Nonsteroidal and Steroidal Aromatase Inhibitors in Breast Cancer

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Anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are members of the third generation of aromatase inhibitors that has now replaced aminoglutethimide (Cytadren), the progestins, and tamoxifen

Introduction

The hormonal dependency of breast cancer was first recognized more than a century ago.[1] Although it has yet to be proven that estrogen is directly responsible for the initiation of breast tumors, it is clear from epidemiologic evidence,[2] from "prevention" studies using the antiestrogen tamoxifen (Nolvadex),[3] and from the clinical impact of hormonal manipulation[4,5] that estrogen is a significant factor in the maintenance and progression of established tumors.

Estrogen is produced by aromatization of androgens. In premenopausal women, androgens are synthesized from cholesterol by the adrenals and the ovaries in roughly equivalent proportions. Approximately 60% of estrogens in premenopausal women are synthesized in the aromatase-rich cytoplasm of the granulosa cells of the ovaries. Aromatization by the cycling ovary is regulated by follicle-stimulating hormone that is regulated, in turn, by estrogen in a negative feedback loop. The remaining 40% of estrogens in premenopausal women are synthesized in the peripheral tissues, particularly in fat.

At menopause, ovarian production of both estrogen and the estrogen precursor androstenedione ceases, so that most of the circulating estrogen in postmenopausal women derives from the peripheral conversion of adrenal androgens. Circulating estrogen levels in postmenopausal women are approximately 20% of those of premenopausal women, and they achieve a steady-state concentration in the absence of cyclical ovarian function.[6]

Intratumoral Aromatase

Although circulating levels of estrogens are relatively low in postmenopausal women, aromatase expression is maintained in breast tissue after menopause. Estrogen levels in the breast tissue of postmenopausal women are thus significantly higher than those detected in plasma, and may be as high as the plasma levels in premenopausal women.[7,8]

Although the exact site of aromatase production in breast cancer tissues has not yet been determined, both immunocytochemistry and in situ hybridization techniques have demonstrated aromatase enzyme and mRNA expression in the epithelial cells of the terminal ductal lobular units and the surrounding stromal cells of the normal human breast.[9] Tumor cells may produce aromatase themselves or they may produce cytokines that induce tumor-stromal-cell expression of aromatase.[10] Importantly, breast cancer tissues that retain aromatase expression may be able to function in an autocrine fashion by producing their own growth factor.[11-13]

The functional significance of tumor aromatase has not been well defined but is suggested by several lines of evidence. Aromatase activity is frequently found to be much higher in tumor tissue than in surrounding benign tissue from the same breast, supporting a role for aromatase activity in the emergence of the malignant phenotype.[14,15] Studies of tumor aromatase levels and known prognostic factors, such as tumor cell proliferative activity or lymph node involvement, have yielded conflicting results. No clear correlation between the level of tumor aromatase activity and the biological behavior of the tumor has yet been demonstrated.[14,16,17]
Studies examining the relationship between aromatase expression and estrogen- and progesterone-receptor positivity have also been inconsistent.[16,18,19] Notably, two small studies have suggested a correlation between tumor aromatase activity and response to aromatase inhibition therapy with aminogluthethimide (Cytadren).[20,21]

The Aromatase Inhibitors

There are two general categories of aromatase inhibitors: (1) the nonsteroidal inhibitors, which bind competitively with aromatase, and (2) the steroidal inhibitors, which bind irreversibly (see Table 1).

First- and Second-Generation Aromatase Inhibitors

The first aromatase inhibitor with documented antitumor efficacy was the nonsteroidal agent aminogluthethimide. Although its use as second- or third-line endocrine therapy achieved response rates of 20% to 40%, the drug was associated with problematic effects. Aminogluthethimide inhibits the production of other adrenal steroids, including cortisol, and therefore must be taken with hydrocortisone. A high incidence of skin rash and fatigue also made the drug difficult for many patients to tolerate. Other early aromatase inhibitors, such as fadrozole (CGS 16949A) and the parenterally administered formestane (4-OHA), demonstrated antitumor activity and fewer adverse effects than aminogluthethimide, but they have now been supplanted by the third-generation inhibitors described below.[22]

Third-Generation Aromatase Inhibitors

The current generation of nonsteroidal inhibitors includes anastrozole (Arimidex), letrozole (Femara), and vorozole (Rivizor), all of which are administered orally as a once-daily dose. The development of vorozole has been terminated, so it will not be discussed below. The only registered steroidal inhibitor of the current generation is exemestane (Aromasin).

