Anastrozole: A New Selective Nonsteroidal Aromatase Inhibitor

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Aromatase (estrogen synthetase) is the enzyme complex responsible for the final step in estrogen synthesis—the conversion of androstenedione and testosterone to estrone and estradiol, respectively. Inhibitors of this enzyme

Introduction

The American Cancer Society estimates that 180,200 women will be diagnosed with breast cancer in 1997, making the breast the leading site of new cancer in women. Breast cancer is also the number two cause of cancer death among Western women.[1]

In 1896, it was established that oophorectomy could result in disease regression in women with metastatic breast cancer.[2] Today, endocrine therapy plays a major role in the treatment of women with hormone-dependent breast cancer.

An important predictor of the likelihood of response to endocrine therapy is estrogen-receptor (ER) and progesterone-receptor (PR) status of the primary tumor. Tumors that are positive for both receptors have a 70% response rate, as compared with an approximate 33% response rate for tumors positive for only one receptor.

Other predictors of response include site of metastases (bone and soft-tissue disease showing a more favorable response than visceral disease), menopausal status (postmenopausal women more responsive than premenopausal women), patient age (response improving with increasing age), disease-free interval (better response associated with prolonged disease-free interval), and prior response to endocrine therapy.[3]

Hormonal therapies for breast cancer include surgical or radiation-induced castration (in premenopausal women with functioning ovaries) or medical treatment with compounds such as antiestrogens, gonadotropin hormone-releasing hormone (GnRH) analogs, progestins, and aromatase inhibitors. All of these agents affect the production or utilization of estrogen or progesterone in premenopausal or postmenopausal women.[4,5]

Current Endocrine Therapies

Antiestrogens

The most widely used endocrine therapy is tamoxifen (Nolvadex), a nonsteroidal antiestrogen. It is presently indicated for: (1) advanced breast cancer (in both premenopausal and postmenopausal women); (2) coadministration with chemotherapeutic agents; and (3) adjuvant monotherapy.[6]

Given as adjuvant therapy, tamoxifen has been shown to prolong survival,[7] extend disease-free survival,[8] and reduce the incidence of new contralateral primary breast tumors.[9]

Although all of its mechanism(s) of action are not completely understood, tamoxifen is known to compete with circulating estrogen to bind to the ER. This binding induces receptor activation, and the complex translocates to the nucleus, where it interacts with specific regions of DNA. As this interaction does not induce gene transcription, cell growth is inhibited.[10,11] Tamoxifen also has partial agonist activity and exerts beneficial estrogenic-like effects on bone and lipids[12]; however, this property may also be associated with detrimental effects. For example, studies have found tamoxifen use to be associated with an increased incidence of endometrial cancer.[13] Moreover, there is evidence from animal models of human breast cancer that the agonist activity of tamoxifen may eventually stimulate breast tumor growth.[14] Thus, new antiestrogens with weak or no agonist activity are in development, which include tamoxifen analogs, such as toremifene (Fareston) and droloxifene, and pure steroidal antiestrogens, such ICI 182,780. The role of these agents in breast cancer is yet to be defined.

Approximately 30% of unselected patients with advanced- or early-stage breast cancer respond to treatment with tamoxifen. Those who do not respond or whose disease progresses after tamoxifen treatment may then be given other hormone therapies, such as progestins or aromatase inhibitors.
Progestins

The most common progestational agents used in the treatment of advanced breast cancer are megestrol acetate (Megace) and medroxyprogesterone acetate. Due to the significant side effects associated with these agents, such as weight gain and fluid retention, they are generally used as second- or third-line therapy. Response rates in unselected patients with advanced disease are in the range of 30%.\[15,16\] However, high- vs low-dose studies have suggested that superior responses may be achieved with higher doses.\[17,18\]

The mechanism of action of progestins is not well understood but may involve a direct action on the cell mediated through the progesterone receptor, as well as an indirect effect mediated through the hypothalamus/pituitary/ovarian and pituitary/adrenal axes. It has been suggested that megestrol and medroxyprogesterone may have different modes of action; however, randomized studies need to be performed to address this issue.

GnRH Analogs

Gonadotropin hormone-releasing analogs, such as leuprolide acetate (Lupron) and goserelin acetate (Zoladex), are used for the treatment of advanced breast cancer patients with intact ovarian function, ie, premenopausal and perimenopausal women. Objective disease response rates of approximately 40% have been reported in patients with advanced disease.\[4\] These compounds bind to luteinizing hormone-releasing hormone (LHRH) receptors in the pituitary and subsequently cause a decrease in estrogen to castrate levels. Gonadotropin hormone-releasing analogs are administered monthly by injection.

