REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Aromatase Inhibitors in Breast Cancer

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THE THIRD-GENERATION AROMATASE INHIBITORS PROVIDE NOVEL approaches to the endocrine treatment of breast cancer. These drugs are effectively challenging tamoxifen, the previous gold standard of care,[1-13] for use in postmenopausal patients with estrogen-receptor–positive cancers, who make up the majority of patients with breast cancer. These agents are also being considered for use in chemoprevention, a strategy in which tamoxifen has already been shown to reduce the incidence of breast cancer.[14,15] In this article, we review the current role of aromatase inhibitors and assess their potential for clinical use. Other reviews that may be of interest to specialists are also available.[16,17]

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BACKGROUND

MECHANISMS OF ACTION

Estrogen is the main hormone involved in the development and growth of breast tumors; oophorectomy was first shown to cause regression of advanced breast cancer more than a century ago,[18] and estrogen deprivation remains a key therapeutic approach.[19] Tamoxifen inhibits the growth of breast tumors by competitive antagonism of estrogen at its receptor site (Fig. 1). Its actions are complex, however, and it also has partial estrogen-agonist effects. These partial agonist effects can be beneficial, since they may help prevent bone demineralization in postmenopausal women,[20,21] but also detrimental, since they are associated with increased risks of uterine cancer[13,22] and thromboembolism.[14] In addition, they may play a part in the development of tamoxifen resistance.[23]

In contrast, aromatase inhibitors markedly suppress plasma estrogen levels in postmenopausal women by inhibiting or inactivating aromatase, the enzyme responsible for the synthesis of estrogens from androgenic substrates (specifically, the synthesis of estrone from the preferred substrate androstenedione and estradiol from testosterone) (Fig. 1). Unlike tamoxifen, aromatase inhibitors have no partial agonist activity.

SOURCES OF AROMATASE

Aromatase, an enzyme of the cytochrome P-450 superfamily and the product of the *CYP19* gene,[24] is highly expressed in the placenta and in the granulosa cells of ovarian follicles, where its expression depends on cyclical gonadotropin stimulation. Aromatase is also present, at lower levels, in several nonglandular tissues, including subcutaneous fat, liver, muscle, brain, normal breast, and breast-cancer tissue.[25,26] Residual estrogen production after menopause is solely from nonglandular sources, in particular from subcutaneous fat. Thus, peripheral aromatase activity and plasma estrogen levels correlate with body-mass index in postmenopausal women.[27] At menopause, mean plasma estradiol levels fall from about 110 pg per milliliter (400 pmol per liter) to low but stable levels of about 7 pg per milliliter (25 pmol per liter). In postmenopausal women, how-

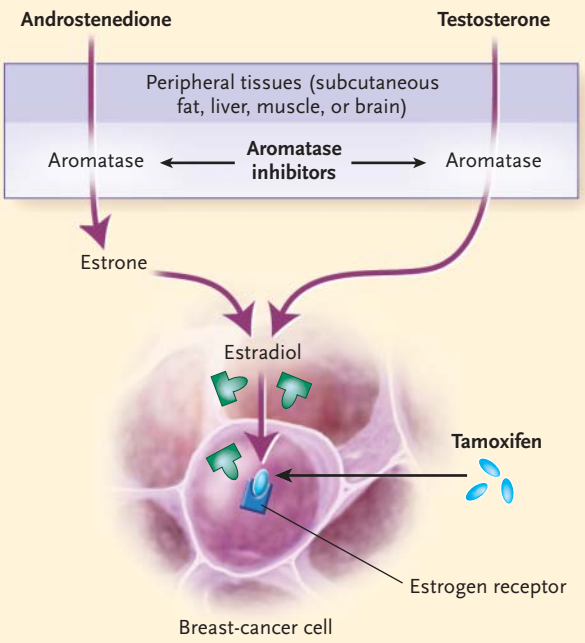

Figure 1. Mechanism of Action of Aromatase Inhibitors and Tamoxifen.

ever, the concentration of estradiol in breast-carcinoma tissue is approximately 10 times the concentration in plasma,[28] probably in part because of the presence of intratumoral aromatase. Early evidence that intratumoral aromatase activity might help predict the response to aromatase inhibitors[29] remains to be confirmed in large-scale studies. Details on the control and importance of the sources of aromatase have recently been published.[30,31]

