetate, with an HR of 0.83 and a median duration of survival of 25.5 months \((P = 0.0951)\), but this difference was not statistically significant. The estimated 2-year survival rates from the combined analysis were 56.1%, 54.6%, and 46.3% for patients receiving anastrozole 1 mg, anastrozole 10 mg, or megestrol acetate, respectively. Clinical benefit was seen in \(~40\)% of patients in all three groups (42.3% with anastrozole 1 mg). The data from the individual and combined analyses of these trials are summarized in Table 1.

The authors concluded that the combined analysis clearly demonstrated that, after disease progression with tamoxifen, anastrozole 1 mg provides a statistically and clinically significant advantage over standard treatment with megestrol acetate. There was no additional benefit observed for anastrozole 10 mg over anastrozole 1 mg in terms of any of the primary end points. These results confirmed the choice of the 1 mg dose for use in clinical practice.

In an additional subgroup analysis of the above combined trial data, it was shown that anastrozole was effective in patients...
with advanced breast cancer with visceral and liver metastases (59). The median duration of clinical benefit in patients with visceral metastases was 16.4 months with anastrozole 1 mg (n = 263) compared with 14.7 months for megestrol acetate (n = 253); for liver metastases, the median duration of clinical benefit was 17.9 months with anastrozole 1 mg compared with 9.9 months for megestrol acetate. Furthermore, in a recent report, overall survival in patients with advanced breast cancer under assessment in one of the large-scale, comparative Phase III trials described above (58) was examined in relation to response type, overall survival in patients with advanced breast cancer under 253); for liver metastases, the median duration of clinical benefit 263) compared with 14.7 months for megestrol acetate (59). The median duration of clinical benefit in patients with advanced breast cancer with visceral and liver metastases (CR/PR or long SD. A similar result was obtained with patients previously treated with antiestrogens (65). Patients in the aminoglutethimide arm received daily oral glucocorticoid supplementation (hydrocortisone 30 mg or cortisone acetate 37.5 mg). The primary end point was overall objective tumor response (CR + PR). The secondary end points were TTP, TTF, and duration of survival.

**Vorozole: Open-Label, Phase III Trials.** In an open-label, multicenter, parallel-group Phase III trial, a total of 452 postmenopausal women with advanced breast cancer previously treated with antiestrogens (61, 63). Vorozole 2.5 mg was, however, statistically significantly superior to aminoglutethimide in terms of overall survival, TTP, and TTF in postmenopausal women with advanced breast cancer previously treated with antiestrogens.

**Letrozole versus Aminoglutethimide.** In an open-label, randomized trial, oral, once-daily letrozole (2.5 mg and 0.5 mg) was compared with aminoglutethimide (250 mg twice daily) in 555 postmenopausal women with advanced breast cancer previously treated with antiestrogens (65). Patients in the aminoglutethimide arm received daily oral glucocorticoid supplementation (hydrocortisone 30 mg or cortisone acetate 37.5 mg). The primary end point was overall objective tumor response (CR + PR). The secondary end points were TTP, TTF, and duration of survival.

Overall, no significant differences in OR were seen in patients receiving letrozole 2.5 mg or 0.5 mg or aminoglutethimide. The absence of a significant dose-response effect for the two letrozole doses (0.5 mg versus 2.5 mg) is in contrast to that found in the trial comparing the same two doses of letrozole (P = 0.03) with megestrol acetate in a similar patient population (61, 63). Letrozole 2.5 mg was, however, statistically significantly superior to aminoglutethimide in terms of overall survival, TTP, and TTF in postmenopausal women with advanced breast cancer previously treated with antiestrogens.

<table>
<thead>
<tr>
<th>Dose</th>
<th>European and US trials combined analysis</th>
<th>European trial a</th>
<th>US trial b</th>
<th>International trial c</th>
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<tbody>
<tr>
<td></td>
<td>A 1 mg o.d. (n = 263)</td>
<td>L 2.5 mg o.d. (n = 174)</td>
<td>L 2.5 mg o.d. (n = 189)</td>
<td>E 25 mg o.d. (n = 366)</td>
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<tr>
<td></td>
<td>MA 40 mg q.i.d. (n = 253)</td>
<td>MA 40 mg q.i.d.</td>
<td>MA 40 mg q.i.d.</td>
<td>MA 40 mg o.d. (n = 403)</td>
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<tr>
<td>Median follow-up (mo)</td>
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<td>33</td>
<td>NS</td>
<td>11</td>
</tr>
<tr>
<td>Median TTP (mo)</td>
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<td>5.6</td>
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<td>Median survival (mo)</td>
<td>26.7</td>
<td>25.3</td>
<td>21.5</td>
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a A, anastrozole; L, letrozole; E, exemestane; NS, nonsignificant; NR, not reported.

3 Internet address: http://fda.gov/ohrms/dockets/ac/backgnd/3671b_01.doc.
postmenopausal women with advanced breast cancer progressing on tamoxifen.

In a second open-label, centrally randomized, multicenter Phase III trial, postmenopausal women with advanced breast cancer failing on tamoxifen therapy were treated with either oral vorozole (2.5 mg once daily; n = 211) or aminoglutethimide (250 mg twice daily; n = 213) until disease progression or death (67). The patients in the aminoglutethimide arm also received supplementary oral hydrocortisone (30 mg daily). There was a higher overall response rate for patients receiving vorozole compared with aminoglutethimide (24% versus 17%; P = 0.07); but in terms of duration of response, TTP, TTF, and survival time, no differences were found between the two treatment arms. It was therefore concluded that vorozole and aminoglutethimide were equivalent with respect to clinical efficacy.