Aromatase Inhibitors

Aromatase inhibitors reduce the synthesis of estrogens by inhibiting the aromatase enzyme complex. As monotherapy, these agents are useful in postmenopausal women, in whom estrogens are produced predominantly by the aromatization of adrenal androgens (androstenedione, testosterone) in peripheral tissues, such as fat, muscle, and skin. By reducing the levels of estrogens in these tissues, aromatase inhibitors decrease ER binding, which, in turn, inhibits estrogen-induced cellular effects.

The most extensively studied first-generation aromatase inhibitor is aminoglutethimide. This compound inhibits the conversion of cholesterol to pregnenolone by blocking the enzyme 20,22-desmolase (cytochrome P450, side-chain cleavage \(\text{cyt P450}_{\text{scc}}\)). However, because this inhibition occurs early in the steroid biosynthesis pathway, hydrocortisone supplementation is necessary to avoid adrenal insufficiency (Figure 1). Thus, this agent is neither a selective nor a powerful inhibitor of aromatase. Reported objective response rates in patients with advanced breast cancer range from 28% to 43%.\[19-22\]

Aminogluthethimide is associated with various side effects, including lethargy, ataxia,\[23\] rash, nausea, and anorexia,\[24\] as well as some potentially serious, but rare, effects, such as hypothyroidism,\[25\] prolonged thrombocytopenia,\[26\] agranulocytosis, pancytopenia,\[27\] and systemic lupus erythematosus.\[28\] In approximately 10% of patients, aminogluthethimide treatment must be discontinued due to toxicity. Research has therefore focused on synthesizing more specific and potent inhibitors of aromatase.

Formestane (4-hydroxyandrostenedione), commercially available in Europe, is a highly specific, selective aromatase inhibitor. It produces an objective response rate of 24% to 35% in the first-line treatment of advanced breast cancer.\[29\] Its use is limited somewhat by its parenteral formulation and associated injection site reactions.\[30\]

Anastrozole

Preclinical Pharmacology

Anastrozole (Arimidex), a potent nonsteroidal aromatase inhibitor, is the first selective, orally administered aromatase inhibitor to be approved in the United States for use in the treatment of advanced breast cancer in postmenopausal women. It has high potency, inhibiting human placental aromatase in vitro with an \(IC_{50}\) (concentration that inhibits enzyme activity by 50%) of 14.6 nM.\[31\]

In mature female rats, 0.1 mg/kg of anastrozole blocks ovulation, and twice-daily administration of \(\geq\) 0.1 mg/kg of anastrozole to male pigtailed monkeys inhibits peripheral aromatase and reduces circulating estradiol by 50% to 60%.\[32\]

The selectivity of this compound was assessed by investigating its effects on the enzymes associated with steroid hormone metabolism (Table 1). These data show that anastrozole is highly selective for aromatase, as inhibition of other enzymes occurs at much higher doses than are required to inhibit aromatase.\[32\]
In various isolated animal tissues in vivo, anastrozole, at concentrations up to $10^5 \text{ M}$, had little or no effect on muscarinic acetylcholine receptors, histamine ($H_1$ or $H_2$) receptors, serotonin ($HT_1$ or $HT_2$) receptors, or alpha-1-, alpha-2-, beta-1-, or beta-2-adrenoreceptors. At doses of 10 mg/kg, anastrozole had no central nervous system effects in mice or rats, no local anesthetic activity, no effect on pain perception, no effect on gastrointestinal motility in mice, and no effect on cardiovascular function, renal function, gastric acid secretion, clotting mechanisms, or inflammatory responses in rats.[33]

**Toxicology**

Anastrozole demonstrated no significant toxicities and was well-tolerated in all animal species tested.[34] Single-dose, acute toxicity studies in mice (250 mg/kg orally, 50 mg/kg intraperitoneally) and rats (100 mg/kg orally, 50 mg/kg intraperitoneally) produced no deaths; thus, the lethal dose was greater than the highest doses tested.[34] Chronic toxicity studies were performed in rats (1-, 5-, 25-, and 50-mg/kg/d doses for 1 and 6 months) and dogs (1-, 3-, 8-, and 12-mg/kg/d doses for 1 and 6 months). At a dose of 10 mg/kg, anastrozole caused small reductions in blood pressure and a shortening of the QT interval (ECG) in dogs, as well as a slight inhibition of the delayed hypersensitivity response in mice.[32]