Relative Potency of Aromatase Inhibitors

The in vivo potency of aromatase inhibitors is defined by their ability to suppress both aromatase activity and plasma estrogen levels. In vivo aromatase activity is assessed by radioimmunoassay of urinary estrogens following administration of radiolabeled androstenedione.[23] Plasma endogenous estrogens are usually measured with highly sensitive radioimmunoassays after separation with high-performance liquid chromatography.[24]

While the early aromatase inhibitors inhibited aromatization by approximately 90% in postmenopausal women, the third-generation aromatase inhibitors are far more potent, suppressing aromatization by approximately 98%.[25] When radioimmunoassays are used to assess estrogen suppression, they generally correlate with the degree of aromatization suppression observed (see Table 2).

The randomized clinical studies of letrozole[26] and vorozole[27] vs aminogluthethimide have demonstrated that the improvement in aromatase inhibition provided by the third-generation inhibitors is clinically meaningful, but the clinical relevance of any differences between members of the third generation is less clear. While most aromatization studies are not randomized studies—so that any comparison of their results must be interpreted with caution—one small (n = 12) randomized, crossover study has compared anastrozole to letrozole.[28] This study demonstrated that letrozole is a more potent aromatase inhibitor than anastrozole (aromatization suppression rates were > 99.1% vs 97%, \( P = .003 \), with confirmatory estrogen suppression data).

The clinical relevance of this small difference, demonstrated at a level of inhibition that is so close to complete, remains uncertain. Equally uncertain is the clinical relevance of exemestane’s irreversible binding to aromatase, compared with the competitive, reversible binding of the nonsteroidal agents.
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Aromatase Inhibitors in Metastatic Breast Cancer

Treatment Following Tamoxifen Failure

Anastrozole,[29] letrozole,[30] and exemestane[31] have all been compared with megestrol acetate, and letrozole has been compared with aminoglutethimide,[29] in multicenter, randomized phase III trials in postmenopausal women with estrogen-receptor-positive or estrogen-receptor-unknown metastatic breast cancer following tamoxifen failure. The results of these studies placed the new generation of aromatase inhibitors ahead of progestins as the hormonal treatments of choice following tamoxifen failure, and rendered the use of aminoglutethimide obsolete.[32]

**Anastrozole vs Megestrol Acetate:** Anastrozole was compared with megestrol acetate in two large randomized trials, the results of which were pooled for publication.[29] A total of 764 patients were randomized to receive megestrol acetate (40 mg qid) or one of two doses of anastrozole (1 mg daily or 10 mg daily). Although no difference was noted between the two agents in response rate, time to progression, or time to treatment failure, median survival was 27 months in patients receiving anastrozole at a dose of 1 mg daily and 23 months in patients receiving megestrol acetate ($P = .02$). There was no significant survival advantage to the 10-mg dose of anastrozole over either 1 mg anastrozole or megestrol acetate.

Anastrozole produced significantly less weight gain than megestrol acetate (2% vs 12%). The toxicity profiles of the two agents were otherwise comparable.

The survival benefit in this study was interpreted cautiously, as it was evident only in patients who received the lower, 1 mg dose. Moreover, no significant improvements in any other efficacy end point were noted, and the survival advantage was evident in only one of the two studies that were combined for publication.