AROMATASE INHIBITION IN PREMENOPAUSAL WOMEN

In premenopausal women, the use of aromatase inhibitors leads to an increase in gonadotropin secretion because of the reduced feedback of estrogen to the hypothalamus and pituitary, and in some animal models aromatase inhibition increases the weight of the ovaries.[32] Investigation of aromatase inhibition in breast cancer before menopause has consequently been minimal, aside from tests of aromatase inhibition in combination with the use of a gonadotropin-releasing–hormone agonist to suppress ovarian function.[33] The short-term application of letrozole, a third-generation aromatase inhibitor, has recently been successful for the induction of ovulation in women with infertility.[34] The data in the current review, however, pertain solely to postmenopausal women.

CLINICAL DEVELOPMENT AND PHARMACOLOGY

Aminoglutethimide, the first aromatase inhibitor, was initially developed as an anticonvulsant but was withdrawn from use after reports of adrenal insufficiency. It was subsequently found to inhibit several cytochrome P-450 enzymes involved in adrenal steroidogenesis and was then redeveloped for use as "medical adrenalectomy" against advanced breast cancer.[35,36] Side effects, including drowsiness and rash, limited its use, but the discovery that its efficacy was mainly due to aromatase inhibition[37,38] stimulated the development of numerous new inhibitors during the 1980s and early 1990s. They are described as first-, second-, and third-generation inhibitors according to the chronologic order of their clinical development, and they are further classified as type 1 or type 2 inhibitors according to their mechanism of action (Table 1). Type 1 inhibitors are steroidal analogues of androstenedione (Fig. 2) and bind to the same site on the aromatase molecule, but unlike androstenedione they bind irreversibly, because of their conversion to reactive intermediates by aromatase. Therefore, they are now commonly known as enzyme inactivators. Type 2 inhibitors are nonsteroidal and bind reversibly to the heme group of the enzyme by way of a basic nitrogen atom; anastrozole and letrozole, both third-generation inhibitors, bind at their triazole groups (Fig. 2).

The second-generation aromatase inhibitors include formestane (4-hydroxyandrostenedione),[39] a type 1 compound, and fadrozole,[40] a type 2 imidazole. Each has been found to have clinical efficacy,[11,12,41] but formestane has the disadvantage of requiring intramuscular injection, and fadrozole causes aldosterone suppression, limiting its use to doses that produce only about 90 percent inhibition.[42] Other second-generation aromatase inhibitors have been investigated clinically but have never been approved for clinical use. The third-generation inhibitors, developed in the early 1990s, include the triazoles anastrozole (Arimidex) and letrozole (Femara) and the steroidal agent exemestane (Aromasin). In contrast to aminoglutethimide and fadrozole, their specificity appears to be nearly complete at clinical doses, with little or no effect on basal levels of cortisol or aldosterone.[43-45]

PHARMACOKINETICS

Anastrozole, letrozole, and exemestane are administered orally. Anastrozole and letrozole have similar pharmacokinetic properties, with half-lives approximating 48 hours,[46,47] allowing a once-daily dosing schedule. The half-life of exemestane is 27 hours.[48] Pharmacokinetic interactions between some inhibitors and tamoxifen have been described. Aminoglutethimide induces cytochrome P-450 activity, which reduces tamoxifen levels.[49] In contrast, the levels of anastrozole and letrozole are reduced (by a mean of 27 percent and 37 percent, respectively) when they are coadministered with tamoxifen, but these reductions are not associated with impaired suppression of plasma estradiol levels.[50,51]

Table 1. Classification of Aromatase Inhibitors.

Generation	Type 1 (Steroidal Inactivator)	Type 2 (Nonsteroidal Inhibitor)
First	None	Aminoglutethimide
Second	Formestane	Fadrozole Rogletimide
Third	Exemestane (Aromasin)	Anastrozole (Arimidex) Letrozole (Femara) Vorozole

COMPARATIVE PHARMACOLOGIC EFFICACY

The third-generation aromatase inhibitors have been found in preclinical studies to be more than three orders of magnitude more potent than aminoglutethimide.[52] All of them markedly suppress plasma estrogen levels, but the very low plasma estrogen levels in postmenopausal women and the limited sensitivity of immunoassays have made it difficult to estimate precisely their relative effectiveness. In contrast, isotopic measurement of whole-body aromatization has greater sensitivity and allows valid comparisons among studies. This method has demonstrated that greater inhibition is achieved