**Clinical Pharmacology**

**Pharmacokinetics**—In humans, anastrozole is rapidly absorbed; peak serum concentration is reached within 2 hours of oral administration. The plasma half-life ranges from 30 to 60 hours, with no difference in half-life observed between healthy women and breast cancer patients. With chronic oral administration, steady state is achieved within 10 to 14 days, and the steady-state serum level is three to four times that seen following a single dose. The total amount of drug absorbed is not significantly affected by food, but the rate of absorption is decreased slightly.[32] Radiolabel studies show that 83% to 85% of orally administered anastrozole is recovered in the urine and feces, mostly in the form of metabolites that have been shown to be inactive. The most important metabolic route is N-dealkylation, which releases free triazole.[32,34] The metabolism of anastrozole is primarily hepatic (85%); renal excretion accounts for an additional 11% of the administered dose. Approximately 10% of the drug is excreted in the urine unchanged.[34]

**Pharmacodynamics/Drug-Hormone Interactions**—Ascending doses of anastrozole ranging from 0.1 to 60 mg were administered to 29 healthy male volunteers. A dose-dependent suppression of estradiol was seen with single doses of $\geq 7.5 \text{ mg}$, which suppressed circulating estradiol levels by approximately 80% of baseline. Maximum suppression occurred after 6 to 12 hours of dosing, and the effect was sustained for at least 24 hours. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations increased; however, no significant changes in other steroid hormones were observed.[33] In multiple daily dosing studies (0.5, 1, 3, 5, and 10 mg/d for 7 to 14 days) in healthy women and postmenopausal breast cancer patients, estradiol concentrations were assessed 24 hours after the administration of the last dose of anastrozole. Estradiol decreased by more than 78% from baseline with each dose, but since only 2 of 6 volunteers receiving the 0.5-mg dose achieved estradiol suppression to the assay limit of detection ($3.7 \text{ pmol/L}$), 1 mg is considered the lowest dose required to maximally suppress serum estradiol levels.[31] Results from the 5- and 10-mg multiple-dose studies demonstrated that estrone levels were lowered by 69% and 86%, respectively, and estrone sulfate levels by 83% and 92%, respectively. No significant changes in androstenedione, cortisol, and aldosterone levels were observed, and response to adrenocorticotropic hormone (ACTH) stimulation was maintained, indicating that at daily doses of up to 10 mg, anastrozole has no effect on mineralocorticoid or glucocorticoid secretion.[29] Data from these studies are summarized in Table 2.[31,33,35,36] These results were used as the basis for dose selection in the phase III efficacy studies.

**Potential Interactions/Populational Differences**—Various in vitro studies have been performed to look for possible interactions between anastrozole and other drugs. Since various P450 enzymes are involved in drug metabolism, inhibition of these enzymes by anastrozole could potentially affect the concentration of other drugs when administered concurrently. Anastrozole, at high concentrations does not inhibit the enzymes that metabolize dextromethorphan or coumarins. High concentrations do, however, inhibit the enzymes that metabolize nifedipine, tolbutamide, and phenacetin; however, 50% inhibition occurs at anastrozole concentrations above 10 $\mu\text{M}$—30 times the serum concentration attained with a dose of 1 mg/d.[34] Pharmacokinetic data indicate that no dose adjustment is required in elderly patients, patients with mild to moderate hepatic disease, or those with mild to moderate renal disease.[34]
**Anastrozole in Breast Cancer Patients**

Two randomized clinical studies have been performed to compare the efficacy and tolerability of anastrozole (1 and 10 mg/d) and megestrol acetate (40 mg four times daily) in postmenopausal women whose disease progressed during first-line hormonal treatment for advanced breast cancer or who relapsed while receiving or after completing adjuvant tamoxifen therapy. One study was performed in Europe, Australia, and South Africa and the other in North America.\[37,38\] Because the trials were identical in design, an analysis of the combined results was performed, thereby strengthening the interpretation of results from each trial.

The primary end points were time to disease progression and tumor response. Secondary end points were duration of response, survival, quality of life, subjective assessment scores, and tolerability.