**Letrozole vs Megestrol Acetate or Aminoglutethimide:** Letrozole has been compared with both megestrol acetate[30] and aminoglutethimide[26] in randomized trials. The first trial was double-blind and randomly assigned 363 patients to receive either megestrol acetate or letrozole at a daily dose of either 0.5 or 2.5 mg. It convincingly demonstrated an advantage for letrozole at the daily dose of 2.5 mg. Letrozole was superior to megestrol acetate in terms of response rate (24% vs 16%, $P = .04$), response duration (not reached vs 18 months, $P = .01$), time to treatment failure (5.1 vs 3.9 months, $P = .04$), quality of life/deterioration in performance status (39% vs 52%), and drug-related serious adverse events (0% vs 12%, $P < .05$). In addition, overall survival favored letrozole, but this did not reach statistical significance (25 vs 22 months, $P = .15$). Weight gain and thromboembolic events occurred less frequently in patients receiving letrozole. The results of this study substantially reinforced the weaker results of the earlier anastrozole vs megestrol acetate trials.

In the aminoglutethimide study, which again tested the two doses of letrozole, 555 patients were randomized. Letrozole (2.5 mg daily) was shown to be superior to aminoglutethimide in terms of time to progression, time to treatment failure, and overall survival (28 vs 20 months, $P = .002$). Response rates also favored letrozole (20% vs 12%) but did not reach statistical significance. Toxicity, particularly rash, was less common in the letrozole treatment arms.

**Exemestane vs Megestrol Acetate:** Exemestane was compared with megestrol acetate in a study of 769 patients.[31] Like the nonsteroidal agents, exemestane was shown to be superior to the progestin. At a dose of 25 mg daily, it displayed a longer time to progression (20 vs 17 weeks, $P = .037$), time to treatment failure, and overall survival at a median follow-up of 11 months (not reached vs 28 months, $P = .039$). Response rates favored exemestane (15% vs 12%) in both visceral and nonvisceral disease, although the difference did not reach statistical significance. Like anastrozole and letrozole, exemestane produced significantly less weight gain than megestrol acetate.

A phase II study also addressed the activity of exemestane after failure of a nonsteroidal aromatase inhibitor.[33] In a study of 242 patients, 44% had received aminoglutethimide and 56%, another aromatase inhibitor. An objective response was seen in 7% of patients, and stabilization of disease.
for at least 6 months occurred in another 17%. The median duration of response was 14 months, and the median time to progression was 15 weeks.

**Aromatase Inhibitor vs Tamoxifen**

All three third-generation aromatase inhibitors have also been compared with tamoxifen as first-line therapy for estrogen-receptor-positive or estrogen-receptor-unknown metastatic breast cancer in postmenopausal women. Preliminary data from these investigations have established the aromatase inhibitors as the therapy of choice for estrogen-receptor-positive metastatic breast cancer in menopausal patients.

**Anastrozole:** Anastrozole[34] was compared with tamoxifen in two double-blind, placebo-controlled studies that enrolled a total of 1,021 patients. In a combined analysis, 40% of patients had unknown estrogen-receptor status, 60% were estrogen-receptor-positive and/or progesterone-receptor-positive, and 9% had received adjuvant hormonal therapy. Anastrozole exhibited a slightly longer time to progression than tamoxifen (8.5 vs 7.0 months), although this difference did not achieve statistical significance in the intention-to-treat analysis ($P = .103$). In the hormone-receptor-positive subgroup ($n = 611$), however, there was a statistically significant advantage to the aromatase inhibitor (10.7 vs 6.4 months, $P = .022$). Importantly, the superiority of anastrozole was more evident in patients who had not received prior hormonal therapy (ie, tamoxifen) than in those who had, so the advantage cannot be dismissed as being the result of preexisting tamoxifen resistance. Response rates and adverse events were comparable in the two treatment arms.

**Letrozole:** Letrozole was compared with tamoxifen in a randomized, double-blind, crossover phase III study of 907 patients with estrogen-receptor-positive (65%) or estrogen-receptor-unknown (35%) tumors who had received no prior hormonal therapy for metastatic disease.[35] The treatment arms were well balanced. As first-line therapy, letrozole was shown to be superior to tamoxifen in terms of response rate (30% vs 20%, $P = .001$), clinical benefit (49% vs 38%, $P = .001$), time to progression (41 vs 26 weeks, $P = .0001$), and time to treatment failure (40 vs 25 weeks, $P = .0001$). Adverse events, thromboembolic events, and duration of response were similar in the two arms.

