Are Differences in the Available Aromatase Inhibitors and Inactivators Significant?1

Paige E. Johnson and Aman Buzdar2
Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

Abstract
Aromatase inhibitors are endocrine agents with a different mode of action than tamoxifen against breast cancer. In postmenopausal women, estrogen concentrations are maintained primarily via aromatase, a cytochrome P-450 enzyme that acts at the final step in the estrogen synthesis pathway. The first clinically available aromatase inhibitor, aminoglutethimide, was introduced for the second-line treatment of advanced breast cancer in the late 1970s. Despite proven efficacy in this setting, its widespread use was limited by its overall toxicity and its lack of selectivity for the aromatase enzyme. 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: (a) anastrozole; (b) letrozole; (c) fadrozole; (d) formestane; and (e) exemestane. Of these, formestane and exemestane are steroidal nonreversible aromatase inhibitors, also known as aromatase inactivators, whereas fadrozole, aminoglutethimide, and letrozole are nonsteroidal reversible aromatase inhibitors. These agents differ in pharmacokinetics, selectivity, and potency, although all are more selective than aminoglutethimide. Some differences in adverse effect profile are also noticeable between and within these two classes of agents. The clinical significance of these differences is not yet evident but may well prove to be relevant in the long-term adjunctive setting.

Introduction
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, primarily by blockade of estrogen activity at the receptor level or by inhibition of estrogen production. However, drug resistance 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.

Aromatase inhibitors are endocrine agents that have a different mode of action than tamoxifen against breast tumors in postmenopausal women. 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 (2–6).

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 P-450 enzyme complex that acts at the final step in the estrogen synthesis pathway and catalyzes the production of estrogens estrone and estradiol by extraglandular conversion from androgens androstenedione and testosterone, respectively. These drugs act by suppression of aromatase activity in fat, liver, and muscle cells and in breast tumor tissue itself. They can be divided into two classes: (a) steroidal drugs; and (b) nonsteroidal drugs (Ref. 7; see Table 1). 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
Anastrozole and letrozole are well absorbed following oral dosing, with long terminal half-lives, allowing for once-daily dosing [anastrozole, 1 mg; letrozole, 2.5 mg (3, 4)]. In contrast, formestane is subject to high first-pass metabolism when given p.o., has a relatively short terminal half-life (approximately 2 h), and has to be administered by i.m. injection (250 mg) every 2 weeks (8). Exemestane is p.o. bioavailable and has a terminal half-life of about 24 h during chronic treatment, allowing once-daily therapy (25 mg) (9).

Mechanism of Action
Steroidal and nonsteroidal aromatase inhibitors differ in their modes of interaction with and inhibition 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. Hence, they are sometimes termed aromatase inactivators. 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. They effectively exclude, therefore, both the natural substrate and oxygen from the enzyme. The coordinate bonding is

1 Presented at the First International Conference on Recent Advances and Future Directions in Endocrine Therapy for Breast Cancer, June 21–23, 2001, Cambridge, MA.
2 To whom requests for reprints should be addressed, at Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 424, Houston, TX 77030. Phone: (713) 792-2817; Fax: (713) 794-4385; E-mail: abuzdar@notes.mdacc.tmc.edu.
Table 1. Structure of aromatase inhibitors, pharmacology, and the selectivity data