Although another open-label, comparative trial in postmenopausal patients with advanced breast cancer showed that vorozole (2.5 mg daily) appeared to be superior to aminoglutethimide (250 mg twice daily) plus hydrocortisone (30 mg once daily), in terms of response rate and clinical benefit (CR + PR + NC ≥ 6 months; P = 0.07 and P = 0.017, respectively; Ref. 68), none of the studies involving vorozole has shown a significant advantage over megestrol acetate or aminoglutethimide in terms of either TTP or overall survival. Vorozole is no longer in clinical development.

**Fadrozole versus Megestrol Acetate.** At present, fadrozole is only clinically available in Japan. Two prospective, randomized, double-blind Phase III trials of similar design were initiated to compare fadrozole with megestrol acetate in 683 postmenopausal women with advanced breast cancer, who had progressed on first-line or adjuvant hormonal therapy (69). The primary efficacy end point was OR. Other efficacy end points were TTP and survival.

In the first trial, 380 patients were randomized to receive either fadrozole (1 mg twice daily) or megestrol acetate (40 mg four times daily), and in the second trial, 303 patients also received a similar regimen. Both treatment arms in each of the two trials received matching placebos. There were no differences in the response rates from either trial between fadrozole and megestrol acetate. The median survival time was longer in the fadrozole group than in the megestrol acetate group in the first trial (26.8 versus 22.8 months, respectively) and in the megestrol acetate group compared with the fadrozole group (25.4 versus 27.5 months, respectively) in the second trial (69). Neither trial showed any significant differences between the two treatments in terms of primary and secondary end points, confirming equivalence of fadrozole and megestrol acetate as second-line endocrine therapy in postmenopausal women with advanced breast cancer.

**Second- and Third-Line Therapy in Advanced Breast Cancer with Steroidal Aromatase Inhibitors**

**Formestane versus Megestrol Acetate.** In a prospective, randomized, crossover Phase III trial, formestane (250 mg i.m. every 14 days) was compared with megestrol acetate (160 mg p.o. daily) in 179 postmenopausal patients with advanced breast cancer who were failing on tamoxifen (24). The trial was planned to test differences in TTF. There were no significant differences between formestane and megestrol acetate in response rates, SD (≥6 months), or TTF (3.9 versus 3.7 months, respectively), and formestane was considered to be as effective as megestrol acetate in this patient population. A second open trial of formestane (250 mg i.m. every 2 weeks) versus megestrol acetate (160 mg p.o. once daily) compared the efficacy and safety of the two drugs as second-line therapy in 547 receptor-positive or receptor-unknown postmenopausal patients with advanced breast cancer previously treated with tamoxifen (70). There were no significant differences between formestane and megestrol acetate in terms of median TTF and overall survival. Formestane was considered a suitable alternative to progestins in patients previously treated with tamoxifen.

**Exemestane versus Megestrol Acetate.** In a randomized, double-blind Phase III trial, 769 postmenopausal women with advanced breast cancer refractory to tamoxifen were randomized to receive either exemestane (25 mg p.o. daily; n = 366) or megestrol acetate (40 mg p.o. four times daily; n = 403; Ref. 71). The overall median duration of follow-up was 48.9 weeks. At the time of data cutoff, median survival had not been reached, and 143 patients were still receiving study medication. The study was designed to demonstrate equivalence between treatment arms. The OR rate was similar in both groups, as was the rate of overall success (CR + PR + SD ≥ 4 weeks; 37.4% for exemestane and 34.6% for megestrol acetate; not statistically significant). Both median TTP (P = 0.037) and median survival (P = 0.039), however, were significantly improved in those patients receiving exemestane (Table 2). It was concluded that, compared with megestrol acetate in postmenopausal women with advanced breast cancer refractory to tamoxifen, exemestane significantly delays tumor progression and significantly prolongs survival.

**Summary and General Conclusions.** Anastrozole, letrozole, and exemestane have all demonstrated improved clinical efficacy over megestrol acetate in the second-line treatment of postmenopausal women who have failed on tamoxifen. Although anastrozole and exemestane have both demonstrated significantly improved survival over megestrol acetate, there has been no statistically significant survival benefit reported with letrozole (63). All three aromatase inhibitors, anastrozole (1 mg, once daily), letrozole (2.5 mg, once daily) and exemestane (25 mg, once daily) have demonstrated clinical benefit in second-line use in postmenopausal with advanced breast cancer (6, 61, 71), and these newer-generation aromatase inhibitors are now established as the second-line agents of choice in this patient population.

**First-Line Therapy in Advanced Breast Cancer with Nonsteroidal Aromatase Inhibitors**

**Anastrozole.** In a major, large-scale, clinical trial program, anastrozole (1 mg once daily) was compared with tamoxifen (20 mg once daily) as first-line therapy in postmenopausal women with advanced breast cancer in two international, multicenter trials involving a total of 1021 patients (72, 73). The two trials were performed in the United States/Canada (“North American” trial) and in Europe/South America/Australia (“European” trial). They were randomized, double-blind, double-dummy trials designed to determine whether or not the two treatments had equivalent efficacy in this patient population. Patients had to be eligible for endocrine therapy and have either...
ER-positive and/or PgR-positive tumors or tumors of unknown receptor status. The patients were either newly diagnosed with advanced disease or had progressed subsequent to diagnosis and treatment for early disease. They may have received prior adjuvant endocrine therapy or chemotherapy; however, a drug-free period of at least 1 year was required for those who had received adjuvant tamoxifen.