**Exemestane:** Exemestane was compared with tamoxifen in a randomized phase II study.[36] To enter the study, patients who had received adjuvant hormonal therapy were required to have had a disease-free interval of at least 6 months if estrogen receptors were positive, and at least 2 years if the estrogen-receptor status was unknown. In an analysis of the first 63 patients, 14 had received adjuvant tamoxifen and 56% had visceral disease. Response rate (42% vs 16%), complete response rate (10% vs 3%), "clinical benefit" (58% vs 31%), and time to progression (8.9 vs 5.2 months) all favored exemestane therapy. Toxicity was similar in the two treatment arms.

**Aromatase Inhibitors in Early Breast Cancer**

**Adjuvant Aromatase Inhibition**

Tamoxifen is the gold standard for hormonal therapy in the adjuvant setting. It effectively antagonizes estrogen in the tumor, reducing relapse by 47% and death by 26%, regardless of menopausal status,[4] and has positive effects on bone mineral density and lipid profiles.[37] While the aromatase inhibitors have been shown to be highly effective in postmenopausal women with estrogen-receptor-positive metastatic disease, their role in the adjuvant setting is not yet established. This is because the long-term effects on bone mineralization and cardiovascular function have not yet been adequately assessed.

The current phase III adjuvant studies are therefore designed to compare the aromatase inhibitors with tamoxifen, primarily in terms of prevention of breast cancer relapse, but effects on bone density and cardiovascular morbidity are major secondary end points. Three basic study designs have been used in the current phase III studies of an aromatase inhibitor vs tamoxifen in the adjuvant setting.

**Substitution for Tamoxifen:** The first design substitutes the aromatase inhibitor for the standard 5
years of tamoxifen. The hypothesis behind this design is that the advantage to the aromatase inhibitors seen in metastatic disease will translate directly into the adjuvant setting, and that any deleterious effects on bone or cardiovascular function will be minimal. The ATAC (Arimidex, Tamoxifen Alone and Combination) trial, coordinated by the British Cancer Research Campaign and AstraZeneca, has accrued a total of 9,100 node-positive and node-negative patients to receive anastrozole or tamoxifen, or anastrozole plus tamoxifen, each for 5 years. The study has completed accrual, and is now in follow-up.

**Partial Substitution for Tamoxifen:** The second design substitutes the aromatase inhibitor for a portion of the standard 5-year period—based on the hypothesis that the benefits of tamoxifen are greatest in the first few years of treatment, after which some tumor cells may develop tamoxifen dependence. If one accepts the premise that relapse is partially due to the emergence of tamoxifen dependence, tamoxifen withdrawal and estrogen deprivation by aromatase inhibition may indeed provide a survival advantage. This strategy assumes that any deleterious effects of aromatase inhibition will be less evident if the period of aromatase inhibition is kept to a minimum.

This strategy looks promising, as evidenced by the preliminary results of an Italian study of tamoxifen for 5 years vs tamoxifen for 3 years followed by aminoglutethimide for 2 years. The study randomized 381 patients; the median age was 66 years, and 70% of patients had positive axillary nodes. At a median follow-up of 45 months, there was no significant difference in disease-free survival (76% vs 74%), but survival was significantly longer in patients who had received aminoglutethimide (95% vs 87%, \( P = .006 \)).[38]

The German Adjuvant Breast Cancer Group (GABG) and the Austrian Breast Cancer Study Group (ABCSG) are both comparing 5 years of tamoxifen with 2 years of tamoxifen followed by 3 years of anastrozole in patients with node-positive or node-negative, low- to moderate-grade tumors. A total of 1,300 patients will be accrued to the German trial GABG IV-C (also known as ARNO), and 1,200 patients will be accrued to ABCSG Study 8.