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Arimidex</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>Regulatory Approved Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>First line</td>
<td>Yes</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Adjuvant use</td>
<td>No (Data ahead of other AIs)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pharmacology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily clinical dose</td>
<td>1 mg qd</td>
<td>2.5 mg qd</td>
<td>25 mg qd</td>
</tr>
<tr>
<td>Monthly dose</td>
<td>30 mg</td>
<td>75 mg</td>
<td>750 mg</td>
</tr>
<tr>
<td>Time to steady state plasma levels</td>
<td>7 days 53</td>
<td>14-42 days 54</td>
<td>4 days 55</td>
</tr>
<tr>
<td>Half-life</td>
<td>48–50 hours 15</td>
<td>2–4 days 54</td>
<td>27 hours 55,57</td>
</tr>
<tr>
<td>Inter-patient variability in steady state blood levels</td>
<td>ND</td>
<td>35% (1.65-fold variation) 54</td>
<td>ND</td>
</tr>
<tr>
<td>Time to maximal E2 suppression</td>
<td>3–4 days 12</td>
<td>2–3 days 56</td>
<td>7 days 63</td>
</tr>
<tr>
<td>Intratumoral activity demonstrated</td>
<td>Yes 58</td>
<td>Yes 59</td>
<td>ND</td>
</tr>
<tr>
<td>Drug-Drug Interactions</td>
<td>Inhibits <em>in vitro</em> CYP1A2, 2C8/9 and 3A4 but only at relatively high concentrations. No activity on CYP2A6 or 2D6. (US Arimidex)</td>
<td>Metabolized by CYP3A4 and CYP 2A6. <em>In vitro</em> letrozole strongly inhibits CYP2A6 and moderately inhibits CYP2C19. (US Femara)</td>
<td>Metabolized by CYP3A4 and aldoketoreductases. No inhibitory action on CYP1A2, 2C9, 2D6, 2E1 or 3A4. (US Aromasin)</td>
</tr>
<tr>
<td>Interactions with cytochrome P450 (CYP)</td>
<td>Antipyrine and cimetidine clinical interaction studies indicate co-administration with other drugs</td>
<td>Pharmacokinetic interaction study with cimetidine showed no clinically significant effect on</td>
<td>Ketoconazole has no influence on exemestane PKs. No other formal drug-drug interaction studies</td>
</tr>
</tbody>
</table>

*Note: *ND = Not determined.
unlikely to result in clinically significant CYP450 mediated interactions. No evidence of interaction in patients treated with Arimidex and other commonly prescribed drugs. (US Arimidex) letrozole PKs. Warfarin interaction study showed no clinically significant effect of letrozole on warfarin PKs. (US Femara) have been performed. However, a possible decrease of exemestane plasma levels by inducers of CYP3A4 cannot be excluded. (US Aromasin)

<table>
<thead>
<tr>
<th>Selectivity</th>
<th>Androgenic properties</th>
<th>Other endocrine effects in addition to desired effects on estrogens</th>
<th>Effect on sex hormone binding globulin (SHBG)</th>
<th>Effect on basal cortisol level</th>
<th>Effect on basal aldosterone level</th>
<th>Effect on ACTH stimulated cortisol synthesis</th>
<th>Effect on ACTH stimulated aldosterone synthesis</th>
<th>Ratio dose affecting cortisol: clinical dose</th>
<th>Ratio dose affecting aldosterone: clinical dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased $(p=0.003)$ or no change $^{18,54}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No $^{60}$</td>
<td>Yes (reduction of cortisol and aldosterone levels)</td>
<td>Increased $(p=0.001)$ $^{14}$</td>
<td>Decreased $^{28}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No $^{63,62}$</td>
<td></td>
<td>No $^{63}$ or reduced $(p&lt;0.03)$ $^{18}$</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (androgenic) $^{32,54,61}$</td>
<td></td>
<td>No $^{18}$ or increased $(p=0.025)$ $^{63}$</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No $^{53}$</td>
<td></td>
<td>Yes (androgenic) $^{32,54,61}$</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No $^{53}$</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced $(p=0.015)$ $^{63}$</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No $^{53}$</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced $(p=0.04)$ $^{63}$</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No $^{53}$</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$&gt;10$ $^{53}$</td>
<td>$1$ $^{18,63}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$&gt;32$ $^{25}$</td>
<td>$&gt;32$ $^{25}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ND = No data available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

First line studies recently completed and results should become available in the near future.

strong but reversible, so that enzyme activity can recover if the inhibitor is removed. Inhibition is sustained whenever the inhibitor is present.

