



Aromatase inhibitors now play a major role in managing patients with both localized and advanced hormone receptor-positive breast cancer.

Leonora Carrington. *Ox*, 1996-98. Intaglio, 16¾" × 19¾". Courtesy of Graphicstudio/USE

Aromatase Inhibitors in Breast Cancer: An Update

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Background: *Tamoxifen has been the endocrine treatment of choice for patients with breast cancer. The development of selective aromatase inhibitors has offered an alternative management approach for patients in whom a hormonal approach is indicated.*

Methods: *The authors reviewed reports in which aromatase inhibitors were compared with tamoxifen for the treatment of metastatic disease, as well as information pertinent to their use as adjuvant therapy.*

Results: *Both nonsteroidal (anastrozole and letrozole) and steroidal (exemestane) aromatase inhibitors for metastatic disease appear to provide superior efficacy and a better toxicity profile in first- and second-line treatment of metastatic disease than tamoxifen. Early results from the ATAC trial suggest anastrozole is superior to tamoxifen for disease-free survival, particularly in receptor-positive patients, and in reducing the incidence of contralateral breast cancer.*

Conclusions: *Aromatase inhibitors have important roles in optimal management of postmenopausal patients with hormone-responsive metastases in both the adjuvant and advanced-disease settings.*

Introduction

Endocrine therapy is the oldest, safest, and best-established systemic treatment for breast cancer, with utility in all stages of disease. Initially used to treat

metastatic disease, it later became a critical component of adjuvant and neoadjuvant treatment.¹ Most recently, hormonal therapies have demonstrated a role in preventing recurrence of noninvasive disease and in preventing breast cancer outright.² The mechanisms of action of endocrine therapies are threefold: they may lower the estrogen level in the tumor (oophorectomy, aromatase inhibitors), they may modulate estrogen receptors (SERMS [tamoxifen, toremifene]), or they may modulate the estrogen receptor (ER) with pure agonist activity, eg, ER down-regulator (fulvestrant). Although high-dose estrogens, progestins, and androgens have activity against ER+ tumors, the exact mechanism of action is unclear. This article focuses on recent devel-

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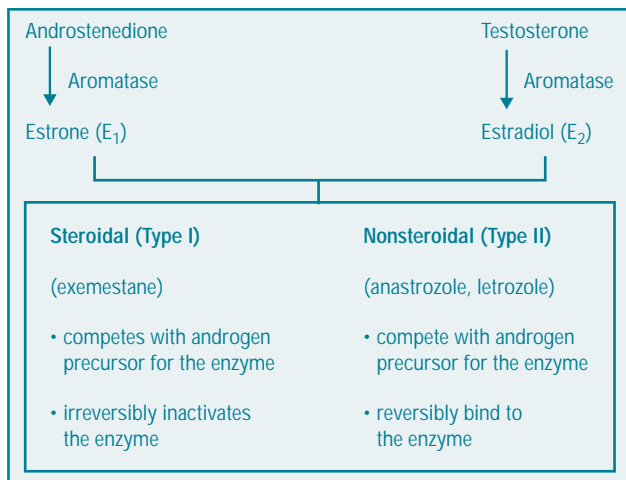


Fig 1. — Third-generation aromatase inhibitors: mechanism of action.

opments in the use of aromatase inhibitors and reviews their roles in the management of breast cancer.

In spite of the numerous choices in endocrine therapies, tamoxifen has remained the “gold standard” of first-line hormonal therapy in patients who have tumors expressing hormone receptors and who have had either no prior tamoxifen exposure or a long hiatus between adjuvant tamoxifen and the metastatic presentation. Tamoxifen was initially approved in the 1970s as treatment for metastatic breast cancer,³ and in 1986, it was approved for adjuvant therapy in postmenopausal women with node-positive breast cancer. In 1990, tamoxifen received approval as adjuvant therapy in pre- and postmenopausal women with node-negative disease.⁴ In the 1990s, it was demonstrated to be effective in breast cancer prevention and in the treatment of ductal carcinoma in situ.⁵ Tamoxifen has been available for more than 20 years, and through multiple clinical trials, we have defined the population that benefits from its use, the long-term toxicity profile, and a standard dose and schedule.