Exemestane is being studied in BIG 02-97 (also known as Study 96 OEXE 031-C/13/96), coordinated by the British-based International Collaboration Cancer Group (ICCG). This study randomizes patients who have already received 2 to 3 years of tamoxifen treatment to either continue tamoxifen or to receive exemestane for a total of 5 years. The study will accrue 2,200 patients.

**Four-Way Treatment Design:** The Breast International Group (BIG) has combined these first two study designs into BIG 01-98 (or IBCSG 18-98), coordinated by the International Breast Cancer Study Group (IBCSG). This study has a four-way treatment design that randomly assigns patients to 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen. It will accrue 3,500 patients.

**Adjuvant Aromatase Inhibition After 5 Years of Tamoxifen:** Another study design addresses whether the introduction of an aromatase inhibitor following 5 years of tamoxifen treatment can further improve survival. The premise here is that 5 years is the optimal duration of tamoxifen therapy, but that late relapse occurs because dormant cells have retained estrogen dependence and subsequently reactivate following tamoxifen withdrawal.

ABCSG study 6A rerandomizes patients, who were treated on ABCSG study 6 (tamoxifen for 5 years vs tamoxifen for 5 years plus aminoglutethimide for 2 years) and who are disease-free at 5 years, to either anastrozole or observation for an additional 3 years. A total of 1,700 patients are expected to be rerandomized.

Protocol B-33 of the National Surgical Adjuvant Breast and Bowel Project (NSABP) is randomizing patients who are disease-free after 5 years of tamoxifen to 2 years of either exemestane or placebo. The study plans to accrue 3,000 patients.

BIG 01-97 (or NCIC CTG MA-17) will randomize 2,400 patients in Canada, Europe, the United States, and Australasia, who remain disease-free after 5 years of adjuvant tamoxifen, to another 5 years of treatment with either letrozole or placebo. Importantly, this study has formal lipid and bone mineral density companion studies.
Neoadjuvant Aromatase Inhibitors

The use of aromatase inhibitors in the neoadjuvant (preoperative) setting has not been widely investigated. Most studies of preoperative therapy have used chemotherapy, and those that have investigated hormonal therapy have used tamoxifen. In the case of aromatase inhibitors, Dixon et al have reported on a series of hormone-receptor-positive patients treated with a 3-month course of letrozole, anastrozole, or tamoxifen.[39] These patients were not part of a randomized study. The response rates for letrozole and anastrozole were high (88% and 94%, respectively), and the median reduction in tumor volume was greatest for letrozole (81%), followed by anastrozole (64%) and tamoxifen (48%).

In premenopausal women, there is evidence that the hormonal environment at the time of surgery may influence the likelihood of relapse. Specifically, some investigators have found that women who undergo surgery during the proliferative phase of the menstrual cycle, a time when circulating estrogens are at their highest levels, are at greater risk of metastases.[40-43] Although the validity of these findings is debated in the literature, they suggest a role for estrogen in the growth of viable metastases from tumor cells disseminated at the time of surgery. It is possible that, at the time of surgery, the inhibition of estrogen with an aromatase inhibitor, alone or in combination with a luteinizing hormone-releasing hormone (LHRH) agonist, could improve the outcome for women undergoing breast cancer surgery.

Aromatase Inhibitors and Breast Cancer Prevention

The approval of the selective estrogen-receptor modifier tamoxifen for the prevention of breast cancer in high-risk women was a recent milestone in the battle against breast cancer. Aromatase inhibitors are candidates for future preventive agents. Many of the epidemiologic factors associated with an increased risk of breast cancer (eg, early menarche, late menopause, increased age at first full-term pregnancy) point to the importance of estrogen exposure, regardless of whether the tumor expresses hormone receptors.[44,45] Several researchers have therefore proposed preventive strategies that decrease breast exposure to estrogen by inhibiting aromatase.[44,46,47]

Total suppression of estrogen production would likely have the adverse effects commonly associated with menopause: increased osteoporosis, cardiovascular disease, and urogenital atrophy. Preclinical models suggest that it may be possible to obtain chemopreventive effects without total suppression of aromatase and circulating estrogen levels.[46] Selectively suppressing local estrogen production in the breast might some day be possible, since researchers have discovered a unique transcriptional promoter of aromatase gene expression found only in breast adipose tissue.[47]