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 for aromatase of the first-generation aromatase inhibitor aminoglutethimide led to concomitant suppression of the important corticosteroids aldosterone and cortisol. In clinical use, it became necessary to concurrently administer a replacement corticosteroid such as hydrocortisone. Although the second-generation aromatase inhibitor fadrozole was shown to be more potent and selective (7), it demonstrated a lack of selectivity through its effect on 11-deoxycorticosterone and aldosterone.
concentrations, as well as on sodium and potassium levels in animals (10–13).

The third-generation aromatase inhibitor anastrozole has a high degree of selectivity for aromatase in clinical pharmacology studies, and no significant effects were observed on either cortisol or aldosterone secretion at up to 10 times the daily recommended dose after 28 days of exposure (14–16) and also when given for up to 3 months (16). Letrozole showed a poorer degree of enzyme selectivity as compared with anastrozole (17). The long-term effects of this difference have yet to be established.

In the case of the steroidal aromatase inhibitors, both formestane (18–20) and exemestane (21) are selective for aromatase and do not affect either cortisol or aldosterone concentrations adversely. However, both have androgenic properties (22).

**Estrogen Suppression and Aromatase Inhibition**

Both steroidal and nonsteroidal aromatase inhibitors result in a significant decrease in serum estrogen concentrations. Aminoglutethimide demonstrated a high level of aromatase inhibition, but there was not a reduction in estrogen concentrations comparable with that seen with the third-generation nonsteroidal aromatase inhibitors (7). An increase in potency was found with the second-generation drug fadrozole (6), but, in comparison, the newer drugs anastrozole and letrozole both produce 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 (4, 7, 23).

Recent data have been reported from a small study in 12 postmenopausal women with advanced breast cancer, comparing plasma estrogen suppression by letrozole and anastrozole (24). This study showed that letrozole led to significantly greater suppression of estrone and estrone sulfate, but not of estradiol, which is widely considered to be the most important estrogen in the etiology of breast cancer. When inhibition of whole-body aromatase was examined (25), it was shown that letrozole achieved a greater inhibition of aromatase than did anastrozole. The clinical significance of these changes remains to be defined.

The injectable steroidal aromatase inhibitor formestane also suppresses estrogen concentrations significantly, but to a lesser extent than anastrozole (26). Formestane is associated with inconsistent suppression of serum estradiol (26, 27), whereby estradiol levels begin to rise between the fortnightly i.m. doses.

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 (28, 29).

It is clear that the newer-generation aromatase inhibitors anastrozole, letrozole, and exemestane provide greater suppression of estrogens than the earlier aromatase inhibitors aminoglutethimide, fadrozole, and formestane.

The clinical data available for the newer aromatase inhibitors versus the previous standard therapies, megestrol acetate and tamoxifen, indicate that step-changes in estrogen suppression are clinically important. However, head-to-head clinical trials are needed to analyze the differences in estrogen suppression by the newer aromatase inhibitors.

**Clinical Efficacy**

**Anastrozole.** Phase III studies analyzed anastrozole as second- and third-line therapy, comparing oral anastrozole (1 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 (30, 31, 33). At 6 months, there were no statistically significant differences between anastrozole and megestrol acetate (32). However, at 31.2 months, anastrozole at 1 mg daily demonstrated a statistically significant survival advantage over megestrol acetate, with a median survival of 26.7 months versus 22.5 months for the megestrol acetate group (33). The combined analysis clearly demonstrated that after disease progression with tamoxifen, treatment with 1 mg of anastrozole provides a statistically and clinically significant advantage over standard treatment with megestrol acetate.

A further subgroup analysis of the above-mentioned trial data showed that anastrozole at 1 mg daily also had benefits among women with visceral and liver metastases compared with megestrol acetate. The median clinical benefit for visceral metastases was 16.4 months with anastrozole versus 14.7 months with megestrol acetate; for liver metastases, it was 17.9 months with anastrozole versus 9.9 months with megestrol acetate.