The primary end points of the trials were TTP, OR, and tolerability. There were nine prespecified adverse events for which a statistical analysis was performed. The secondary end points were TTF and survival. The studies were designed prospectively to allow combined analysis of the data and were “powered” for equivalency.

In total, 353 patients from 97 centers in the United States and Canada were entered into the North American trial (anastrozole, n = 171; tamoxifen, n = 182) and followed for a median of 18 months (73). The two patient groups were well balanced with respect to demographic data, and a positive tumor ER status was confirmed in 89% of patients. Median TTP was 11.1 months for anastrozole versus 5.6 months for tamoxifen (P = 0.005; two-sided; Fig. 3).

On the basis of the derived HR of 1.44, at any given time point, patients receiving tamoxifen were 44% more likely to progress than those treated with anastrozole. OR was 21% for anastrozole and 17% for tamoxifen. Clinical benefit rates were 59% for anastrozole and 46% for tamoxifen (P = 0.0098; two-sided retrospective analysis). These data suggest that anastrozole is superior to tamoxifen as a first-line treatment of advanced breast cancer in postmenopausal women.

In the second trial (European), 668 postmenopausal women with advanced breast cancer (anastrozole, n = 340; tamoxifen, n = 328) from 83 centers worldwide were recruited and followed for a median of 19 months (72). The two patient groups were again well balanced with respect to demographic data, but a positive tumor ER status was only reported in 45% of patients. In this trial, median TTP was 8.2 and 8.3 months, and OR was 32.9 and 32.6% in the anastrozole and tamoxifen arms, respectively, confirming that anastrozole was at least as effective as tamoxifen in terms of the primary efficacy end points. Clinical benefit rates were 56.2% for anastrozole and 55.5% for tamoxifen.

This difference in the TTP results between the two trials has mainly been attributed to the percentage of patients with confirmed positive tumor ER. An exploratory subgroup analysis for the 45% of ER-positive patients in the European trial showed a median TTP of 8.9 months on anastrozole compared with 7.8 months on tamoxifen (Fig. 4; Ref. 72).

A prospectively planned combined analysis was performed on the efficacy and tolerability data from the total of 1021 patients recruited into the two trials (74). The data obtained in this large patient population indicate that anastrozole is at least as effective as tamoxifen for the treatment of postmenopausal women with advanced breast cancer, with an observed advantage in terms of TTP: median TTP was 8.5 months for anastrozole and 7 months for tamoxifen (HR = 1.12; lower 95% CI, 1.00; Table 3). A total of 57% of patients on anastrozole showed clinical benefit compared with 52% on tamoxifen.

A subgroup analysis was performed on the combined data from the European and North American trials. These analyses confirmed that receptor status was a key factor affecting the relative efficacy of anastrozole in relation to tamoxifen. Anastrozole showed a statistically significant advantage over tamoxifen in median TTP (P = 0.022; two-sided, retrospective analysis) in a combined analysis of 611 patients who were known to be ER-positive/PgR-positive (75).

The significance of whether or not prior adjuvant treatment impacted treatment outcome was investigated in the combined first-line trial population. Overall, 14.2% of patients had received prior hormonal therapy, 19.5% in the North American trial and 11.4% in the European trial.4 In 97% of cases, the prior adjuvant hormonal therapy was tamoxifen. Although no formal statistical analyses within subgroups were carried out, the data observed for TTP and OR rates in those patients not receiving prior adjuvant hormonal therapy were similar to those observed in patients who did receive therapy, which in turn is similar to data for the overall patient population.4

These data on the efficacy of anastrozole in the first-line setting versus tamoxifen are supported by the results of a recently reported, independent, prospective, randomized, first-line study in which 238 postmenopausal women with hormone-sensitive, ER-positive, metastatic breast cancer, who had not received previous therapy for advanced disease, were treated with either anastrozole (1 mg once daily; n = 121) or tamoxifen (40 mg daily; n = 117) (76). At the time of data cutoff, 61% of

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4 AstraZeneca; data on file.
patients had died in the anastrozole-treated group, compared with 92% in the tamoxifen-treated group (HR = 0.63; 95% CI, 0.51–0.89; P < 0.05; Table 3). Median TTP was 10.6 months for anastrozole and 5.3 months for tamoxifen, with a higher risk of progression in the tamoxifen group, as indicated by the HR of 0.77 (95% CI, 0.56–0.91; P < 0.05) (79).

It was the conclusion of all of these studies that anastrozole should now be considered as an alternative first-line treatment to tamoxifen in postmenopausal women with advanced breast cancer.

**Letrozole.** Preliminary data have recently been reported from a large, multicenter, double-blind, first-line Phase III clinical trial in postmenopausal women (n = 907) with locally advanced or metastatic breast cancer, which compared letrozole (2.5 mg once daily) with tamoxifen (20 mg once daily; Ref. 77). The primary end point was TTP and secondary end points included OR, TTF, time to response, and survival. A total of 65% of patients had ER-positive/PgR-positive status. Statistically significant superiority for letrozole was shown for the primary end point, TTP (median TTP, 9.4 months for letrozole versus 6.0 months for tamoxifen; P = 0.0001; Cox regression; Table 3).

In contrast to the anastrozole trials, prior adjuvant tamoxifen in this trial was seen to impact upon subsequent response to treatment. For instance, after adjuvant tamoxifen, patients receiving tamoxifen for metastatic disease were seen to have a low response rate compared with letrozole (29% versus 8% for letrozole and tamoxifen, respectively). Additional data and a full publication from this trial are awaited.