Since virtually all patients with metastatic disease will eventually progress on tamoxifen, additional hormonal treatments are needed. Historically, nonselective aromatase inhibitors offered an option, but their toxicity was limiting and a progestin (megestrol acetate)

was frequently employed following tamoxifen. The recent development of selective aromatase inhibitors has changed the options and approach for patients in whom treatment with tamoxifen has failed.

Aromatase inhibitors lower the level of estrogen in the tumor. In postmenopausal women, the primary estrogen source is derived from conversion of androstenedione (produced by the adrenals) to estrone and estradiol in the peripheral tissues, including skin, adipose tissue, and breast. Because premenopausal women have such robust estrogen production in the ovaries, these agents are not effective in these women. The enzyme responsible for the conversion is aromatase. Aromatase inhibitors block the conversion of androstenedione to estrone and testosterone to estradiol (Fig 1). Earlier aromatase inhibitors also affected adrenal corticosteroidal metabolism, resulting in marked toxicities. Currently, three selective aromatase inhibitors are available in the United States that offer significant safety advantages over their nonselective predecessors. These new agents are divided into two categories: steroidal/irreversible and nonsteroidal/reversible inhibitors of estrogen synthesis. The nonsteroidal aromatase inhibitors are anastrozole and letrozole, and the steroidal compound is exemestane (Fig 2). Both classes reduce circulating estrogen to 1% to 10% of pretreatment levels.⁶ Issues involving the indications for aromatase inhibitors in the treatment of breast cancer concern their roles in adjuvant therapy, treatment of metastases, and prevention.

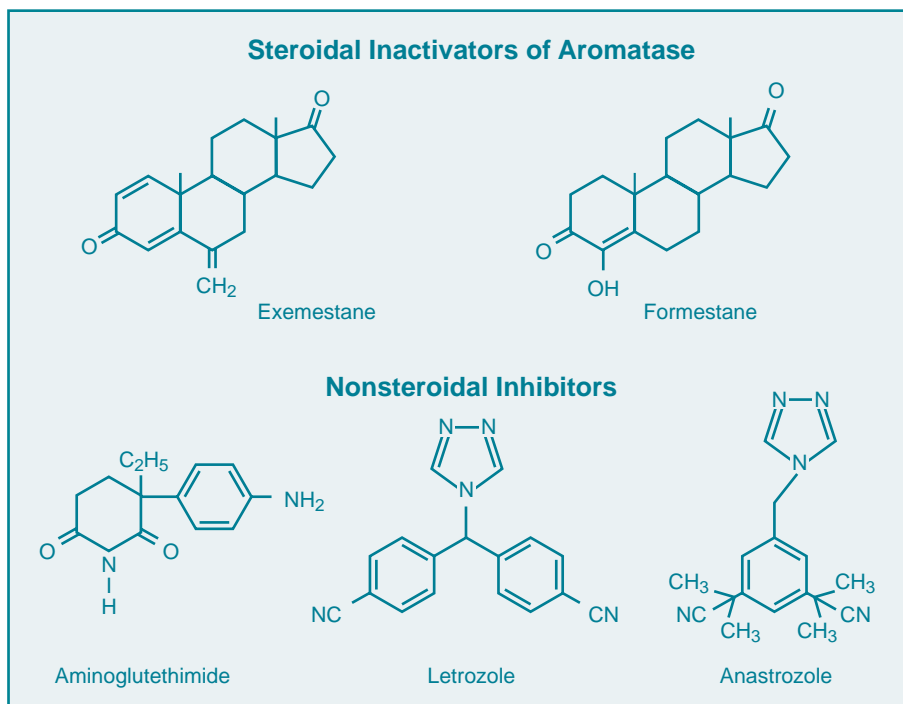


Fig 2. — Structures of aromatase inhibitors. From Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. *J Clin Oncol.* 2001;19:881-894.

