



Michele Sassi. La Digue Island, c. 2001. Seychelles Islands, Indian Ocean. Photograph.

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# Anti-aromatase Agents in the Treatment and Prevention of Breast Cancer

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**A***nti-aromatase agents now have a central role in the management of breast cancer in postmenopausal women; they are superior to megestrol acetate as second-line therapy and to tamoxifen for initial therapy of metastatic disease. They also are highly active as neoadjuvant therapy. Two classes of anti-aromatase agents are available: steroidal (eg, exemestane) and nonsteroidal (eg, anastrozole, letrozole). Although both types of agents act on the aromatase enzyme, they do so by different mechanisms and have different effects on cellular aromatase activity. Nonsteroidal agents are associated with increased aromatase enzyme content and steroidal agents are associated with decreased content. The increase in aromatase content seen with the nonsteroidal agents may in part explain the development of resistance with these agents and the ability of the steroidal agent exemestane to induce a response when nonsteroidal agents fail.*

*Because the anti-aromatase agents almost completely eliminate endogenous estrogen production, they not only affect breast cancer tissues, but also may alter the function of other estrogen-responsive tissues. However, preclinical data show that the steroidal agent exemestane may actually improve bone and lipid metabolism. In addition, no increase in clinical fracture rate has been noted in women treated with exemestane in metastatic trials; the fracture risk has not yet been studied following prolonged exposure in healthy women. Exemestane-associated beneficial effects on these end organs may be due to the steroidal nature of both the parent compound and its principal metabolite, 17-hydroexemestane. Similar benefits have not been reported with nonsteroidal anti-aromatase agents. Based on their excellent activity in the metastatic setting, anti-aromatase agents are now being evaluated in the adjuvant setting and in pilot studies for chemoprevention. These studies will provide long-term data in healthy women and will help to differentiate anti-aromatase agents, in terms of their efficacy in the treatment of breast cancer and their effects on end organs.*

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## Introduction

We are in the midst of a revolution in the endocrine therapy of breast cancer. After two decades of clinical development, the anti-aromatase agents are challenging tamoxifen, which until recently has been the most important hormonal therapy for breast cancer. Recent clinical trials demonstrate that anti-aromatase agents are superior to megestrol acetate in postmenopausal women with metastatic breast cancer in whom tamoxifen has failed,<sup>1,4</sup> they are superior to tamoxifen for initial therapy in metastatic disease,<sup>5-9</sup> and they are highly active when compared with tamoxifen as neoadjuvant therapy in postmenopausal receptor-positive women.<sup>10</sup> Research is underway to investigate the use of anti-aromatase agents as adjuvant therapy of early postmenopausal breast cancer and for breast cancer prevention in healthy women at increased risk of breast cancer.

Exemestane, anastrozole, and letrozole exert their anti-tumor effect by blocking the aromatase enzyme, which is the final step in estrogen biosynthesis. Their blockade is so efficient that after administration, residual peripheral aromatase activity is approximately 3% or less based on *in vivo* measurements in women.<sup>11,12</sup> Because estrogens play a central role in women's health, the implications of this nearly complete elimination of endogenous estrogen must be considered, as estrogens are thought not only to have a role in breast cancer initiation, proliferation, and metastasis,<sup>13</sup> but also to affect the functioning of multiple end organs.<sup>14</sup>

Despite the fact that each of the anti-aromatase agents has similar effects on plasma estradiol concentrations, there are potentially important dissimilarities at the tissue level. Such dissimilarities are just now beginning to emerge. We now know that these agents do not interfere with aromatase in the same way and do not have the same effect on cellular aromatase activity.<sup>15</sup> Because estrogen biosynthesis is complex and tissue-specific, tissue-specific promoters may alter the production and metabolism of estrogens locally at the level of bone, breast, and other tissues.<sup>13</sup> Therefore, it is likely that clinical differences among the anti-aromatase agents will emerge over time, particularly as we collect long-term data in healthy women enrolled in adjuvant breast cancer trials.

This article reviews the pharmacology, clinical trial results, and current research with the anti-aromatase agents, with a focus on characteristics that may clinically differentiate them over time.