In a major North American and European randomized, double-blind, double-dummy, 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 (34, 35). The patients were either newly diagnosed with advanced disease or had progressed following diagnosis and treatment for early disease.

In the North American trial, the median TTP3 was 11.1 months for anastrozole versus 5.6 months for tamoxifen. Based on the derived hazards ratio 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 (CR + PR + SD) rates were 59% for anastrozole and 46% for tamoxifen. These data suggest that anastrozole is superior to tamoxifen as a first-line treatment of advanced breast cancer in postmenopausal women (35).

In the European trial, median TTP was 8.2 and 8.3 months in the anastrozole and tamoxifen arms, respectively, and OR was 32.9% and 32.6% in the anastrozole and tamoxifen arms, respectively, confirming that anastrozole was 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 (34).

A prospectively planned combined analysis was performed on the efficacy and tolerability data from the total number of

---

3 The abbreviations used are: TTP, time to progression; OR, overall response; CR, complete response; PR, partial response; SD, stable disease; TTF, time to treatment failure; ACTH, adrenocorticotropic hormone.
patients recruited into the two trials (36). 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. A total of 57% of patients on anastrozole showed clinical benefit compared with 52% on tamoxifen.

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 patients with estrogen receptor-positive, metastatic breast cancer who had not received previous therapy for advanced disease and were treated with either anastrozole (1 mg, once daily) or tamoxifen (40 mg, daily). At the time of data cutoff, 61% of patients had died in the anastrozole-treated group, as compared with 92% of patients in the tamoxifen-treated group. 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 a hazards ratio of 0.77. 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 (38).

**Letrozole.** Two doses of oral letrozole (2.5 or 0.5 mg, once daily) were compared against each other and against megestrol acetate (160 mg, once daily) as second-line therapy in postmenopausal women with advanced breast cancer previously treated with antiestrogen endocrine therapy (39). For overall survival, there was a significant dose effect for 2.5 mg of letrozole (25.3 months) over 0.5 mg of letrozole (21.5 months), although 2.5 mg of letrozole showed no significant survival advantage over megestrol acetate, even in an updated analysis at follow-up of 51 months (40). It was concluded that 2.5 mg of letrozole was superior to the 0.5-mg dose and was more effective than megestrol acetate in the treatment of advanced breast cancer in postmenopausal women treated previously with an antiestrogen (40, 41). However, in a second similar trial, letrozole did not show this dose-dependent antitumor activity at the 0.5- or the 2.5-mg dose in comparison with megestrol acetate (41). The TTP and survival of patients treated with 2.5 mg of letrozole were similar to those of patients in the progestin arm of the study. Patients treated with 0.5 mg of letrozole tended to have longer TTP and survival, which is consistent with anastrozole studies in which higher doses of anastrozole failed to show superiority over lower doses of the same drug. These disparate results raise the issue of what should be the appropriate therapeutic dose of this drug.

In a randomized trial, oral once-daily letrozole (2.5 and 0.5 mg) was compared with aminoglutethimide (250 mg, twice daily) among postmenopausal women with advanced breast cancer previously treated with antiestrogens (42). Overall, no significant differences in OR were seen in patients receiving 2.5 mg of letrozole, 0.5 mg of letrozole, or aminoglutethimide. However, 2.5 mg of letrozole was significantly superior statistically to aminoglutethimide in terms of overall survival, TTP, and TTF in postmenopausal women with advanced breast cancer previously treated with antiestrogens. (39, 40, 43).

Letrozole has been evaluated against tamoxifen as initial therapy in postmenopausal women with metastatic disease. TTP and response rate were significantly superior in the letrozole arm of the study as compared with the tamoxifen arm of the study (37). In this study, the antitumor activity of tamoxifen was very low (8%) in patients previously exposed to tamoxifen. This is in contrast to other studies in which tamoxifen had substantially higher antitumor activity in similar subgroups of this population (34, 35).