It is important to recognize whether the aromatase inhibitor that is chosen for treatment is of a steroidal or nonsteroidal nature because there is a relative lack of cross-resistance between these two classes; clinical benefits may occur when a nonsteroidal aromatase inhibitor is prescribed following a steroidal agent, and vice versa. There is benefit from anastrozole given after exemestane⁷ and also from exemestane given after anastrozole.⁸

Aromatase Inhibitors vs Tamoxifen

The currently available aromatase inhibitors have been compared with tamoxifen⁹⁻¹⁴ in randomized trials for the treatment of metastatic disease (Table 1), as well as with megestrol⁸ and the nonselective aromatase inhibitor, aminoglutethimide.

The Target trial⁹ was a randomized study comparing anastrozole 1 mg vs tamoxifen 20 mg. Eligibility for this trial included patients with metastatic breast cancers that were ER+ or unknown. Of the 668 patients studied, 340 were randomized to anastrozole and 328 to tamoxifen. More than half had tumors of unknown receptor status. The objective response rate was 33% in both arms; time to progression was 8.2 months in the anastrozole arm and 8.3 months in the tamoxifen arm. No statistically significant difference was demonstrated.

A similar North American study¹⁰ evaluated patients with tumors that were ER+ or ER-/PR+. Of the 353 evaluable patients, 182 were treated with 20 mg of

tamoxifen alone and 171 with 1 mg of anastrozole. The response rate was 17% in the tamoxifen arm and 21% in the anastrozole arm, a statistically nonsignificant result. Time to progression was 5.6 months in the tamoxifen arm and 11.1 months in the anastrozole arm ($P=.005$).

The Barcelona trial¹¹ evaluated 238 patients who were ER+. The two arms consisted of 40 mg of tamoxifen daily given to 117 patients and 1 mg of anastrozole given to 121 patients. Response rates were not statistically different: 23% in the tamoxifen arm and 34% in the anastrozole arm. However, time to progression was 5 months in the tamoxifen arm vs 9 months in the anastrozole arm ($P\leq.05$).

Hence, several randomized trials have confirmed similar or perhaps greater benefit for anastrozole compared with tamoxifen, the “gold standard.” In these studies, anastrozole did not appear to be more toxic than tamoxifen, and in many cases it appeared safer.

The European Organization for Research and Treatment of Cancer (EORTC) reported a randomized phase II trial of exemestane vs tamoxifen.¹³ Fifty-six patients received 20 mg of tamoxifen, and 56 received 25 mg of exemestane. The response rate for exemestane was 44%, and the response rate for tamoxifen was 14% ($P\leq.05$).

A trial comparing the aromatase inhibitor letrozole with tamoxifen as first-line treatment for advanced breast cancer (Protocol 025) was reported by Mourid-