## Pharmacology

Much of the pharmacology of the anti-aromatase agents is reviewed by William R. Miller and J. Michael Dixon in this issue. In brief, there are two types of anti-aromatase agents — steroidal (eg, exemestane) and nonsteroidal (eg, anastrozole, letrozole). Steroidal agents bind irreversibly to the substrate-binding site of aromatase and are associated with a decrease in aromatase activity when tested in *in vitro* systems. In *in vivo* studies, exemestane causes a profound decrease in aromatase activity in breast cancer tissue and surrounding nonmalignant tissue. In contrast, the nonsteroidal agents bind reversibly to the heme portion of the aromatase molecule and are associated with an increase in aromatase activity when tested in *in vitro* systems.<sup>15</sup> Whereas the biosynthesis of estrogens in the presence of an irreversible steroidal agent requires the production of new aromatase, the biosynthesis of estrogens may occur in the presence of reversible steroidal agents without the need for synthesis of new aromatase.<sup>15</sup>

There are potential implications of these pharmacologic differences. The increase in aromatase activity with the nonsteroidal agents may be important to the development of tumor resistance, particularly with long-term treatment. Moreover, it now appears that the steroidal nature of exemestane vs the other anti-aromatase agents may not be a trivial difference. Estrogen deprivation in postmenopausal women has been associated with altered plasma lipid profiles and increased bone mineral loss, leading to osteoporosis and an increased risk of bone fracture, heart disease, and stroke.<sup>14,16</sup> There is concern, therefore, that because they induce estrogen deprivation, anti-aromatase agents given at full therapeutic doses may increase the risk of these events, especially with long-term use. Because of their structures, both exemestane and its major 17-hydroexemestane metabolite have the potential to exert minimal steroidal activity, which may counter the effects of estrogen deprivation on some tissues.<sup>17</sup>

This hypothesis is supported by preclinical and clinical data. We conducted a study in Sprague-Dawley rats to determine the effects of ovariectomy and exemestane on lipid and bone metabolism. Rats were sorted into 5 groups: control, intact control (sham-operated), sham plus exemestane 100 mg/kg weekly, ovariectomized control, and ovariectomized plus exemestane 100 mg/kg weekly. Exemestane completely protected against the adverse changes in lipid and bone metabolism associated with ovariectomy.<sup>18</sup> In a phase II study, there was no difference in the incidence of pathologic fractures in postmenopausal women with metastatic breast cancer treated with exemestane vs

megestrol acetate.<sup>19</sup> In a phase II study in women with metastatic breast cancer, there were also no negative effects on the lipid profile after 24 weeks of treatment with exemestane as initial therapy.<sup>17</sup>

## Clinical Efficacy

### *Efficacy Following Failure of Tamoxifen and an Anti-aromatase Agent*

Although it may seem counterintuitive that one anti-aromatase agent might be effective after failure of another, a clinical benefit of 24% and a median duration of objective response of more than 1 year were reported in 241 postmenopausal breast cancer patients treated with exemestane after failure of both tamoxifen and a nonsteroidal anti-aromatase agent.<sup>20</sup> These results are impressive in this highly pretreated population and may be due to pharmacologic differences between steroidal and nonsteroidal agents.

### *Efficacy Following Failure of Tamoxifen*

All three available oral anti-aromatase agents have been compared with megestrol acetate in large phase III randomized trials conducted in postmenopausal women with receptor-positive or unknown metastatic breast cancer in whom tamoxifen failed.<sup>1,4</sup> These are the largest and best-conducted studies of endocrine therapy in metastatic breast cancer to date. Collective-

ly, they demonstrate that anti-aromatase agents have superior efficacy and safety compared with megestrol acetate in this setting, that stable disease is an important end point in this population, and that objective response rate to the best second-line endocrine therapy is less than 25% when trials are properly audited by an external peer review committee. Because of differences in study design, it is not appropriate to make direct comparisons among these trials.

In this setting, letrozole demonstrated a statistically significantly superior objective response rate and time to treatment failure (TTF) vs megestrol acetate in one study<sup>2</sup> and similar efficacy in a second study.<sup>4</sup> Anastrozole was statistically superior to megestrol acetate in median survival, but only in an updated pooled analysis.<sup>3</sup> Median survival, time to tumor progression (TTP), and TTF were significantly longer in women treated with exemestane than with megestrol acetate.<sup>1</sup> All three of the anti-aromatase agents were better tolerated than megestrol acetate (Table 1).