**Fadrozole.** In a Phase III randomized trial, fadrozole (1 mg twice daily) was compared directly with tamoxifen (20 mg once daily) as first-line therapy in the treatment of 221 postmenopausal women with advanced breast cancer (78). The study was not double-blind, and patients with disease progression or an unacceptable level of toxicity were given the opportunity to cross over to the alternative drug where feasible. The two groups were well balanced with respect to prognostic factors except for metastatic disease; patients in the fadrozole arm had significantly more visceral metastases and disease than those in the tamoxifen arm.

There was no significant difference between treatments in terms of OR rate. TTF was longer with tamoxifen (8.5 months) compared with fadrozole (6.1 months; P = 0.05; P = 0.09, after adjustment for prognostic factors; Fig. 5), although duration of response and survival were comparable in the two groups.

**First-line Therapy in Advanced Breast Cancer with Steroidal Aromatase Inhibitors**

**Formestane.** In a comparative trial of first-line therapy for postmenopausal women with advanced breast cancer, the steroidal aromatase inhibitor, formestane (250 mg i.m. every 2 weeks), gave comparable results to those of tamoxifen (30 mg p.o. daily) for both efficacy and tolerability (43). In total, 409 patients were randomized into two groups, well matched for pretreatment characteristics, although there was a higher proportion of patients with soft tissue metastases in the formestane-treated group compared with the tamoxifen-treated group. Patients were assessed for antitumor efficacy using UICC criteria. A total of 61 patients were not evaluable, either because they were not eligible for the trial (mainly attributable to a lack of confirmation of postmenopausal status) or because they were nonevaluable for tumor response. There were no statistically significant differences found between the two groups (n = 348) for OR, median duration of response, and survival. However, results significantly favored tamoxifen compared with formestane in terms of TTP (9.7 months versus 7.0 months, respectively; adjusted P = 0.003) and TTF (9.7 months versus 6.5 months; adjusted P = 0.001) compared with formestane.

**Exemestane.** A Phase II study was recently conducted in which exemestane (25 mg daily) was compared with tamoxifen
(20 mg daily) as first-line treatment of metastatic breast cancer in postmenopausal women \( (n = 93; \text{Ref. 79}) \). Median TTP for exemestane \( (n = 31) \) was 8.9 months compared with 5.2 months for tamoxifen \( (n = 32) \), and OR (CR + PR) was 42% versus 16%, respectively. No statistical data from this Phase II study are available at the present time. It was concluded that exemestane had promising activity in the first-line treatment of metastatic disease and warranted a Phase III trial.

**Conclusions.** The results of the first-line Phase III comparative trials between anastrozole and tamoxifen now support the use of anastrozole in the first-line treatment of advanced disease in postmenopausal women. Notwithstanding earlier investigations into the first-line use of the aromatase inhibitors fadrozole and formestane, compared with tamoxifen in advanced breast cancer in postmenopausal women, this is the first full report from a large-scale, randomized study of a newer-generation aromatase inhibitor having superior efficacy to that of tamoxifen. Preliminary data have recently been reported showing a statistically significant advantage for letrozole versus tamoxifen in terms of TTP in the first-line treatment of advanced disease, and a full report of these data are awaited.

**Tolerability of Steroidal and Nonsteroidal Aromatase Inhibitors**

**Adverse Events.** In clinical use, both steroidal and nonsteroidal aromatase inhibitors are generally well tolerated. The main adverse events observed are hot flushes and gastrointestinal events, *i.e.*, nausea and vomiting, which are either anticipated via the pharmacological actions of aromatase inhibitors or are the most commonly seen type of events with this class of drug (18, 21, 43, 71, 72, 80–82). There are, however, certain specific side effects observed with exemestane, but not anastrozole and letrozole, that relate to the androgenic nature of the drug.

When compared with megestrol acetate in second-line studies in advanced breast cancer, the nonsteroidal drugs, anastrozole and letrozole, were associated with a significantly lower incidence of weight gain (55, 61). When exemestane was compared with megestrol acetate, there was also a significantly lower incidence of weight gain with exemestane \( (P = 0.001) \), as would be anticipated when comparing aromatase inhibitors with progestins in this patient population (71). However, the observed value for grade 3–4 weight gain (excessive weight gain >10% of baseline weight) of 7.6% in patients receiving exemestane is higher than that reported for the nonsteroidal aromatase inhibitors, anastrozole and letrozole, in similar trials in a comparable patient population (Table 4; Refs. 55 and 61); this higher value for exemestane probably reflects the androgenic nature of the drug. Additionally, weight gain changes of ≥10% after exemestane were noted in 4% of overweight patients (71).

At higher than normal therapeutic doses of exemestane (200 mg daily), androgenic events have been reported, such as alopecia (10%), hypertrichosis (55%), and acne (4%; Ref. 84). Exemestane has been reported to lead to statistically significant dose-dependent falls in plasma sex hormone binding globulin levels at the 25-mg dose level (52). At 200 mg daily, exemestane gave rise to a case of mild hirsutism after 52 weeks’ treatment. In a Phase II trial, symptoms which may have been androgenic in nature were reported, again using the clinical dose of exemestane of 25 mg daily (two cases of grade 1 alopecia, one patient each with hypertrichosis and acne among 91 treated patients; Ref. 53).

In a Phase III trial comparing exemestane and megestrol acetate, significantly more women receiving exemestane experienced hot flushes (12.0% versus 5.0%), nausea (9.2% versus 5.0%), and vomiting (2.8% versus 0.8%) than did women receiving megestrol acetate, respectively. Significantly more women receiving megestrol acetate reported dyspnoea than did women receiving exemestane (3.0% versus 0.3%, respectively; Ref. 71).