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sen et al¹² and subsequently was updated at the San Antonio Breast Conference with a median follow-up of 33 months.¹⁴ The study population consisted of 907 postmenopausal, locally advanced, locoregionally recurrent, or metastatic breast cancer patients with tumors that were ER+ and/or PR+ or unknown. In this double-blind, randomized trial, patients were treated with either tamoxifen 20 mg daily or letrozole 2.5 mg daily and, at the time of progression, had an option to cross over to treatment with the “opposite” drug. If after progression of disease or stopping treatment the patient remained suitable for further endocrine therapy, changing to the alternative treatment in a double-blind fashion was optional (crossover). Crossover upon disease progression occurred in 52% of patients in the letrozole arm and in 50% in the tamoxifen arm. The median time to crossover in the letrozole group was 17 months compared with 13 months in the tamoxifen group. Hence, time to progression, which was the primary endpoint of the study, favored the first-line use of letrozole instead of tamoxifen. Secondary endpoints were overall response rate (ie, a confirmed complete or partial response), duration of objective response, rate of clinical benefit (defined as a confirmed CR or PR or no change for ≥ 24 weeks), duration of the clinical benefit, time to treatment failure, overall survival, and safety/tolerability. The study arms were evenly populated, with 453 patients using letrozole and 454 using tamoxifen. The groups were well balanced in terms of age, performance status, disease-free survival, dominant sites of disease, and hormone receptor status (65% of patients were hormone receptor-positive for letrozole vs 67% for tamoxifen). Prior chemotherapy and prior adjuvant antiestrogen therapy was 19% on letrozole and 18% on tamoxifen. The median time to progression, which was the primary endpoint, was 9.4 months in the letrozole arm and 6 months in the tamoxifen arm ($P=.0001$). The percentage of patients progressing was 79% letrozole and 85% tamoxifen, with a hazard ratio of 0.72 ($P\leq .0001$). The time to treatment failure was 9 months in the letrozole arm and 5.7 months in the tamoxifen arm, with a hazard ratio of .73 ($P\leq .0001$). As of September 2001, 11% of patients were still receiving initial treatment of letrozole in the letrozole arm vs 6% in the tamoxifen arm. Response to letrozole was independent of prior adjuvant therapy. Patients in the tamoxifen arm with prior exposure to tamoxifen had low response rates. Letrozole was superior to tamoxifen in the overall response and clinical benefit rate: 32% CR and PR vs 21% (odds ratio, 1.78). Clinical benefit was documented in 50% of patients treated with letrozole and 38% in those treated with tamoxifen, with an odds ratio of 1.62. However, the median duration of response was short. The median time to chemotherapy was 16 months for letrozole and 9 months for tamoxifen ($P=.005$). The medi-

an overall survival was 34 months in the letrozole arm and 30 months in the tamoxifen arm, although the impact of crossover appeared to be significant early on. By 36 months, 99% of the patients had crossed over, and this likely affected the overall survival outcome. With censoring the survival curve at the time of crossover, letrozole was reported to have a median survival of 42 months and tamoxifen 30 months. Of those who did not cross over, median survival for letrozole was 33 months and 19 months for tamoxifen.

Drug toxicity is an important variable in the choice of therapy for stage IV disease, and letrozole and tamoxifen appear similar in terms of nausea, vomiting, and hot flushes. The incidence of hot flushes was 14% with tamoxifen vs 17% with letrozole; nausea was reported in 7% with tamoxifen vs 6% with letrozole. Alopecia and hair thinning were slightly greater with the aromatase inhibitors, which may be due to the increase in circulating androgens with the use of letrozole.^{12,14}

Thrombotic events are another area of concern. These events include phlebitis and venous thrombosis of a limb (deep venous thrombosis and superficial venous thrombosis). Considering all of the thrombotic adverse events, the results are similar with tamoxifen and the aromatase inhibitors. Significant adverse thrombotic events occurred at a rate of 1% for letrozole and 2% for tamoxifen.

Combining these data, we can conclude that in postmenopausal patients with ER+ metastatic breast cancer, the overall response rate with aromatase inhibitors is at least as high as — and sometimes higher than — tamoxifen, and the time to progression is often longer with aromatase inhibitors than with tamoxifen. Survival is similar, but the toxicity profiles of these endocrine agents tend to favor the aromatase inhibitors.

Adjuvant Therapy

Having demonstrated meaningful activity in postmenopausal patients with metastatic breast cancer, the use of an aromatase inhibitor in adjuvant therapy was the next logical step. The purpose of adjuvant hormonal therapy in breast cancer is to prevent recurrence and to improve survival in patients with hormone receptor-positive disease. These effects have been well documented with tamoxifen.¹⁵⁻¹⁷ Tamoxifen received FDA approval in 1986 as adjuvant therapy in node-positive postmenopausal women with breast cancer,⁴ and in 1990, tamoxifen was approved for women of any age with node-negative disease, as long as hormone receptors were positive or unknown.