Combined Hormonal Therapy

Aromatase Inhibitors Plus Tamoxifen

In the 1980s, four studies were published that compared tamoxifen alone with tamoxifen plus aminoglutethimide in metastatic disease.[48-51] None of the studies displayed any advantage to the combination, and sequential single-agent hormonal therapy was subsequently established as the standard of care. In the adjuvant setting, a recent Austrian study comparing tamoxifen with tamoxifen plus aminoglutethimide in 2,021 patients also failed to demonstrate any advantage to the combination regimen.[52] A pharmacokinetic interaction between these agents has been demonstrated, however, with the concentration of tamoxifen and its metabolites decreased by coadministration of aminoglutethimide.[53] This may partially explain the clinical findings.

As neither anastrozole nor letrozole influences tamoxifen pharmacokinetics,[54,55] the issue of combined therapy has been revisited in the previously mentioned ATAC trial. Studies in nude mice, on the other hand, would predict that there is unlikely to be any clinical benefit from combining tamoxifen with either anastrozole or letrozole.[56] Likewise, there is no rationale for combining letrozole with tamoxifen, as coadministration of these agents results in a significant (38%) reduction of plasma letrozole levels.[57]
Aromatase Inhibitors Plus LHRH Agonists in Premenopausal Women

There are few clinical data on aromatase inhibitors in premenopausal women, since early studies showed that these agents were unable to effectively inhibit estrogen synthesis in the presence of an intact premenopausal estrogen-follicle-stimulating hormone feedback loop.[58-60] The role of aromatase inhibitors in premenopausal women is now being revisited, however, for a number of reasons.

First, the clinical studies discussed in the preceding paragraphs have conclusively demonstrated that the new aromatase inhibitors are more potent than aminogluthethimide. Second, current data have not established any significant clinical differences among the members of the current generation of aromatase inhibitors. The irreversible nature of the binding between exemestane and aromatase may realize some advantage in this setting, particularly if the drug is administered at higher doses than those used in postmenopausal disease. Third, the addition of LHRH agonists to tamoxifen in premenopausal women has been shown to be an effective treatment strategy in both metastatic disease[61] and the adjuvant setting.[62,63] Long-acting LHRH agonists, such as goserelin (Zoladex) or buserelin (Suprefact), may be used to inhibit ovarian cycling, thereby suppressing ovarian estrogen production to postmenopausal levels.

Combinations of the new aromatase inhibitors with LHRH agonists are therefore now being prospectively studied. British investigators have made a preliminary report of their study of premenopausal women who received anastrozole with goserelin for locally advanced or metastatic breast cancer. Eight of nine evaluable patients were progression-free after 6 months of treatment.[64] The ABCSG is conducting an adjuvant study of goserelin plus anastrozole vs goserelin plus tamoxifen (ABCSG Study 12).

Aromatase Inhibitors in Male Breast Cancer

Male breast cancer comprises approximately 1% of all breast cancer cases. Since the disease arises in a hormonal environment of low levels of circulating estrogens and high levels of circulating androgens, intratumoral aromatase may well be important in its pathogenesis. In fact, aromatase overexpression in intratumoral stromal cells appears to be much more frequent in men than in women.[17]

While the small number of patients precludes meaningful clinical trials, breast cancer in men is generally treated according to the same principles as in women, and tamoxifen therapy appears to be effective in hormone-receptor-positive tumors. Aromatase inhibitors decrease levels of serum estrogen in volunteer male subjects,[65] and they are likely to be useful in the treatment of male breast cancer.

Conclusions

The third generation of aromatase inhibitors—comprising anastrozole, letrozole, and exemestane—is now the standard of care for postmenopausal patients with estrogen-receptor-positive metastatic breast cancer. Numerous large randomized studies are being conducted to address the value of these agents in the adjuvant setting. Additional information regarding the value of new aromatase inhibitors in combination with LHRH agonists will be available from studies in premenopausal women.

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