### *Efficacy as Initial Therapy*

Anastrozole and letrozole have been compared with tamoxifen in large phase III studies as initial therapy of metastatic breast cancer in postmenopausal women with estrogen receptor-positive or unknown disease (Table 2). Anastrozole 1 mg daily had similar efficacy to tamoxifen 20 mg daily. Two studies were conducted; in one trial, no reported differences were reported

Table 1. — Anti-aromatase Agents vs Megestrol Acetate After Failure of Tamoxifen

	Anti-aromatase Agent vs Megestrol Acetate 160 mg daily			
	Exemestane 25 mg/q.d. x 4 <sup>1</sup>	Anastrozole* 1 mg/q.d. x 4 <sup>3</sup>	Letrozole 2.5 mg/q.d. x 4 <sup>2</sup>	Letrozole 2.5 mg/q.d. x 4 <sup>4</sup>
Number of patients	366 vs 403	263 vs 253	174 vs 189	199 vs 201
% OR	15.0 vs 12.4	12.5 vs 12.2	23.6 vs 16.4 <sup>†</sup>	16.1 vs 14.9
% Clinical benefit <sup>‡</sup>	37.4 vs 34.6	42.2 vs 40.3	34.5 vs 31.7	31.2 vs 25.4
Median TTP (months)	4.7 vs 3.8 <sup>†</sup>	4.8 vs 4.6	5.6 vs 5.5	3.2 vs 3.4
Median TTF (months)	3.8 vs 3.6 <sup>†</sup>	NR	5.1 vs 3.9 <sup>†</sup>	3 vs 3
Median survival (months)	NR vs 28.4 <sup>†</sup>	26.7 vs 22.5 <sup>†</sup>	23.3 vs 21.5	29 vs 26
% ADR discontinuation <sup>§</sup>	1.7 vs 5.0	1.9 vs 4.0	3.0 vs 11.0	6.6 vs 11.4

NR = not reported  
OR = objective response (complete + partial response)  
q.d. = once daily  
ADR = adverse drug reaction  
TTF = time to treatment failure  
TTP = time to tumor progression  
\* based on a pooled updated analysis  
<sup>†</sup> statistically significant difference  
<sup>‡</sup> complete response + partial response + stable disease ≥24 weeks  
<sup>§</sup> discontinuation rate due to adverse drug reactions

Table 2. — Studies of Anti-aromatase Agents vs Tamoxifen for Initial Therapy of Metastatic Breast Cancer

	Anti-aromatase Agent vs Tamoxifen			
	Phase III Studies			Phase II Study
	Anastrozole <sup>5</sup>	Anastrozole <sup>6</sup>	Letrozole <sup>7</sup>	Exemestane <sup>8,9</sup>
% Objective response	21 vs 17	33 vs 33	30 vs 20*	41 vs 14
% Clinical benefit <sup>†</sup>	59 vs 46*	56 vs 56	49 vs 38*	56 vs 42
Time to tumor progression (months)	11 vs 6**	8 vs 8	9 vs 6*	8.9 vs 5.2
Time to treatment failure (months)	8 vs 5	6 vs 6	9 vs 6*	Not reported

\* Between-group difference is statistically significant  
<sup>†</sup> Complete response + partial response + stable disease ≥24 weeks  
<sup>\*\*</sup> Nonprotocol analysis

between anastrozole and tamoxifen,<sup>6</sup> but a significantly higher clinical benefit (complete response + partial response + stable disease ≥24 weeks) and longer TTP (in a non-protocol-specified analysis) with anastrozole was noted in the second.<sup>5</sup> Conversely, the data on letrozole are more clear-cut and demonstrate superiority over tamoxifen, with statistically significant improvement in objective response rate, clinical benefit, TTP, and TTF<sup>7</sup>

In a randomized phase II study, patients with advanced breast cancer were randomized to receive either exemestane or tamoxifen.<sup>8,9</sup> Initial results were promising, and the European Organization for Research and Treatment of Cancer (EORTC) has extended the study to a full phase III evaluation. Objective response rate was 41% vs 14%, clinical benefit 56% vs 42%, and TTP 8.9 months vs 5.2 months for exemestane and tamoxifen, respectively, in the phase II portion of the study.