In a first-line study comparing fadrozole with tamoxifen, a 4% incidence in thromboembolic events was reported in the tamoxifen group, whereas no events were observed in fadrozole-treated patients (78). In the first-line studies comparing anastrozole with tamoxifen (72–75), anastrozole-treated patients had a significantly lower incidence of thromboembolic events (combined analysis). Whereas patients treated with anastrozole had hot

### Table 4 Tolerability data: indirect comparison of newer aromatase inhibitors versus megestrol acetate in second-line trials

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>Anastrozole (^{a}) 1 mg o.d. (^{b})</th>
<th>Letrozole (^{c}) 2.5 mg o.d.</th>
<th>Exemestane (^{d}) 25 mg o.d.</th>
<th>Megestrol acetate 160 mg q.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14</td>
<td>13</td>
<td>NA</td>
<td>9–13</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td>4–11</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>11</td>
<td>9</td>
<td>5–23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>8</td>
<td>3</td>
<td>5–7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>6</td>
<td>NA</td>
<td>3–11</td>
</tr>
<tr>
<td>Weight gain</td>
<td>3</td>
<td>6</td>
<td>NA</td>
<td>3–12</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>3–28</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>7–20</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18</td>
<td>NA</td>
<td>8</td>
<td>10–22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NA</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Adapted from Ref. 83.

\(^{b}\) Commonly reported adverse events, irrespective of causality.

\(^{c}\) Adverse experiences in >5% of patients, irrespective of causality.

\(^{d}\) Adverse events considered to be drug-related.

\(^{e}\) Incidence of weight gain from baseline.

\(^{f}\) NA Data not available in published literature.
flushes and vaginal dryness, whereas more patients treated with tamoxifen had vaginal bleeding and vaginal discharge, although the differences were not significant. Although gastrointestinal disturbances are widely recognized as a class effect of aromatase inhibitors, it should be noted that the incidence of gastrointestinal disturbances was similar in the cases of anastrozole and tamoxifen in each trial [24% anastrozole versus 28% tamoxifen, respectively (72) and 54% anastrozole versus 57% tamoxifen, respectively (73)]. Finally, despite its lack of estrogenic effect, anastrozole showed no increase in myocardial infarction or fractures compared with tamoxifen.

Overall, very few patients withdrew from first- or second-line comparative Phase III trials because of drug-related adverse events with aromatase inhibitors (19, 54, 55, 61, 66, 72, 73). In the large-scale, randomized trials of anastrozole versus tamoxifen for first-line treatment, the incidence of withdrawals was similar in both treatment groups, showing that anastrozole is at least as well tolerated as tamoxifen (72, 73). No tolerability data are available, as yet, from the first-line study comparing letrozole with tamoxifen (77).

The newer-generation aromatase inhibitors have the additional advantage of simple, oral, once-daily dosing. This avoids such problems as local reactions (7–13%) at the site of injection, which have been reported after the twice-weekly i.m. administration of the steroidal aromatase inhibitor, formestane, thus limiting the potential, long-term usefulness of this drug in the adjuvant setting (11, 12, 43, 85).

**Neoadjuvant Therapy with Aromatase Inhibitors**

**Anastrozole.** A small, randomized, double-blind, single-center study was performed in which anastrozole (1 mg and 10 mg daily, for 3 months) was used as neoadjuvant therapy in 23 postmenopausal women with newly diagnosed, ER-rich, locally advanced, or large (>3 cm), operable breast tumors (86). Anastrozole at the normal clinical dose of 1 mg daily was shown by ultrasound measurements to be effective in leading to a decrease in tumor volume in the great majority of patients (80.5%). This had a dramatic influence on subsequent breast surgery, in that, of 17 patients who would have required mastectomy at the initiation of treatment, 15 were found to be suitable for breast conservation after 3 months’ treatment with anastrozole. These results suggest that anastrozole is highly effective as neoadjuvant therapy in postmenopausal women with ER-rich breast tumors. In the same group of patients, anastrozole was shown to suppress effectively aromatase activity within the breast, thereby reducing endogenous estrogens (87). This observation is compatible with the known antitumor effects of anastrozole.

In another small study in 12 postmenopausal women with locally advanced (T3–T4) breast cancer, anastrozole 1 mg daily for 15 weeks was evaluated for its effects on plasma and tumor tissue estrogen levels in the same patient group (88). Treatment with anastrozole suppressed tumor tissue concentrations of estradiol, estrone, and estrone sulfate by 88.9%, 82.3%, and 73.4%, respectively, and plasma concentrations by 86.1%, 83.9%, and 95.8%, respectively. It was concluded that anastrozole is a potent suppressor of plasma and intratumoral estrogen levels in patients with locally advanced breast cancer.

**Letrozole.** In a similar study, letrozole 2.5 mg daily for 3 months as primary medical therapy was investigated for its effects on *in situ* estrogen synthesis in 11 postmenopausal women with large, primary, ER-positive breast tumors (89). Of 10 tumors which showed evidence of *in situ* estrogen synthesis, 9 displayed a significant decrease in activity after letrozole treatment (P = 0.022 by sign test). It was concluded that letrozole brought about a decrease in endogenous levels of estrogen within the breast tumors of postmenopausal women. Letrozole (2.5 mg daily; n = 12; 10 mg daily, n = 12) was administered to 24 patients with ER-positive breast tumors as primary systemic therapy (90). The patients were monitored by monthly ultrasound and change in tumor volume over a 3-month period. The resulting median reduction in tumor volume was 81%. Fifteen patients who would have been considered for mastectomy before letrozole therapy were found to be suitable for breast conservation after 3 months’ treatment with the drug.