Buzdar et al have published a detailed review of these studies.\[39\]

Eligible patients were postmenopausal women with ER-positive disease or with ER-negative disease but a previous response to tamoxifen. Patients were excluded if they had received more than one course of chemotherapy for metastatic disease or more than one previous hormonal therapy for advanced breast cancer, or if they had any medical illness or laboratory abnormalities that would compromise either their safety or the interpretation of results. Response categories were strictly defined using International Union Against Cancer (UICC) criteria.

A total of 764 patients were entered into the two trials (378 at 73 centers in the Europe/Australia/South Africa trial and 386 at 49 centers in the North American trial). Patients were randomized to one of three treatment groups: 1 mg/d of anastrozole (N = 263), 10 mg/d of anastrozole (N = 248), or 40 mg of megestrol acetate four times daily (N = 253); those receiving anastrozole were blinded with respect to dose. The groups were well-balanced with respect to demographic and pretreatment characteristics, including age, weight, previous treatments, receptor status, duration of previous tamoxifen treatment, previous best response to tamoxifen, performance status, percentage with measurable vs nonmeasurable disease, and sites and extent of metastatic disease.

**Efficacy**—At evaluation (median follow-up duration of approximately 6 months), approximately 61% of the patients had experienced disease progression. There were no significant differences between the three treatment groups in terms of time to progression, with an overall median time to progression of 21 weeks. The estimated progression hazard ratio for anastrozole (1 mg) vs megestrol acetate was 0.97 (97.5% confidence interval [CI], 0.75 to 1.24). The estimated progression hazard ratio for anastrozole (10 mg) vs megestrol acetate was 0.92 (97.5% CI, 0.71 to 1.19).

Objective tumor responses (complete or partial) were seen in 27 (10.3%) patients receiving 1 mg/d of anastrozole, 22 (8.9%) of those receiving the 10-mg/d dose, and 20 (7.9%) treated with megestrol acetate. Stable disease (24 weeks or longer in duration) was seen in 66 (25.1%) of those receiving 1 mg/d of anastrozole, 56 (22.6%) of those receiving the 10-mg dose, and 66 (26.1%) of patients in the megestrol acetate group.

There were no significant differences between the anastrozole groups, indicating that the two doses are equally effective and are comparable to the standard agent, megestrol acetate. The response rates in all three groups were lower than have been traditionally reported. However, approximately 30% of the patients studied had nonmeasurable disease and, thus, could not be classified as either complete or partial responders. The duration of responses ranged from approximately 3 to 18 months.

There were no significant differences between treatments with regard to overall survival at the time of the initial data analysis. However, later data did indicate that anastrozole may increase overall survival.\[A. U. Buzdar, md, unpublished data, 1997\]

**Tolerability**—Rates of patient withdrawal due to adverse events were low: 2.7% in the 1-mg anastrozole group, 3.3% in the 10-mg anastrozole group, and 4% in the megestrol acetate group. The most commonly observed adverse events with the 1-mg/d dose of anastrozole included asthenia, nausea, headache, hot flushes, and pain. Other than one episode of dyspnea, none of these events led to withdrawal of therapy.

The adverse event profile of the 10-mg dose of anastrozole was similar to that of the 1-mg dose. However, nausea and vomiting were more common in the higher-dose group (nausea: 15.6% for the 1-mg dose and 19.5% for the 10-mg dose; vomiting: 9.2% and 10.6% for the two respective doses), suggesting that these effects were dose-related. In patients treated with megestrol acetate, the most common adverse events were dyspnea, pain, weight gain, nausea, peripheral edema, and headache.

Analysis of anticipated adverse events indicated that (1) gastrointestinal disturbance was more frequent with anastrozole (both doses) than with megestrol acetate (the difference between the
10-mg anastrozole dose and megestrol acetate was significant \([P = .005]\), and (2) significantly fewer patients in the anastrozole groups complained of weight gain compared with those in the megestrol acetate group \((P < .0001\) for the 1 mg of anastrozole dose vs megestrol acetate; \(P = .002\) for 10 mg of anastrozole dose vs megestrol). A weight gain of \(\geq 5\%\) of body weight was experienced by 34.4% of megestrol-treated patients compared with 13% and 14% of patients in the 1- and 10-mg anastrozole groups, respectively; 10.7% of megestrol acetate patients gained \(\geq 10\%\) of body weight, as compared with 2% and 3% of patients in the two respective anastrozole groups.