Such benefits seem additive to prior chemotherapy, and tamoxifen decreases the risk of contralateral breast cancer.¹⁵ The optimum length of treatment with tamoxifen appears to be 5 years, which is superior to treatment for 1 or 2 years and may be superior to longer durations.^{15,18} Ten years of treatment have not been shown to be better than 5 years, but additional studies are pending.^{19,20} Benefits seem to persist beyond the completion of therapy — a so-called “carryover effect” — with a lower risk of recurrence and death beyond the end of active treatment. The absolute overall survival benefit with tamoxifen at 10 years is 5.6% in patients with negative axillary nodes and 10.9% in patients with positive axillary nodes.^{4,15}

The toxicities of tamoxifen have been well documented. These include hot flushes, vaginal discharge, increased risk of thrombotic events, increased risk of endometrial cancer and uterine sarcoma, and a probable increased risk of cerebral vascular disease. In the adjuvant setting, these toxicities assume even greater importance than for treatment of metastatic disease. Given the millions of patient-years of experience with tamoxifen and its proven efficacy and safety, any newer hormonal therapy in the adjuvant setting must demonstrate at least equal efficacy to tamoxifen and fewer side effects to gain acceptance and broad use.

It is noted that there are other established hormonal adjuvant therapies in addition to tamoxifen, including ovarian ablation or suppression in premenopausal women with hormone receptor-positive breast cancer, as well as data supporting other SERMS, the nonselective aromatase inhibitors, and aminoglutethimide.²¹⁻²³

The aromatase inhibitors are being tested for efficacy as adjuvant therapy in three different randomized trial designs: to compare directly with tamoxifen, to test the hypothesis of an additive effect following tamoxifen, and to compare first-line sequential hormonal therapy of tamoxifen followed by an aromatase inhibitor or vice versa each for a period of 5 years.

The availability of the modern selective aromatase inhibitors, given their promising results in the metastatic setting and coupled with increased experience and understanding of the need for adequately powered adjuvant therapy trials, led to the ATAC trial (Fig 3).²⁴ This trial was designed to address a comparison between tamoxifen and anastrozole as single agents and between tamoxifen and a combination of the two drugs. A total of 9,366 postmenopausal women with invasive breast cancer completed the primary therapy of the breast and were then randomized to one of three arms: (1) anastrozole 1 mg daily plus tamoxifen placebo (3,125

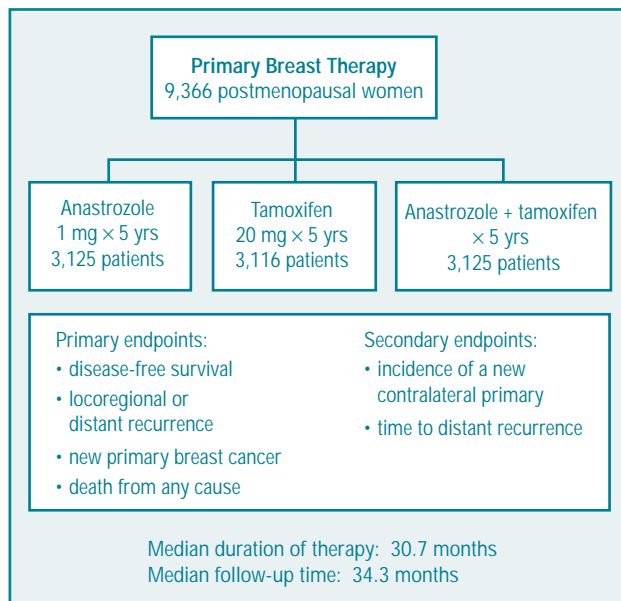


Fig 3. — Trial design: ATAC (Arimidex, Tamoxifen, Alone or in Combination).

patients), (2) anastrozole placebo plus tamoxifen 20 mg daily (3,116 patients), and (3) anastrozole plus tamoxifen (3,125 patients). Treatment was planned for 5 years. Among the multiple primary endpoints included in the first-event analysis planned for this trial were disease-free survival, locoregional and distant recurrence, new primary breast cancer, or death from any cause. Safety and tolerability were also evaluated. Secondary endpoints included the incidence of a new contralateral primary breast cancer and the time to distant recurrence. The survival of the hormone receptor-positive population was a protocol-defined subgroup. Although initial data have been reported, survival data will not mature for approximately 2 more years. With respect to median patient age, weight, hormone receptor status, and primary treatment, which included surgery and chemotherapy, the treatment arms were similar. A small percentage of patients had received prior tamoxifen. The majority of the patients in the trial had T2 tumors or smaller, and one third of the patients were node positive. Approximately one fifth received chemotherapy in addition to study medication.