In a double-blind, randomized, multicenter study, letrozole (2.5 mg daily) was compared with tamoxifen (20 mg daily) as neoadjuvant treatment of 337 postmenopausal women with ER-positive primary breast cancer, over a 4-month period (91). All patients at baseline were not considered eligible for breast-conserving surgery. The primary end point was tumor response. Another important end point was the resultant impact of treatment on the down-staging of the extent of surgery. OR rates were 55% for letrozole (n = 154) versus 36% for tamoxifen (n = 170), a difference which was statistically significantly different (P < 0.001; Mantel-Haenszel low rank test). After 4 months’ therapy, 45% of letrozole-treated patients underwent a lumpectomy/quadrantectomy versus 35% of tamoxifen-treated patients (P = 0.022; Mantel-Haenszel). It was concluded that letrozole was significantly superior to tamoxifen in terms of tumor reduction, which resulted in a superior rate of breast-conserving surgery in the letrozole-treated group.

**Conclusions.** From the results of the above studies, both anastrozole and letrozole are shown to be effective as neoadjuvant therapy in postmenopausal women with large, operable breast tumors. Treatment for up to 3 months with either aromatase inhibitor led to a marked reduction in mastectomy rates. Results to date for letrozole versus tamoxifen, and from an indirect comparison of anastrozole with tamoxifen as neoadjuvant therapy in a similar patient population, indicate that these newer-generation aromatase inhibitors appear to offer an advantage over neoadjuvant therapy with antiestrogens, and additional comparative studies between these two classes of endocrine agents are under way.

**Adjuvant Therapy with Aromatase Inhibitors**

Tamoxifen is the most widely used endocrine agent for the adjuvant therapy of early breast cancer in postmenopausal women (79). Nevertheless, tamoxifen does have limitations in use, most notably its recognized pharmacological properties and side effects. For instance, tamoxifen has been associated with an increased risk of both thromboembolic events and endometrial changes, including endometrial cancer (9, 92). It is feasible, therefore, that other endocrine drugs can provide at least equivalent, if not superior, efficacy, together with improved tolerability, in patients with early disease. In this context, the newer-generation aromatase inhibitors are now under investigation in the adjuvant setting (Table 5).
Anastrozole. Anastrozole is currently being compared directly with tamoxifen as initial adjuvant therapy in postmenopausal women with early breast cancer (82, 93–95). The ATAC trial is a randomized, double-blind trial designed to compare the efficacy and tolerability of 5 years of treatment with tamoxifen with that of anastrozole versus the combination of anastrozole and tamoxifen (92, 93). The primary end points are time to recurrence and safety. Other criteria for evaluation include time to distant metastases, survival, and occurrence of contralateral breast cancer. Separate subprotocols include assessments of pharmacokinetics, endometrial status, bone mineral density, and quality of life. The ATAC trial has now completed recruitment of over 9300 patients and is expected to report in the year 2001.

A second trial, the Arimidex-Nolvadex (ARNO) trial, being conducted by the German Breast Cancer Group, involves the randomization of patients who have received adjuvant tamoxifen for 2 years to receive either anastrozole for 3 years or tamoxifen for an additional 3 years (82, 92–94). The primary end points in this trial are overall survival, relapse-free survival, tolerability, and quality of life.

Two other adjuvant studies of endocrine therapy with aromatase inhibitors in early breast cancer are in progress with the ABCSG (95). The first study compares the addition of the first-generation aromatase inhibitor, aminoglutethimide, to tamoxifen treatment in postmenopausal patients with hormone-responsive, stage I and stage II breast cancer. After 5 years’ endocrine treatment in either arm, patients who are recurrence-free are being rerandomized to compare anastrozole with placebo for another 3 years. In the second ABCSG study, adjuvant tamoxifen for 3 years is being compared with adjuvant anastrozole for 3 years after 2 years’ exposure to tamoxifen in postmenopausal patients presenting with hormone-responsive, G1 and G2, stage I and stage II breast cancer.

Letrozole. The Femera-Tamoxifen Breast International Group (FEMTABIG) trials of letrozole and tamoxifen are being conducted by the Breast International Group to compare letrozole with tamoxifen over 5 years in postmenopausal women with ER-positive/PgR-positive early breast cancer and to compare a sequence of adjuvant endocrine therapies versus a continuous course of a single endocrine agent. The trial consists of an option of randomization into two single arms of either tamoxifen (20 mg daily) or letrozole (2.5 mg daily) for 5 years or randomization into a four-arm trial comprising either arm of the first option above (two-arm trial); and a third arm of 3 years of tamoxifen (20 mg daily) and then letrozole (2.5 mg daily) for 2 years; and a fourth arm of letrozole (2.5 mg daily) for 3 years and then tamoxifen (20 mg daily) for 2 years (82).

Another adjuvant trial, the MA.17 study, evaluates patients from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) who are disease-free after initially being treated with 5 years of tamoxifen and then randomized to receive either 5 years of placebo or 5 years of letrozole. This trial also incorporates assessments of incidence of bone fractures and bone mineral density measurements together with lipid profiles (81).

Exemestane. The steroidal aromatase inhibitor, exemestane is also being studied in the adjuvant setting (81, 82, 92). In the International Collaboration Cancer Group (ICCG) trial, patients with early breast cancer are randomized to receive tamoxifen (20 mg daily for 2–3 years) and then either tamoxifen (20 mg daily) or exemestane (25 mg daily) for the remainder of the 5-year period (92). In the National Surgical Adjuvant Breast and Bowel Project (NSABP; B-33) trial, patients with early breast cancer are being randomized to receive either exemestane or placebo for 2 years after a standard 5 years of tamoxifen therapy (82).