**Fadrozole.** A double-blind study compared fadrozole (only available in Japan) to megestrol acetate in 683 postmenopausal women with advanced breast cancer who had progressed on first-line or adjuvant hormonal therapy (44). 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-treated group than in the megestrol acetate-treated group (44). Neither trial showed any significant difference between the two treatments in terms of primary and secondary end points.

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 postmenopausal women with advanced breast cancer (45). The study was not double-blind, and patients with disease progression or an unacceptable level of toxicity were given the opportunity to crossover to the alternative drug, when feasible. There was no significant difference between treatments in terms of the OR rate. TTF was longer with tamoxifen (8.5 months) as compared with fadrozole (6.1 months), although duration of response and survival were comparable in the two groups.

**Formestane.** In a prospective, randomized, cross-over Phase III trial, formestane (250 mg i.m., every 14 days) was compared with megestrol acetate (160 mg p.o., daily) in postmenopausal patients with advanced breast cancer progressing on tamoxifen (8). The trial was planned to test differences in TTF. There were no significant differences in response rates between formestane and megestrol acetate. A second open-label trial of formestane versus megestrol acetate compared the efficacy and safety of the two drugs as second-line therapy in receptor-positive or receptor-unknown postmenopausal patients with advanced breast cancer previously treated with tamoxifen (46). 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.

In a comparative trial of first-line therapy for postmenopausal women with advanced breast cancer, formestane (250 mg i.m., every 2 weeks) gave results comparable with those of tamoxifen (30 mg p.o., daily) with regard to both efficacy and tolerability (18). There were no statistically significant differences found between the two groups for OR, median duration of response, or survival. However, results significantly favored tamoxifen over formestane in terms of TTP (9.7 versus 7.0 months) and TTF (9.7 versus 6.5 months).

**Exemestane.** In a randomized, double-blind Phase III trial, postmenopausal women with advanced breast cancer refractory to tamoxifen were randomized to receive either exemestane (25 mg p.o., daily) or megestrol acetate (40 mg p.o., four times daily) to demonstrate equivalence between the drugs (47). The overall median duration of follow-up was 48.9 weeks.
The OR rate and overall rate of success (CR + PR + SD > 24 months) were similar in both groups. However, both median TTP and median survival were significantly improved in patients taking exemestane. 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.

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 (48). Median TTP for exemestane was 8.9 months compared with 5.2 months for tamoxifen, and ORs (CR + PR) were 42% versus 16%, respectively. It was concluded that exemestane had promising activity in the first-line treatment of metastatic disease and warranted a Phase III trial.

Sequential Utilization of Aromatase Inhibitors

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 a further response to endocrine therapy, even after progression on second-line treatment. This is illustrated by the response of patients to anastrozole following progression on second-line therapy with formestane (49); 9 of 12 patients who had initially achieved either a PR or SD on formestane before progressing showed further SD on anastrozole. Seven of these nine responding patients had estrogen receptor-positive tumors. Similarly, exemestane produced complete response in 3 patients and PR in 13 patients when given to postmenopausal women with metastatic breast cancer following progression on second-line therapy with nonsteroidal aromatase inhibitor, aminoglutethimide, anastrozole, letrozole, or vorozole (49). This lack of cross-resistance might be predicted when steroid aromatase inhibitors are used sequentially following nonsteroidal aromatase inhibitors and vice versa because of their different mechanisms of action on the aromatase enzyme.

Adverse Events

In clinical use, both steroidal and nonsteroidal aromatase inhibitors are generally well tolerated. The main adverse events observed are hot flashes and gastrointestinal disturbances, such as nausea and vomiting (18, 34, 46, 50–52). There are, however, certain specific side effects observed with exemestane, but not with 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 (31, 39). When exemestane was compared with megestrol acetate, there was also a significantly lower incidence of weight gain with exemestane, as would be anticipated when comparing aromatase inhibitors with progestins in this patient population (47). 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 (31, 39).