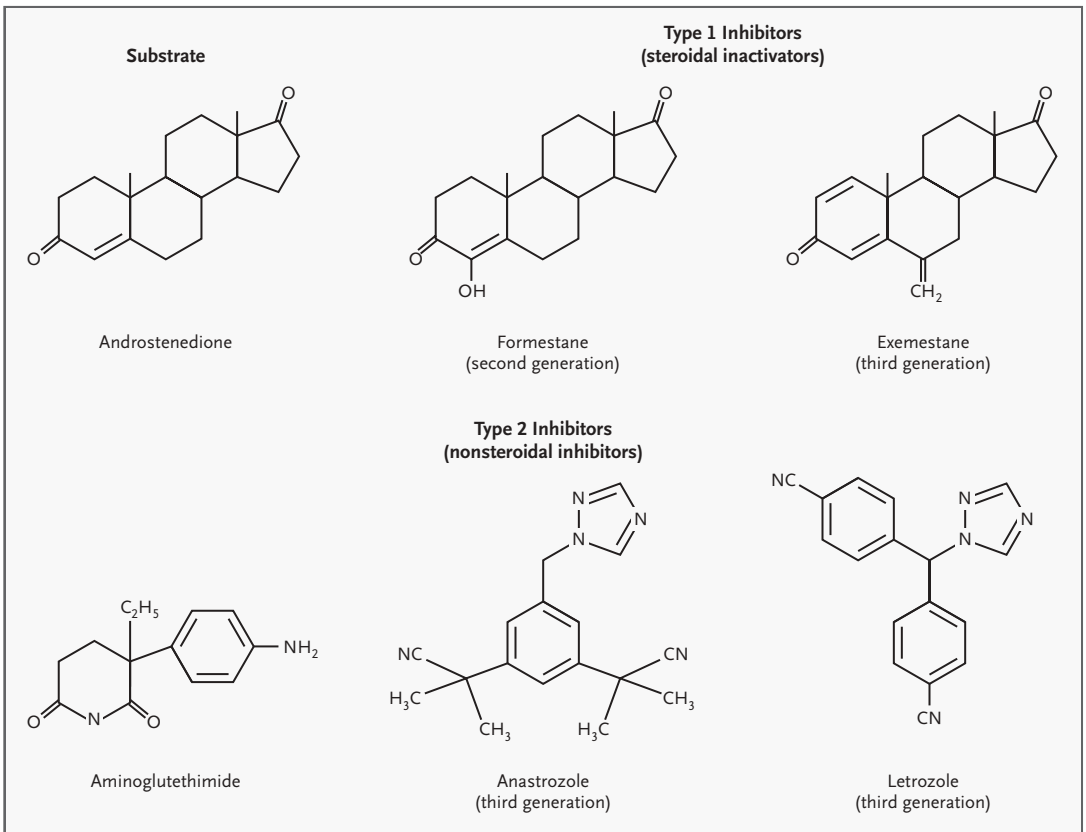

Figure 2. Structures of the Main Aromatase Inhibitors and the Natural Substrate Androstenedione.

with third-generation compounds than with earlier inhibitors: the mean degree of inhibition with anastrozole, exemestane, and letrozole at clinical doses is greater than 97 percent,[53,54] as compared with about 90 percent for aminoglutethimide.[55] The increased potency of the third-generation inhibitors is associated with better clinical efficacy than that offered by aminoglutethimide or the second-generation inhibitor fadrozole.[56-58]

Recently, subtle differences in potency between two of the third-generation inhibitors have been demonstrated. In a small, double-blind crossover trial, letrozole was associated with greater aromatase inhibition than anastrozole and lower plasma levels of estrone and estrone sulfate.[54]

Aromatase has intratumoral activity in the majority of breast carcinomas, and isotopic assays have shown that such activity contributes substantially to intratumoral estrogen levels; anastrozole, letrozole, and exemestane all markedly inhibit it.[59] However, the relative clinical significance of the effects of these agents on peripheral and intratumoral aromatase activity is unknown.

CURRENT CLINICAL ROLE

As already noted, the data reviewed in this article pertain solely to postmenopausal women; the use of aromatase inhibitors in premenopausal women with breast cancer who have normal ovarian function is contraindicated. Their use is also, in general, contraindicated in women with estrogen-receptor–negative and progesterone-receptor–negative cancer, given that such tumors are unresponsive to other forms of endocrine therapy.