Conclusions. The above adjuvant trials of aromatase inhibitors versus tamoxifen in the treatment of early breast cancer offer the opportunity for the measurement of parameters such as disease recurrence, contralateral breast cancer occurrence, disease-free survival, and overall survival. It is hoped that the current trials with anastrozole, letrozole, and exemestane as adjuvant endocrine treatment in early breast cancer will be beneficial in terms of efficacy, tolerability and quality-of-life parameters in postmenopausal women. The data from the ATAC trial will be available in the near future, and the recent data from the first-line comparative trials between anastrozole and tamoxifen and letrozole and tamoxifen suggest that there is also

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**Table 5** Key adjuvant studies with aromatase inhibitors (see Refs. 81, 82, 91, and 92)

<table>
<thead>
<tr>
<th>Adjuvant study</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>Tamoxifen alone (20 mg daily, 5 yr) versus Tamoxifen (20 mg daily) + anastrozole (1 mg daily, 5 yr) versus Anastrozole alone (1 mg daily 5 yr)</td>
</tr>
<tr>
<td>ARNO</td>
<td>Tamoxifen (20 mg daily, 2 yr) followed by tamoxifen (20 mg daily, 3 yr) versus Tamoxifen (20 mg daily, 2 yr) followed by anastrozole (1 mg daily, 3 yr)</td>
</tr>
<tr>
<td>ABCSG</td>
<td>Comparison of addition of aminoglutethimide to tamoxifen for 5 yr, followed by rerandomization to compare anastrozole for 3 years versus placebo for an additional 3 yr Tamoxifen (20 mg daily) versus anastrozole (1 mg daily) after 2-yr exposure to tamoxifen (20 mg daily)</td>
</tr>
<tr>
<td>FEMTABIG</td>
<td>Tamoxifen (20 mg daily, 5 yr) versus Letrozole (2.5 mg daily, 5 yr) versus Letrozole (2.5 mg daily, 2 yr) followed by tamoxifen (20 mg daily, 3 yr) versus Tamoxifen (20 mg daily, 2 yr) followed by letrozole (2.5 mg daily, 3 yr)</td>
</tr>
<tr>
<td>MA.17</td>
<td>Tamoxifen (5 yr) followed by letrozole (5 yr) versus Tamoxifen (5 yr) followed by placebo (5 yr)</td>
</tr>
<tr>
<td>ICCG</td>
<td>Tamoxifen (20 mg daily, 2–3 yr) followed by either tamoxifen (20 mg daily) or exemestane (25 mg daily) for the remainder of the 5-yr period</td>
</tr>
<tr>
<td>NSABP (B-33)</td>
<td>Tamoxifen (5 yr) followed by either exemestane (25 mg daily) for 2 yr or placebo for 2 yr</td>
</tr>
</tbody>
</table>

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**Conclusions.** The above adjuvant trials of aromatase inhibitors versus tamoxifen in the treatment of early breast cancer offer the opportunity for the measurement of parameters such as disease recurrence, contralateral breast cancer occurrence, disease-free survival, and overall survival. It is hoped that the current trials with anastrozole, letrozole, and exemestane as adjuvant endocrine treatment in early breast cancer will be beneficial in terms of efficacy, tolerability and quality-of-life parameters in postmenopausal women. The data from the ATAC trial will be available in the near future, and the recent data from the first-line comparative trials between anastrozole and tamoxifen and letrozole and tamoxifen suggest that there is also...
Potential for aromatase inhibitors to provide an advantage over tamoxifen in the adjuvant setting.

**Overall Conclusions**

The data for the second-line use of endocrine therapy with steroidal and nonsteroidal aromatase inhibitors has fully established this class of drugs as the new treatment of choice in postmenopausal women with advanced breast cancer failing on prior treatment with an antiestrogen such as tamoxifen (20, 58, 61, 71). In terms of efficacy, anastrozole, letrozole, and exemestane each have shown advantages over the standard second-line therapy, megestrol acetate. Anastrozole was the first nonsteroidal, newer-generation aromatase inhibitor to demonstrate a mature efficacy and survival advantage over another second-line endocrine drug (58), although exemestane has now also been reported to improve survival compared with megestrol acetate (71). All of the newer-generation aromatase inhibitors are well tolerated, with hot flushes and gastrointestinal disturbance being the major adverse events reported in second-line comparative studies. The nonsteroidal aromatase inhibitors, anastrozole and letrozole, both display a clear benefit in terms of weight gain over megestrol acetate.

The properties of aromatase inhibitors reviewed in this article are shown in Table 6.

Many reviewers have attempted to draw indirect comparisons between drugs within this class of aromatase inhibitors in an effort to identify the optimal aromatase inhibitor for the second-line therapy of advanced breast cancer. This is fraught with difficulties, because randomized, controlled trials involving these agents have study designs with different response criteria and different methods of assessment in different patient populations (20, 80). As a result, such indirect comparisons between trials cannot possibly lead to a clear outcome in favor of any single drug. Some investigators even have attempted to reach conclusions based on the degree of estrogen suppression exhibited by aromatase inhibitors; but it should be noted that the net clinical relevance of plasma estrogen reduction still needs to be carefully evaluated (81).