### Efficacy for Neoadjuvant Therapy

Each of the anti-aromatase agents has been studied in the neoadjuvant setting. A large phase III study comparing letrozole (n=154) with tamoxifen (n=170) provides evidence of the superiority of letrozole. Statistically significant improvements were reported in the objective response rate based on clinical examination (55% vs 36%;  $P<.001$ ) as well as ultrasound (35% vs 25%;  $P=.042$ ) and mammographic assessment (34% vs 17%;  $P<.001$ ) with letrozole vs tamoxifen. In addition, a statistically significantly larger proportion of women were able to undergo breast-conserving surgery after treatment with letrozole compared with tamoxifen (45% vs 35%;  $P=.022$ ).<sup>10</sup>

Anastrozole and exemestane have been studied in smaller phase II uncontrolled trials.<sup>21-23</sup> In these studies, the median reduction in tumor volume was 75% to 90% based on clinical examination, ultrasound, and mammography, and the percentage of patients able to undergo breast-conserving surgery ranged from 80% to

88%. A comprehensive review of the exemestane data is provided elsewhere in this issue.

### Planned and Ongoing Research

Each of the anti-aromatase agents is being evaluated in the adjuvant setting (Table 3). Companion studies will assess their effect on lipid and bone metabolism. Demonstration of end-organ safety, or even protection, and a reduction in contralateral breast cancer will support their use in chemoprevention. Trials in which the anti-aromatase agent is evaluated against a placebo, such as the NCIC MA17 and NSABP B-33 trials, will provide the best assessment of the toxicities and end-organ effects of these agents.

The first adjuvant therapy study for which preliminary results are available is the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.<sup>24</sup> Enrolling more than 9,000 postmenopausal women with early breast cancer, this is the largest randomized trial ever reported in cancer patients. Patients were randomized to treatment with anastrozole or tamoxifen alone or to a combination of both. After a median follow-up of 2.5 years, there was a statistically significant reduction in events (death due to any cause, recurrence, DCIS, or contralateral breast cancer) in women treated with anastrozole compared with tamoxifen, but not for the combination compared with tamoxifen. Although follow-up was relatively short, these results are very promising.

The potential role of anti-aromatase agents in breast cancer prevention is being evaluated in several pilot studies. The basis for their use is evidence that estrogens and estrogen metabolites may actually initiate breast cancer.<sup>13</sup> The administration of anti-aromatase agents will decrease estrogen exposure and should therefore, reduce the risk of breast cancer. Their use is also under investigation in premenopausal women in conjunction with ovarian ablation.

Table 3. — Adjuvant Therapy Studies Using Anti-aromatase Agents

Agent	Study	Randomization Scheme	Status
Anastrozole	ATAC Trial	A × 5 y T × 5 y A 1 mg + T 20 mg × 5 y	Closed (9,300 patients), preliminary results available
	German Breast Cancer Group (ARNO Trial)	T × 2 y → T × 3 y T × 2 y → A × 3 y	Enrolling
Exemestane	Worldwide Intergroup Study 031/BIG 9702	T × 5 y T × 2-3 y → E × 2-3 y	Enrolling
	TEAM Trials	E × 5 y T × 5 y	Enrolling
	NSABP B-33	T × 5 y → E × 2 y T × 5 y → P × 2 y	Enrolling
Letrozole	BIG-FEMTA	L × 5 y T × 5 y T × 2 y → L × 3 y L × 2 y → T × 3 y	Enrollment complete (n=1,721) for comparison of T vs L; enrollment continues for the sequential portion
	Canadian NCI and US Intergroup MA-17	T × 5 y → L × 5 y T × 5 y → P × 5 y	Enrolling

A = anastrozole      E = exemestane  
L = letrozole        P = placebo  
T = tamoxifen        y = year

## Discussion

Anti-aromatase agents are more effective than tamoxifen as initial therapy of metastatic disease and offer a new option in the management of postmenopausal women with breast cancer. They represent a substantial step forward because they not only may be better than tamoxifen but may add an additional line of defense against this disease over and above tamoxifen. As these agents move to the forefront, questions arise regarding the appropriate role for tamoxifen, particularly in light of in vitro and in vivo evidence that tamoxifen causes breast cancer cells to become vulnerable to subsequent treatment with an anti-aromatase agent.<sup>25</sup> More research is required to assess the implications of these data. The optimal sequence of administration of hormonal therapy and the potential benefits of combination therapy remain to be defined.