ADVANCED DISEASE

First-Line Therapy

One of the most important recent developments in therapy for breast cancer has been the demonstration that letrozole and probably also anastrozole are superior to tamoxifen as first-line treatment for advanced disease. Previous trials in which tamoxifen was compared with other endocrine agents, including diethylstilbestrol,[1] progestins,[2-4] androgens,[5] other antiestrogens,[6,7] and first- and second-generation aromatase inhibitors,[8-12] consistently failed to show such a difference. By current standards, these trials were underpowered, and most of them were not blinded, but nevertheless their results were interpreted as suggesting that tamoxifen, through estrogen-receptor blockade, provided the maximal possible endocrine control of breast cancer. Results with the third-generation aromatase inhibitors have refuted this hypothesis and suggest further possibilities for the development of endocrine therapy.

Three key trials of aromatase inhibitors as first-line therapy[60-62] — all of them multicenter, double-blind studies involving patients whose tumors were hormone-receptor–positive (or of unknown receptor status) — have been published (Table 2). In the largest (a study involving 907 women, with a median follow-up of 18 months), letrozole resulted in more tumor regressions and was associated with a longer time to disease progression than tamoxifen (9.4 vs. 6.0 months; P=0.0001).[60] This benefit was significant irrespective of previous adjuvant treatment with tamoxifen, the site of disease, or knowledge of the estrogen-receptor status. In the other two trials, anastrozole was compared with tamoxifen, with conflicting results. One of them showed that anastrozole, like letrozole, resulted in a longer time to disease progression than tamoxifen (11.1 vs. 5.6 months; P=0.005) and a trend towards more tumor regressions.[61] The other, which was similar in design, failed to confirm these findings: for each outcome variable, anastrozole was as effective as tamoxifen but not superior.[62] Several reasons for these differences have been proposed, including differences in the proportions of patients whose estrogen-receptor status was unknown or who had previously received adjuvant tamoxifen therapy, but none of these explanations are entirely adequate. Trials comparing exemestane with tamoxifen as first-line treatment are under way; promising early results[65] have led to an expanded European trial.

In summary, in advanced disease, letrozole is clearly superior to tamoxifen as first-line therapy. For anastrozole, the data on superiority are contradictory, but the drug is convincingly at least as good as tamoxifen.

Second-Line Therapy

In the 1990s, the clinical importance of several third-generation inhibitors became clear when a series of trials showed them to be more effective than megestrol acetate as second-line therapy after tamoxifen, despite some variation in the study results[66-71] (Table 3). Trials of the second-generation inhibitors fadrozole and formestane and a trial of another third-generation agent, vorozole, now discontinued from clinical study, failed to show any such advantage.[41,72,73] The margin of additional

benefit with anastrozole, letrozole, and exemestane was generally small, and the results differed slightly among the drugs,[74] but they were all associated with a very low incidence of serious side effects and with less unwanted weight gain than megestrol acetate. In practice, developments in first-line therapy rapidly diminished the clinical relevance of these findings.

Table 2. Trials of Aromatase Inhibitors as Compared with Tamoxifen as First-Line Therapy.*

Reference	Drugs Studied	No. of Subjects	Response	Clinical Benefit†	Median Time to Progression
			%	%	*mo*
Mouridsen et al.[60]	Letrozole	453	30‡	49‡	9.4‡
	Tamoxifen	454	20	38	6.0
Nabholtz et al.[61]	Anastrozole	171	21	59‡	11.1‡
	Tamoxifen	182	17	46	5.6
Bonneterre et al.[62]	Anastrozole	340	33	56	8.2
	Tamoxifen	328	33	56	8.3
Eiermann et al.[63]§	Letrozole	154	55‡	—	—
	Tamoxifen	170	36	—	—
Ellis et al.[64]¶	Letrozole	17	88‡	—	—
	Tamoxifen	19	21	—	—

* Dashes indicate not applicable.
† Clinical benefit is shown as the total percentage of patients who had a response or whose disease stabilized for at least six months.
‡ There was a significant difference from the result with tamoxifen.
§ Eiermann et al.[63] compared letrozole and tamoxifen as preoperative therapy. Breast-conserving surgery was possible in 45 percent of the subjects receiving letrozole and 35 percent of those receiving tamoxifen.
¶ The data of Ellis et al.[64] refer to a subgroup from the study by Eiermann et al.[63] (positive for epidermal growth factor receptor or positive for HER2) receiving preoperative treatment.