Reporting of the first analysis required 1,056 events to occur, and data reported at the San Antonio Breast Cancer Symposium was based on 1,079 events.^{24,25} The total number of first events in the receptor-positive population was 766. The median duration of therapy was 30.7 months, and the median follow-up time was 34.3 months. Kaplan-Meier curves of the intent-to-treat population for disease-free survival demonstrated an advantage in patients treated with anastrozole in comparison to those treated with tamoxifen alone or in combination. The disease-free survival at 3 years was 89.4% with anastrozole and 87.4% with

tamoxifen (hazard ratio, 0.83; 95% confidence interval [CI], 0.71 to 0.96, $P=.013$). The combination-therapy arm had similar results to the tamoxifen-alone arm. Analysis of first events in this population showed that 317 events occurred in patients treated with anastrozole, 379 events in patients treated with tamoxifen, and 383 events in patients treated with both drugs. Distant disease comprised the majority of the first events. Of note, contralateral invasive and noninvasive breast cancer occurred to a greater degree in both the combination and tamoxifen arms: 30 and 23 events, respectively, vs 9 events in the anastrozole arm. Deaths from other reasons were similar in all groups: 78 patients on anastrozole, 81 on tamoxifen, and 70 on the combination. In receptor-positive patients, the hazard ratio for disease-free survival was greater with anastrozole (.78) compared with the combination of anastrozole and tamoxifen (1.02). A subanalysis of time to first new contralateral breast primary demonstrated an advantage for anastrozole compared with either the combination or tamoxifen arms, which were similar to each other. Fewer musculoskeletal disorders and fractures occurred in the tamoxifen group.

Early results from the ATAC trial indicate that anastrozole is superior to tamoxifen regarding disease-free survival in the overall population and particularly in the receptor-positive subpopulation of patients, as well as in terms of reducing the incidence of contralateral breast cancer in the overall population. All of the treatment arms were generally well tolerated. Advantages of anastrozole over tamoxifen appear to be a lower risk of endometrial carcinoma and a lower incidence of vaginal side effects such as bleeding and discharge. Also, fewer ischemic cerebral vascular events, fewer thrombotic events (including deep vein thrombosis), less weight gain, and fewer hot flushes were reported.

From the ATAC trial, we may conclude that at a median treatment duration of 2.5 years, anastrozole appears to be superior to tamoxifen in terms of efficacy and tolerability. However, a complete risk-benefit analysis needs longer follow-up with particular attention to issues of overall survival and specific toxicities such as coagulopathy, cognition, and bone density. Based on the ATAC trial, the FDA has approved anastrozole for use as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer.

An important question that may arise from the results of the ATAC trial and other pending studies is whether a patient should change treatment from tamoxifen to an aromatase inhibitor in the adjuvant setting. It is noted that the ATAC trial does not address this question, but ongoing trials with a sequential therapy design will do so. One such trial is the European Breast Inter-

national Group BIG 01-98, a randomized trial of early-stage ER+ or PR+ patients to one of four arms: (1) tamoxifen for 5 years, (2) letrozole for 5 years, (3) tamoxifen for 2 years followed by letrozole for 3 years, and (4) letrozole for 2 years followed by tamoxifen for 3 years.²⁶ The NCCTG-CAN-MA-17 trial,²⁷ an intergroup study that completed accrual of 4,800 postmenopausal women in the spring of 2002, randomized patients to receive 5 years of letrozole or a placebo after they completed 5 years of tamoxifen. The endpoints are disease-free/overall survival and the issues of quality of life and safety. Results are pending, but at present no direct evidence suggests that patients should be switched from tamoxifen to an aromatase inhibitor outside of a clinical trial. However, if patients have unacceptable toxicity with tamoxifen and have not completed 5 years of adjuvant hormonal therapy, such a switch might be justified based on the indirect evidence discussed.⁴