In a Phase III trial comparing exemestane and megestrol acetate, significantly more women receiving exemestane experienced hot flashes (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 dyspnea than did women receiving exemestane (3.0% versus 0.3%, respectively; Ref. 46).

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 (45). In the first-line studies comparing anastrozole with tamoxifen (34, 35), anastrozole-treated patients had a significantly lower incidence of thromboembolic events (combined analysis; AstraZeneca; data on file). With respect to other adverse events in these same trials, more patients treated with anastrozole had hot 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 that the incidence of gastrointestinal disturbances was similar in the case of anastrozole and tamoxifen in each trial: in these trials, the incidence of gastrointestinal disturbance was 24% versus 28% (34) and 54% versus 57% (35) for anastrozole versus tamoxifen. Finally, despite its lack of estrogenic effect, anastrozole showed no increase in myocardial infarction or fractures compared with tamoxifen, likely reflecting the short duration of treatment and observation in these trials.

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 (34, 35).

Overall Conclusions

The data for the second-line use of endocrine therapy with steroidal and nonsteroidal aromatase inhibitors have 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 (32, 39, 47). In terms of efficacy, anastrozole, letrozole, and exemestane have each 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 (32), although exemestane has now also been reported to improve survival compared with megestrol acetate (47). All of the newer-generation aromatase inhibitors are well tolerated, with hot flashes and gastrointestinal disturbance being the major adverse events reported in second-line comparative studies. There is a partial lack of cross-resistance between steroidal and nonsteroidal aromatase inhibitors. Therefore, steroidal aromatase inhibitors can be used following progression on nonsteroidal aromatase inhibitors.

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 (36, 48). 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.

There are differences in both the chemistry and the pharmacological properties of the newer-generation aromatase inhibitors. These differences appear to have an impact on the selectivity of the drugs for aromatase (e.g., effect on ACTH-stimulated cortisol levels) and may possibly affect 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 are expected to be the first reported. Whereas all of these aromatase inhibitors are generally well tolerated in the metastatic setting, it will be their tolerability profiles following 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, thromboembolic events, bones, and lipids and also whether any differences in “selectivity” among these drugs have clinical consequences. The ongoing clinical trial programs will provide the answers to many of these points, and the data are awaited with great interest.

Open Discussion

Dr. James Ingle: With the EORTC data in the premenopausal patient, are you still comfortable using tamoxifen or an LHRH alone or ovarian ablation alone, given the superiority shown for the combination? As we all know, the sample sizes in the premenopausal studies are incredibly low. Even in the meta-analyses, they are not of a size that any of us would consider a reasonable study.

Dr. Buzdar: The question you are raising is whether using combined tamoxifen and LHRH agonist in premenopausal patients is showing survival advantage. I have serious reservations about the data. At our institute, we discuss and debate every patient we see in that scenario. My bias is that until we see stronger data, I tend to use sequential endocrine therapy in metastatic settings.

Dr. Kathleen Pritchard: If you look through the meta-analysis as well, which I think has been put together as well as it can be, and how the toxicity data were collected in the individual papers, it’s in a plus/minus fashion. I think the comment that toxicity is not different between the combination and the single agents is based on very little data indeed, and I would really like to see more data in that area.

Dr. Carlos Arteaga: Can you give us a sense of the proportion of patients in these trials that have seen prior chemotherapy? In your JCO study and in these other studies, how heterogeneous was that factor? Could that perhaps explain the difference between the United States and European trials?

Dr. Buzdar: We looked at all potential confounding factors that might skew the result. That’s why it took so long to publish the data.

Dr. Arteaga: So you looked at all these trials with aromatase inhibitors?

Dr. Buzdar: Not aromatase inhibitors, but specifically the second study of letrozole versus megestrol acetate.