EARLY DISEASE

Neoadjuvant Therapy

Trials of tamoxifen as an alternative to surgery in elderly women have consistently shown high rates of short-term tumor regression but poor long-term local control.[75] The option of endocrine therapy before, rather than instead of, surgery is more attractive, both as a means of down-staging primary cancers to avoid mastectomy[76] and as an in vivo measure of tumor responsiveness.[77] In small, nonrandomized studies in older women (age, 59 to 88 years) with large primary tumors (diameter, >3 cm), preoperative administration of anastrozole, letrozole, or exemestane has resulted in rates of tumor regression higher than those previously reported for tamoxifen.[78,79] However, in a small, randomized trial of preoperative therapy, no difference was found between vorozole and tamoxifen.[80]

Evidence confirming that letrozole is superior to tamoxifen as neoadjuvant therapy has recently come from a randomized, double-blind trial in which use of the two agents for four months before surgery was assessed in older patients (median age, 67 years) with estrogen-receptor–positive or progesterone-receptor–positive large breast cancers usually requiring a mastectomy. The patients assigned to letrozole had a higher rate of regression than those assigned to tamoxifen, and more of them had tumor regression sufficient to allow breast-conserving surgery[63,64] (Table 2).

There was also an unexpected and potentially important finding in a subgroup of patients whose tumors were available for further analysis: of 17 patients whose tumors overexpressed the cell-surface growth factor receptor c-ErbB-2 (HER2), c-ErbB-1 (epidermal growth factor receptor [EGFR]) or both, 15 (88 percent) had a response to letrozole, as compared with only 4 of 19 (21 percent) with a response to tamoxifen (Table 2).[64] These findings are consistent with the in vitro and in vivo observations that MCF-7 breast cancer cells and xenografts transfected with the c-*erbB*-2 gene do not grow without estrogen, whereas their growth continues in the presence of tamoxifen.[81] The results also support the concept of "crosstalk" between the signal-transduction pathways for steroids and those for growth factors.

These data on the use of letrozole for neoadjuvant therapy are preliminary, however, and require verification in additional trials of aromatase inhibitors for neoadjuvant therapy, which are currently under way. If those trials provide confirmatory data, they will support preoperative therapy with aromatase inhibitors as an effective and well-tolerated alternative to mastectomy for older patients with large, estrogen-receptor–positive cancers.

Adjuvant Therapy

Tamoxifen given for approximately five years after surgery to patients with early, estrogen-receptor–positive breast cancer is the current standard of care worldwide. This approach reduces the risk of death by about 25 percent, a reduction that translates into an absolute improvement in 10-year survival of more than 10 percent for patients with involved nodes and 5 percent for those without.[13] This seemingly limited increase translates into many thousands of lives saved annually and almost certainly has contributed to the decline in mortality from

Table 3. Trials of Aromatase Inhibitors as Compared with Megestrol Acetate as Second-Line Therapy.

Reference	Drugs and Daily Doses Studied	No. of Subjects	Response	Clinical Benefit*	Median Time to Progression	Median Overall Survival
			%	%	*mo*	*mo*
Buzdar et al.[68]	Anastrozole, 1 mg	263	10	35	4.8	Not given
	Megestrol acetate, 160 mg	253	8	34	4.8	Not given
Dombernowsky et al.[69]	Letrozole, 2.5 mg	174	24†	35	5.6	25
	Megestrol acetate, 160 mg	189	16	32	5.5	22
Buzdar et al.[70]	Letrozole, 2.5 mg	199	16	27	3†‡	29
	Megestrol acetate, 160 mg	201	15	24	3‡	26
Kaufmann et al.[71]	Exemestane, 25 mg	366	15	37	4.7†	Not reached†
	Megestrol acetate, 160 mg	403	12	35	3.8	28
Goss et al.[72]	Vorozole, 2.5 g	225	10	24	2.6	26
	Megestrol acetate, 160 mg	227	7	27	3.3	29

* Clinical benefit is shown as the total percentage of patients who had a response or whose disease stabilized for at least six months.
† There was a significant difference from the result with megestrol acetate.
‡ There was a significant difference from the result in the third group of subjects, who received 0.5 mg of letrozole (median time to progression, six months). Other data from this trial are not included in this table.

breast cancer seen over the past decade. It thus represents one of the main success stories in cancer medicine. However, the efficacy of tamoxifen is only partial. Furthermore, as described above, it is associated with an increased risk of uterine cancer — a risk that is small in absolute terms and far outweighed by the number of lives saved from breast cancer, but one that is very real in the public perception. Tamoxifen also increases the incidence of thromboembolism and often causes troublesome side effects, including hot flashes and vaginal discharge.[14] Thus, despite the benefits offered by tamoxifen, there is room for improvement.