Current clinical data with the anti-aromatase agents are primarily in the metastatic setting. It is difficult to tease out differences among agents in this heavily pretreated population of women who generally do not undergo long-term treatment. However, as we evaluate use in healthy women in the adjuvant and

chemoprevention settings, we may see clinical differences among these agents in their effects on breast tumors and peripheral organs. Such differences are suggested in metastatic trials. In each of the metastatic settings (first- and second-line therapy and neoadjuvant therapy), there appears to be a correlation between residual aromatase activity and clinical activity with the nonsteroidal agents. Letrozole, which is associated with the lowest residual aromatase activity among the nonsteroidal agents, may have better clinical activity than anastrozole, which has higher residual aromatase activity (Table 4).<sup>11,12</sup> It is possible that breast cancer cells become supersensitive to even very low residual estrogen levels as the disease progresses. Metastases may themselves work in an autocrine way to make their own estrogen. Therefore, a more potent anti-aromatase agent may be able to exert a discernible clinical benefit when compared with a less potent agent.

It is interesting to note that in head-to-head phase III comparisons, no dramatic differences in tolerability have been noted between tamoxifen and the nonsteroidal agents anastrozole and letrozole.<sup>5-7</sup> A larger treated population is needed to determine comparative thromboembolic effects, while long-term studies are

Table 4. — In Vivo Residual Aromatase Inhibition<sup>11,12</sup>

Anti-aromatase Agent	Type	% Residual Aromatase Inhibition
Aminoglutethimide	Nonsteroidal	9.4
Formestane (IM)	Steroidal	8.1
Anastrozole	Nonsteroidal	3.3
Exemestane	Steroidal	2.1
Letrozole	Nonsteroidal	1.1

needed to determine differences in the risk of endometrial cancer. In terms of short-term effects, both anti-aromatase agents and tamoxifen cause hot flashes. Interestingly, however, although the incidence of hot flashes with the nonsteroidal agents is similar to that reported with tamoxifen,<sup>5-7</sup> this is not the case with the steroidal agent exemestane. In a phase II study in which patients were randomized to exemestane or tamoxifen for initial treatment of metastatic disease, the incidence of grade 2/3 hot flashes was 3.2% with exemestane and 13.5% with tamoxifen.<sup>9</sup> The low incidence of hot flashes with exemestane may be another example of the steroidal effect of this agent. These data must be corroborated in the larger ongoing EORTC phase III trial.

Anti-aromatase agents may have their greatest impact in chemoprevention. A challenge in studying anti-aromatase agents in breast cancer prevention is identifying populations of women who are at high risk for the disease and thus would gain the greatest potential benefit from anti-aromatase use. There are several new markers of life-long increased exposure to estrogens, which could be used to identify women who are uniquely vulnerable to breast cancer. The first is increased plasma estradiol levels in postmenopausal women. As estradiol levels increase, there is an increased relative risk of breast cancer.<sup>26</sup> The second potential marker of increased breast cancer risk is postmenopausal bone mineral density. Postmenopausal women whose bone mineral density falls into the upper quartile of aged-matched values have elevated estrogen levels and are at increased risk of breast cancer.<sup>27</sup> The third potentially useful marker is mammographic density. Postmenopausal women with increased breast density are at increased relative risk of breast cancer.<sup>28</sup>

The willingness of women at increased risk of breast cancer to take a preventive agent will depend on the therapeutic index of the intervention. Breast cancer efficacy and positive end-organ effects must be balanced with negative end-organ effects and drug toxicities. Women considered to be at high risk of breast cancer might include well women above a certain age,

women with premalignant lesions, or those with a history of prolonged exposure to hormone replacement therapy, as well as women with an increased Gail breast cancer risk score, mammographic density, bone density, or plasma estradiol levels.

Anti-aromatase agents are replacing tamoxifen as the cornerstone of hormonal therapy of postmenopausal breast cancer. Even with relatively limited use, pharmacologic and clinical differences among the anti-aromatase agents are beginning to emerge. As more experience is gained in healthy women in the adjuvant setting, these differences will become more obvious and may drive the selection of a specific anti-aromatase agent for use in a particular setting.

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