Prevention

One of the endpoints of the ATAC trial — new invasive breast cancer incidence — suggests that prevention strategies with the aromatase inhibitors warrant investigation. In the ATAC trial, anastrozole compared with tamoxifen was associated with a 58% reduction in the incidence of contralateral invasive breast cancer.²⁵ Three ongoing pilot programs are testing this preventive role (Table 2).²⁸⁻³⁰

The Royal Marsden Hospital²⁸ is conducting a study of 29 postmenopausal, healthy women treated with letrozole. Study parameters include breast cell proliferation, bone density, and lipid metabolism. Increase in bone resorption was documented after 3 months of treatment with letrozole.

Memorial Sloan-Kettering Cancer Center²⁹ has an ongoing clinical trial for postmenopausal women with stage 0 to III breast cancer who have had no prior anti-estrogen therapy. Hence, most of these patients are ER-. They are being treated with a combination of the aromatase inhibitor exemestane and the SERM raloxifene. The endpoints are bone and lipid changes and second breast cancer incidence. The correlative science component to this study is breast cell proliferation. This group of 30 planned patients was targeted for endocrine therapy as a pilot study only. The investigator is aware that most hormone receptor-positive patients are treated with tamoxifen in the adjuvant setting. However, with endpoints of bone density, lipid profile changes, and breast cell proliferation, hormone receptor-negative patients may clearly be studied. The issues addressed by this pilot study are somewhat different from those in the ATAC trial, where the combi-

Table 2. — Selected Studies of Aromatase Inhibitors for Prevention of Breast Cancer

Ongoing Trials	No. of Patients	Patient Population	Drug	Study Parameters
Royal Marsden Hospital ²⁸	29	Postmenopausal, healthy	Letrozole	Breast cell proliferation Bone mineral density Lipid metabolism
Memorial Sloan-Kettering Cancer Center ²⁹	30*	Postmenopausal, early-stage breast cancer (ER-) or ductal carcinoma in situ	Exemestane/raloxifene	Bone mineral density Lipid metabolism Second breast cancer incidence Breast cell proliferation
Aromasin Prevention Study (ApreS) ³⁰	666*	Women with BRCA1/2 mutations	Exemestane vs placebo	Incidence of breast cancer in high-risk group

*target number

nation arm, consisting of tamoxifen and anastrozole, demonstrated no improvement over tamoxifen alone.

The ApreS group (Aromasin Prevention Study)³⁰ is a randomized trial for women with BRCA1/BRCA2 mutations. The anticipated number of patients to accrue is 666. These patients will be treated with either exemestane or placebo.

In addition, the NSABP B-35 study randomizes patients with breast-conserving therapy to treatment with either tamoxifen or anastrozole.

Aromatase Inhibitors and HER2 Overexpression

Several provocative observations have addressed the potential interaction between HER2 expression level and response or benefit from hormonal treatment for breast cancers.³¹⁻³⁶ Ellis et al³⁴ reported a randomized neoadjuvant trial comparing preoperative tamoxifen with preoperative letrozole. Thirty-nine patients had HER1 or HER2 overexpressing tumors, and the response to treatment was 69% in the letrozole-treated group vs 17% in the tamoxifen-treated group. Further subanalysis of the hormone receptor-positive plus HER1- or HER2-positive patients was associated with an 88% response to letrozole and a 21% response to tamoxifen.

Lipton³⁵ reported a retrospective serum analysis from a trial of letrozole vs tamoxifen for metastatic breast cancer. Twenty-nine percent of the patients had elevated serum levels of HER2, defined as an extracellular domain concentration of greater than 15 ng/mL. Overall response rate, clinical benefit, and time to treatment failure were reduced in patients with increased HER2 levels in contrast to those with normal levels. In patients with elevated levels, there