**Discussion**

With the incidence of breast cancer increasing worldwide, particularly in postmenopausal women, the development of new therapeutic approaches is imperative. At present, progestins and aromatase inhibitors, such as aminogluthethimide, are commonly used in the treatment of advanced breast cancer. Although randomized trials have demonstrated that both classes of agents are comparable in efficacy to tamoxifen,[40-44] side effects have restricted their use to second- and third-line treatment following tamoxifen therapy.

With the development of effective, highly selective aromatase inhibitors, such as anastrozole and the newly approved letrozole (Femara), this approach may now be reconsidered. In a randomized study comparing formestane to tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer, comparable objective response rates (33% and 37%, respectively) were observed.[45] These observations, along with the increased use of tamoxifen in the adjuvant setting, may lead to the eventual use of third-generation aromatase inhibitors as first-line therapy in advanced metastatic breast cancer. Anastrozole, with its excellent pharmacokinetic profile, clinical efficacy, and good tolerability, is an important member of this class of agents.

**Potential Future Applications**

The full clinical application of aromatase inhibitors remains to be defined, because to date they have been investigated most extensively as single agents in postmenopausal metastatic breast cancer. However, other therapeutic uses may be possible.

**Combination Therapy**—The efficacy of combination endocrine therapy has been studied.[46,47] Although in some phase II trials, combination therapy yielded response rates that were higher than single-agent therapy, randomized trials have not demonstrated convincingly that combination therapy improves survival over single-agent therapy.

The clinical use of tamoxifen in combination with aminogluthethimide plus hydrocortisone showed no clinical benefit over tamoxifen alone or aminogluthethimide plus hydrocortisone.[48] Of interest is a pharmacokinetic study in postmenopausal women demonstrating that the combination of aminogluthethimide and tamoxifen reduced serum levels of tamoxifen and most of its metabolites, findings consistent with induction of tamoxifen metabolism during aminogluthethimide exposure.[49] This might account for the lack of improvement in patient outcome and, indeed, must be considered if the combination of tamoxifen plus anastrozole is evaluated clinically.

A phase II study examining aminogluthethimide plus medroxyprogesterone acetate in 128 women with advanced breast cancer demonstrated an objective response rate of 21.9%, with the highest response rate seen in patients with bone-only disease. It was considered that these results justify a prospective trial combining these two drugs with other endocrine therapies.[50]

Certainly, the possibility of synergism between existing therapies and the new-generation aromatase inhibitors should be investigated. Very few studies of combined endocrine treatment have been conducted, and no such studies comparing combinations including new-generation aromatase inhibitors with traditional hormone therapies have been carried out thus far.

**Treatment of Premenopausal Women**—There are several obstacles to the use of aromatase inhibitors as monotherapy in premenopausal women:

1. Complete ovarian aromatase inhibition may not be achieved; and
2. The functional pituitary/hypothalamus axis may lead to a reflex increase in gonadotropin levels, which may result in an ovarian hyperstimulation syndrome.

However, given in combination with an LHRH agonist or ovarian ablation (surgical or radiation-induced), the use of aromatase inhibitors, such as anastrozole, could be expanded to include premenopausal women, in both the metastatic and adjuvant settings.

**Adjuvant Therapy**—Given the good safety profile of anastrozole, its use in the adjuvant setting
should be explored. However, no data are presently available on the long-term effects of aromatase inhibitor administration, and the theoretical possibility of provoking or aggravating osteoporosis and/or cardiovascular disease needs to be taken into account. In contrast, it is well established that tamoxifen has beneficial effects on bone metabolism and blood lipids (and cardiovascular risk).

Ongoing adjuvant studies are comparing tamoxifen to anastrozole, 1 mg/d, in postmenopausal women. These studies will address the long-term safety concerns. If equivalent efficacy and superior tolerability and safety compared with tamoxifen are demonstrated, anastrozole and other new aromatase inhibitors could offer an alternative to tamoxifen in the adjuvant setting.

**Chemoprevention of Breast Cancer**—Tamoxifen is currently being investigated in the primary prevention of breast cancer in both premenopausal and postmenopausal women. With the advent of new, highly specific aromatase inhibitors with good side effect profiles, the use of these compounds as chemopreventive agents in postmenopausal women may also be considered.

**Conclusions**

With their improved selectivity and good safety profiles, third-generation aromatase inhibitors, such as anastrozole, may have other clinical applications besides their use as single agents in the treatment of metastatic breast cancer in postmenopausal women. Further testing needs to be done to fully define the spectrum of clinical use of these compounds.

**References:**


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