The first trial of an aromatase inhibitor given as adjuvant therapy was started more than 20 years ago with aminoglutethimide. By today's standards, this study was very small, but it showed an early reduction in the risk of relapse or death; the reduction disappeared with longer follow-up.[82,83] In a more recent study, sequential administration of aminoglutethimide after tamoxifen therapy, as compared with tamoxifen alone,[84] was associated with a trend toward improved survival.

Trials of adjuvant therapy with the third-generation aromatase inhibitors began roughly seven years ago. Currently, there are at least 10 ongoing studies of the use of these agents in postmenopausal women; they are scheduled to recruit almost 40,000 participants, and more such studies have been planned. The designs of these trials differ, and among the key issues addressed are the use of these agents in direct comparison with tamoxifen, as combination therapy with tamoxifen, as sequential therapy with tamoxifen for a total of five years, and as maintenance therapy after five years of tamoxifen therapy. In the first and largest of these trials (Arimidex and Tamoxifen Alone or in Combination [ATAC] trial), which has three study groups, tamoxifen is being compared with anastrozole or with a combination of tamoxifen and anastrozole; 9366 patients have been enrolled. The first analysis, conducted at a median follow-up of 33 months, showed a small but statistically significant reduction in the rate of relapse with anastrozole as compared with tamoxifen: 89 percent of the patients assigned to anastrozole were relapse-free at 3 years, as compared with 87 percent of those assigned to tamoxifen (relative risk reduction, 17 percent; P=0.013).[85] The effect was seen only in patients whose tumors were known to be hormone-receptor–positive (relative risk reduction, 22 percent). So far, the ATAC trial has shown no differences in the rates of death from any cause, and there have been very few breast cancer-related deaths.

Of interest, the combination of anastrozole and tamoxifen in the ATAC trial has not been found to be superior to tamoxifen alone. A possible explanation is that tamoxifen saturates available estrogen

receptors and has partial agonist activity. The activated tamoxifen–estrogen-receptor complex cannot then be further modified by anastrozole-induced decreases in estrogen levels, and the anticancer effect remains the same as that provided by tamoxifen alone. Another finding, and one of potential relevance to breast-cancer prevention, is that the incidence of contralateral invasive breast cancer was significantly lower in the patients receiving anastrozole alone (0.3 percent [9 cancers]) than in those receiving tamoxifen alone (1.0 percent [30 cancers], P=0.001) or combined treatment (0.7 percent [23 cancers]).[85]

These findings are promising but preliminary. The absolute benefit in terms of freedom from relapse appears to be very small thus far, and no survival benefit has emerged. In addition, the anastrozole group has had a higher rate of fractures than the other two groups. No data on tolerability during five years of treatment with any of the inhibitors are so far available. Long-term problems with tamoxifen, especially uterine cancer, emerged only after many years' experience. It is our view that tamoxifen should remain the standard of care for most patients with early estrogen-receptor–positive breast cancer until further data become available. In patients with a history of thromboembolism, however, or those in whom tamoxifen is poorly tolerated, adjuvant therapy with anastrozole is now a useful alternative. This opinion is in accord with a recent American Society of Clinical Oncology evidence-based technology assessment,[86] which also appropriately advises against switching treatments in women who have already begun tamoxifen therapy. (Anastrozole has very recently been granted fast-track approval in the United States and elsewhere for adjuvant treatment of early hormone-receptor–positive breast cancer in postmenopausal women, particularly if tamoxifen is contraindicated.)