appeared to be no difference in any outcome measured for patients treated with letrozole or tamoxifen. Lipton and colleagues³⁷ recently published a larger analysis of serum from 719 patients who had been randomized in three comparable second-line endocrine therapy trials. Results have lent further support to the conclusion that HER2 is a molecular marker that predicts decreased response to hormonal therapy in breast cancer. In this study, all patients had metastatic disease. Hormonal therapy received included megestrol acetate vs fadrozole (in two studies) and megestrol acetate vs letrozole (in one study). The overall chance of achieving a clinical benefit from hormonal therapy was noted to be lower by 50% if serum levels of extracellular domain were elevated (ie, >15 ng/mL). The response rate (CR, PR, and stable disease) was 23% for those with elevated serum HER2 vs 45% for those with normal levels. The median response duration was 11.7 months in patients with elevated serum HER2 levels and 17.4 months in those with normal levels. The time to progression and the time to treatment failure were also significantly shorter (3 vs 6 months, $P < .0001$) in the patients with elevated levels. The mechanism of action for this effect is being studied. Lipton et al³⁷ offer as a possible mechanism of action the enhanced phosphorylation of both serine and tyrosine residues in the ER, as well as the activation of the RAS/MAPK signaling pathway in breast cancer with HER2 overexpression. Both of these may interfere with the inhibitory effect of tamoxifen on ER transcription.

Colomer et al³⁶ reported a prospective trial addressing this issue. Eligible patients were postmenopausal, with tumors that were ER+ or PR+. All of the patients had prior tamoxifen exposure. The endpoint of this study was time to treatment failure on letrozole in HER2 overexpressors in contrast to HER2 nonoverexpressors. The serum level of the extracellular domain was considered positive if it was 30 ng/mL or greater. Of the

211 evaluable patients, 16 (8%) had HER2 overexpression. Time to treatment failure was 5.6 months in HER2-overexpressing patients and 11.6 months in HER2-normal patients ($P=.005$), which is consistent with the possibility that HER2 expression influences the amount of benefit from hormonal treatment.

In situations where an aromatase inhibitor is selected for use, a difficult question concerns which agent is preferred among the three available — anastrozole, letrozole, or exemestane. One trial designed to answer this question is ongoing and needs further analysis. The trial FEMINT-01³⁸ enrolled 713 postmenopausal, hormone receptor-positive women with metastatic or locally advanced breast cancer after failure on tamoxifen. These patients were randomly assigned to treatment with letrozole 2.5 mg per day (356 patients) or anastrozole 1 mg daily (357 patients). For the primary endpoint (time to treatment failure), no difference was seen. For one secondary endpoint (response rate), there was an advantage for letrozole, although this was only seen in the slight majority of patients whose tumors had unknown receptor status. In receptor-positive patients, anastrozole and letrozole had comparable antitumor activity. The significance of this result in communities where knowledge of receptor status is nearly 100% is uncertain. Currently, there is no clearly demonstrated difference in efficacy between these two nonsteroidal aromatase inhibitors.

Provocative preclinical data suggest that exemestane, the steroidal aromatase inhibitor, may protect against bone mineral loss.²³ If confirmed in ongoing clinical trials, this may be an important criterion in selecting among these agents in the adjuvant setting. On the other hand, infrequent dosing with an intravenous bisphosphonate, or continued use of an oral one, may mitigate the negative impact of any of the aromatase inhibitors on bone metabolism.

Conclusions

The modern selective aromatase inhibitors clearly represent an important clinical advance for postmenopausal women with breast cancer. They offer greater or equal activity than tamoxifen in a variety of settings including first- and second-line treatment of metastatic disease as well as in the adjuvant setting, and they may also offer advantages in prevention. These benefits are coupled with, at least thus far, equal or lesser toxicities in most cases. Therefore, they have assumed an important role in optimal management of postmenopausal patients with hormone-responsive metastases and have an evolving role in the adjuvant setting. Teasing out the optimal means of incorporating

these agents, their potential combined with ovarian ablation for younger women, and the potential differences among them, will require active participation in the many appropriate and ongoing studies. At the same time, it is perhaps humbling to consider that more than a century after the first demonstration by George Beatson in 1896 that hormones have an impact on the natural history of breast cancer, we are still actively studying this area of treatment.

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