Dr. Per Lonning: I have some concerns about the combined analysis of the two aromatase-tamoxifen studies. The American study is very well conducted with a very high percentage of ER-positive patients. More than 50% of the European patients are ER unknown. When you look at the time-to-progression curves for the total European study and then take the ER-positive subgroups, it doesn’t change so much. So it’s likely that the bulk of the patient with ER unknown are ER positive. Zeneca should collect the blocks and do the estrogen receptor analysis retrospectively.

Dr. Buzdar: The point you’re making is very valid: to do clinical studies, you need to have receptor status information. I think it would be ideal to look at it and see that whether the ER-positive patient distribution was similar between the groups with unknown and known receptor status. But the only thing you can compare are the patient populations for which you know the ER receptor information, and in the known receptor subgroup in the European study, the data were consistent with North American trial findings.

Dr. Paul Goss: The patients with ER-unknown tumors did better on tamoxifen than the patients with ER-positive tumors in that study. So that again suggests that the populations are very similar.

Dr. Osborne: I will never participate in any study that, number one, allows ER-negative or ER-unknown patients to be enrolled, and number two, does not collect the blocks.

Dr. Buzdar: The point you are making is absolutely true. The European philosophy for the longest time was that they did not believe the ER information—partly because the older competitive assays were more cumbersome. With the immunohistochemistry, you can do it much easier, and the results are very reproducible.

Dr. Ellis: There’s a dose issue with letrozole that I think reflects the nature of the second-line endocrine therapy setting. You get a lot of resistance and therefore a lot of noise, as well as the potential for imbalances between arms depending on how many endocrine therapy-resistant patients ended up on each arm. If you look at the letrozole dose in the aminoglutethimide studies, 2.5 mg is better than 0.5 mg. In one megestrol study, 2.5 mg is better than 0.5 mg of letrozole, and then in another study against Megace, it’s the other way around. You see the same thing more or less in the Arimidex data with 10 mg being not as good as 1 mg.

Dr. Buzdar: No, with anastrozole, the trend is consistently in the direction of 1 mg. There’s no trial in which 10 mg looked better than 1 mg. With the trial of 2.5 mg of letrozole versus 0.5 mg versus aminoglutethimide, although there was a trend that was not statistically significant between 0.5 and 2.5 mg letrozole, the difference was highly significant against the aminoglutethimide.

Dr. Angela Brodie: I would certainly support that view, because all of the data we have in the animal models showed a dose-response effect with letrozole; clinically, it correlates reasonably in that direction, and the lack of statistical significance probably is due to the population difference.

Dr. Anthony Howell: The studies we’ve done recently seem to be very big. But in fact, as pointed out, 60 of 100
patients are noninformative because they have no chance of responding one way or another, so that’s why we’ve got this noise. Until we do larger trials, I don’t think we can say one is better than another.

**Dr. Pritchard:** With data like this, it’s really important to step back and look at the big picture to see how the trends go. While you can pick the data apart and look for subsets, once you’ve done that, I think you have to say that you really can’t base any firm conclusions on that sort of analysis.

**Dr. Ellis:** If you look at the trials overall, just forget who manufactures which drug, you can see what the big picture looks like as a class effect.

**Dr. Buzdar:** If we look at it as a class, all three of the available aromatase inhibitors are superior to tamoxifen in the data we have. The question is whether there are any differences between these compounds. These are interesting discussions but only the head-on comparisons in the ongoing studies will be of interest, once the data become public.

**Dr. Ellis:** Some interest, but again, they’re in the second-line setting, so you’re probably not going to see a significant difference.

**References**


31. Dowsett, M., Geisler, J., Haynes, B. P., et al. A Phase III trial comparing anastrozole (1 and 10 mg), a potent and selective aromatase
Aromatase Inhibitors

32. Buzdar, A., Jonat, W., Howell, A., et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmeno-

Are Differences in the Available Aromatase Inhibitors and Inactivators Significant?

Paige E. Johnson and Aman Buzdar

*Clin Cancer Res* 2001;7:4360s-4368s.

Updated version  Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/7/12/4360s

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.