ADVERSE EFFECTS AND LONG-TERM RISKS AND BENEFITS

The third-generation aromatase inhibitors appear to be very well tolerated, with a remarkably low incidence of serious short-term adverse effects, reflecting the remarkable specificity of their action. The commonest of these effects are hot flashes, vaginal dryness, musculoskeletal pain, and headache, but they are usually mild. Comparative trials indicate that such adverse effects are very similar in nature and frequency to those of tamoxifen.[60-63] Data from the ATAC trial, by far the largest trial of adjuvant therapy (and one that is not confounded by tumor-related symptoms), indicate that both treatments are well tolerated; however, the patients receiving anastrozole had a significantly lower incidence of hot flashes, vaginal bleeding, vaginal discharge, and venous thromboembolism and a significantly higher incidence of musculoskeletal symptoms and fractures than those receiving tamoxifen (Table 4).[85]

Differences between the aromatase inhibitors and tamoxifen in long-term adverse effects are only starting to emerge. In contrast to findings with tamoxifen, there is no evidence to suggest an increased risk of uterine carcinoma with aromatase inhibitors (incidence, 0.1 percent, vs. 0.5 percent with tamoxifen) or venous thromboembolism (2.1 percent and 3.5 percent, respectively) (Table 4).[85]

Table 4. Incidence of Adverse Effects Associated with Anastrozole and Tamoxifen in the ATAC Trial.*

Adverse Effect	Anastrozole (N=3092)	Tamoxifen (N=3094)	P Value
	percent		
Hot flashes	34.3	39.7	<0.0001
Nausea and vomiting	10.5	10.2	0.7
Fatigue	15.6	15.2	0.5
Mood disturbance	15.5	15.2	0.7
Musculoskeletal disorder	27.8	21.3	<0.001
Vaginal bleeding	4.5	8.2	<0.001
Vaginal discharge	2.8	11.4	<0.001
Endometrial cancer	0.1	0.5	0.02
Fracture	5.9	3.7	<0.001
Hip	0.4	0.4	—
Spine	0.7	0.3	—
Wrist or radius (Colles' fracture)	1.2	0.8	—
Ischemic cardiovascular disease	2.5	1.9	0.14
Ischemic cerebrovascular event	1.0	2.1	<0.001
Any venous thromboembolic event	2.1	3.5	<0.001
Deep venous thromboembolic event, including pulmonary embolism	1.0	1.7	0.02
Cataract	3.5	3.7	0.6

* The table is modified from the ATAC Trialists' Group,[85] with the permission of the publisher. ATAC denotes Arimidex and Tamoxifen Alone or in Combination, and dashes indicate not available.

SKELETAL EFFECTS

The risk of important long-term skeletal problems, including osteoporosis, may increase with the use of aromatase inhibitors. The maintenance of bone density depends in part on estrogen. Tamoxifen reduces bone demineralization through its agonist effect, at least in postmenopausal women,[20,21] whereas aromatase inhibitors may enhance this process by lowering circulating estrogen levels. Short-term use of letrozole has been shown to be associated with an increase in bone-resorption markers in plasma and urine,[87,88] and (as mentioned earlier) adjuvant therapy with anastrozole appears to be associated with a higher incidence of fractures than adjuvant therapy with tamoxifen.[85] However, it is possible that osteopenia might be prevented or modified with concurrent use of bisphosphonates.[89]

CARDIOVASCULAR EFFECTS

The cardiovascular effects of aromatase inhibitors are currently unknown. Tamoxifen appears to be estrogenic in this regard; in postmenopausal women it reduces the level of low-density lipoprotein cholesterol but causes high-density lipoprotein cholesterol to rise.[90,91] Whether such effects on lipids translate into clinical gain remains uncertain. Some trials have suggested that tamoxifen is associated with a reduction in coronary artery disease,[92-94] but so far such findings have not been confirmed, either in an overview[13] or in a large chemoprevention trial.[14] In contrast, the estrogen-lowering effects of aromatase inhibitors may prove to have an adverse effect on blood lipids: one small, short-term study in postmenopausal women with breast cancer has shown an increase in total serum cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and serum-lipid risk ratios for cardiovascular disease after 16 weeks of letrozole treatment.[95] The effect of aromatase inhibitors on lipids remains an important area for further research.

EFFECTS ON COGNITION

The brain is rich in estrogen receptors and contains aromatase,[26] and it has been suggested that estrogen-replacement therapy is associated with a reduced risk of Alzheimer's disease.[96] The results of randomized trials on the cognitive effect of estrogen in postmenopausal women are conflicting, but in one study estrogen replacement improved brain-activation patterns during working-memory tasks.[97] The long-term effects of aromatase inhibitors on cognitive function are unknown, and a great deal of careful follow-up will be required to assess this issue.