One major area of considerable interest for these newer-generation aromatase inhibitors lies in their potential for lack of cross-resistance with other drugs of the same class, thereby allowing the possibility for an additional response to endocrine therapy, even after progression on second-line treatment. This is illustrated by the response of patients to anastrozole after progression on second-line therapy with formestane (96); 9 of 12 patients who had initially achieved either a PR or SD on formestane before progressing showed additional SD on anastrozole. Seven of these nine responding patients had ER-positive tumors. Similarly, exemestane produced CR in 3 patients and PR in 13 patients when given to postmenopausal women with metastatic breast cancer after progression on second-line therapy with the nonsteroidal aromatase inhibitors, aminoglutethimide, anastrozole, letrozole, or vorozole (97). This lack of cross-resistance might be predicted when steroidal aromatase inhibitors are used sequentially after nonsteroidal aromatase inhibitors and *vice versa* because of their different mechanisms of action on the aromatase enzyme.

The neoadjuvant use of newer-generation aromatase inhibitors in women with ER-rich, locally advanced, or large operable breast tumors gives rise to optimism because of their ability...

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**Table 6** Properties of aromatase inhibitors

<table>
<thead>
<tr>
<th>Aromatase inhibitor</th>
<th>Class</th>
<th>Type</th>
<th>Normal clinical dose and route of administration</th>
<th>Phase III clinical data available for second-line use versus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>Nonsteroidal</td>
<td>II: Inhibitor</td>
<td>1 mg daily p.o.</td>
<td>Megestrol acetate&lt;sup&gt;54,55,58&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fadrozole</td>
<td>Nonsteroidal</td>
<td>II: Inhibitor</td>
<td>1 mg twice daily p.o.</td>
<td>Megestrol acetate&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Nonsteroidal</td>
<td>II: Inhibitor</td>
<td>2.5 mg daily p.o.</td>
<td>Megestrol acetate&lt;sup&gt;61-63&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vorozole</td>
<td>Nonsteroidal</td>
<td>II: Inhibitor</td>
<td>2.5 mg daily p.o.</td>
<td>Aminoglutethimide&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Steroidal</td>
<td>I: Inactivator</td>
<td>25 mg daily p.o.</td>
<td>Megestrol acetate&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Formestane</td>
<td>Steroidal</td>
<td>I: Inactivator</td>
<td>250 mg twice weekly i.m.</td>
<td>Aminoglutethimide&lt;sup&gt;67,68&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 7** First-line clinical trials of aromatase inhibitors

<table>
<thead>
<tr>
<th>Aromatase inhibitor</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole vs. tamoxifen&lt;sup&gt;72-75&lt;/sup&gt;</td>
<td>Anastrozole at least as effective as tamoxifen. Significant difference in favor of anastrozole for patients with ER-positive and/or PgR-positive tumors (<em>P</em> = 0.022; two-sided).</td>
</tr>
<tr>
<td>Fadrozole vs. tamoxifen&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Numerical (nonsignificant) advantage for tamoxifen over fadrozole in terms of TTF. No significant difference in terms of OR rate. Duration of response and survival comparable.</td>
</tr>
<tr>
<td>Formestane vs. tamoxifen&lt;sup&gt;43&lt;/sup&gt;</td>
<td>No statistically significant differences for OR, median duration of response, and survival. Results significantly favored tamoxifen compared with formestane in terms of TTP and TTF.</td>
</tr>
<tr>
<td>Exemestane vs. tamoxifen&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Promising antitumor activity vs. tamoxifen in a Phase II study (<em>n</em> = 97). A Phase III trial is planned.</td>
</tr>
<tr>
<td>Letrozole vs. tamoxifen&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Preliminary data available showing significant superiority for letrozole over tamoxifen in terms of TTP.</td>
</tr>
<tr>
<td>Vorozole</td>
<td>No data available.</td>
</tr>
</tbody>
</table>
to reduce mastectomy rates while providing an early indication of likely tumor response to endocrine therapy.

In the first-line therapy of advanced breast cancer, anastrozole and letrozole have now challenged the position of the long-established, standard therapy, tamoxifen, showing significant benefits in terms of TTP (74, 77). Both aromatase inhibitors are very well tolerated, but anastrozole has shown fewer thromboembolic complications and instances of vaginal bleeding than tamoxifen and is not associated with an increased risk of endometrial cancer. Tolerability data for letrozole in this setting are not yet available. Undoubtedly, as more results from first-line trials become available (Table 7), aromatase inhibitors will become more widely used as first-line agents, as an alternative to tamoxifen, in the treatment of postmenopausal women with advanced disease.

There are differences in both the chemistry and the pharmacological properties of the newer-generation aromatase inhibitors. These differences seem to have an impact upon selectivity of the drugs for aromatase (e.g., effect on adrenocorticotropic hormone-stimulated cortisol levels) and may possibly have an effect on the clinical efficacy of aromatase inhibitors in the adjuvant setting on a long-term basis. Data on the adjuvant use of anastrozole, letrozole, and exemestane will become available in the near future; data on anastrozole is expected to be the first to report. Although each of these aromatase inhibitors are generally well tolerated in the metastatic setting, it will be their tolerability profiles after long-term use in the adjuvant setting that will ultimately determine whether or not tamoxifen is replaced as the “gold standard” adjuvant treatment. It will be important to determine whether there are any long-term effects on the endometrium or on thromboembolic events and, additionally, whether any differences in “selectivity” between the drugs have any clinical consequences.

Currently, there are no data available on possible interactions between aromatase inhibitors and standard chemotherapeutic agents. The ongoing clinical trial program will provide the answers to many of these points, the data being awaited with great interest.

References
27. Santen, R. J., Demers, L. M., Lynch, J., Harvey, H., Lipton, A., Mulagha, M., Hanagan, J., Garber, J. E., Henderson, I. C., Navari,


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dex” (anastrozole) on plasma and intratumor tissue estrogen levels in postmenopausal breast cancer patients. Breast, 8: 241, 1999.


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