HORMONE-REPLACEMENT THERAPY AND ADJUVANT BREAST-CANCER THERAPY

Menopausal symptoms are an important source of morbidity in patients with breast cancer. Traditional wisdom has argued against the use of hormone-replacement therapy in such patients, but recently this belief has been challenged. Retrospective analyses have failed to confirm any increased risk of recurrence in women using hormone-replacement therapy after treatment for breast cancer,[98,99] and prospective trials are now addressing this issue. Theoretically, hormone-replacement therapy could be given in conjunction with adjuvant therapy with tamoxifen, on the basis of the efficacy of tamoxifen in premenopausal women, who have high circulating levels of estrogens. In contrast, hormone-replacement therapy would negate the action of aromatase-inhibitor therapy, and the combination would therefore be illogical.

On balance, therefore, the potential gains in efficacy with the aromatase inhibitors as compared with tamoxifen should be weighed carefully against the long-term risks and short-term quality-of-life issues associated with hormone-replacement therapy. For some women at relatively low risk of recurrence, a decision on the balance between efficacy and side effects may be difficult, since background information is currently inadequate.

CHEMOPREVENTION

A substantial body of evidence supports the role of estrogen in the development of breast cancer.[100] Such evidence includes data from prospective studies relating plasma sex-steroid levels to the risk of subsequent breast cancer.[101] Chemoprevention with aromatase inhibitors might be particularly suitable for women with relatively high plasma estrogen levels. Two chemoprevention trials have already shown that tamoxifen reduces the incidence of breast cancer,[14,15] and previous trials of adjuvant tamoxifen have likewise shown an almost 50 percent reduction in the development of cancer in the contralateral breast.[13] The results of the ATAC trial with regard to the development of contralateral invasive breast cancer (in 30 [1.0 percent] of those receiving tamoxifen vs. 9 [0.3 percent] of those receiving anastrozole after a median of 33 months of

follow-up) suggest, by extrapolation, that anastrozole might reduce the early incidence of breast cancer to an even greater extent and thus have more potential in chemoprevention than tamoxifen.

Strategies to avoid the anticipated loss of bone density induced by aromatase inhibitors would first need to be developed. An alternative approach might be to use a much smaller dose of aromatase inhibitor in order to lower the levels of circulating estrogens but not obliterate them. Such an approach might offer a substantial chemopreventive effect and reduce the risk of serious long-term complications.

OTHER ISSUES

IS THERE A BEST THIRD-GENERATION AROMATASE INHIBITOR?

Letrozole resulted in greater inhibition of aromatase than anastrozole in a crossover pharmacodynamic trial,[54] and evidence of the superiority of letrozole over tamoxifen in advanced disease is solid. Preliminary data from a comparative trial of these two inhibitors in advanced breast cancer after tamoxifen are confusing: letrozole was associated with significantly more tumor regressions overall than anastrozole, but not in the subgroup with known estrogen-receptor–positive tumors.[102] There are no comparative data on exemestane, although occasional further responses have been reported for it and the second-generation inhibitor formestane in patients with relapses after therapy with anastrozole, letrozole, or the other nonsteroidal inhibitors.[103,104] This absence of total cross-resistance is not explained by the degree of estrogen suppression and must involve other biochemical effects. Overall, current circumstantial evidence suggests that there are unlikely to be major clinical differences among these agents.

AROMATASE INHIBITORS IN COMBINATION WITH CHEMOTHERAPY

No studies have compared concurrent use of aromatase inhibitors and chemotherapy with sequential use. The concurrent use of tamoxifen and chemotherapy increases the risk of thromboembolism,[105] but this problem does not appear to occur with the aromatase inhibitors.

CONCLUSIONS

The third-generation aromatase inhibitors are a new development in the endocrine treatment of estrogen-receptor–positive breast cancer in postmenopausal women. In the treatment of advanced disease, letrozole is convincingly better than tamoxifen, and anastrozole is at least as good. In early breast cancer, adjuvant therapy with anastrozole already appears to be superior to adjuvant therapy with tamoxifen in reducing the risk of relapse, and letrozole appears to be more effective than tamoxifen as preoperative therapy. It is possible that third-generation aromatase inhibitors will have a future role in chemoprevention, but the long-term effects of profound estrogen suppression in postmenopausal women are unknown, and careful monitoring for bone demineralization and other potential problems is essential as their role evolves.

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