Cancer Investigation, 16(6), 385–390 (1998)

NEW DRUG

Anastrozole (Arimidex®), a New Aromatase Inhibitor for Advanced Breast Cancer: Mechanism of Action and Role in Management

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INTRODUCTION

Breast cancer is the most common cancer in American women, and is estimated to be the cause of 46,000 deaths per year (1–3). The incidence of breast cancer increases with age, with breast cancer more common in menopausal and postmenopausal women than in younger women (4). Approximately one-third of all breast cancers are hormone dependent; because estrogen is the primary steroidal mitogen, hormonal manipulation has proven to be a successful modality in these cases (3,5,6). Tumors likely to respond to endocrine therapy can be identified through the presence of estrogen and progesterone receptors, with positive response rates as high as 60% in patients with estrogen receptor (ER)-positive tumors and 75% in cases in which both estrogen and progesterone receptors have been detected (6,7). Postmenopausal women are more likely than younger women to have breast tumors positive for both estrogen and progesterone receptors; in addition, the absolute concentration of these receptors may also be higher in tumors in postmenopausal women (8). A relatively new strategy for the blockade of estrogen synthesis in the management of advanced breast cancer in postmenopausal women is aromatase inhibition with the selective, nonsteroidal inhibitor anastrozole (Arimidex®) (9–15). Aromatase inhibition presents a number of advantages over other endocrine therapies, including a well-defined mechanism of action, specific inhibition of estrogen synthesis, a lack of estrogenic effects, and lack of cross-resistance with antiestrogens (5). When compared with other aromatase inhibitors (e.g., aminoglutethimide, formestane, fadrozole), anastrozole has a number of advantages, including high potency, high specificity for the aromatase enzyme, a favorable safety profile, a convenient mode of administration, and no requirement for corticosteroid replacement therapy (9–12,15,16).

ESTROGEN SYNTHESIS AND AROMATASE INHIBITION

Steroid hormones (aldosterone, cortisol, androgens, and estrogens) are synthesized via a well-defined series of complex reactions involving cytochrome P450 hydrolases, lyases, and/or aromatase, with cholesterol as a precursor

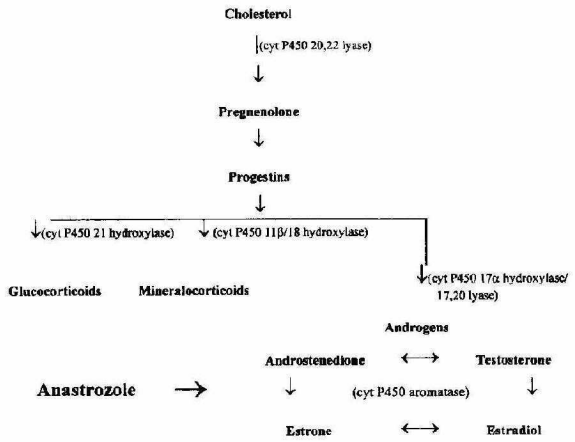

Figure 1. Estrogen synthesis (16).

(16,17) (Fig. 1). The aromatase enzyme acts at the last step in the estrogen-synthesis pathway, catalyzing the conversion of androgens to estrogens (16,17). Thus, inhibition of the aromatase reaction does not impair the synthesis of progestins, glucocorticoids, mineralcorticoids, or androgens (3,16,17).

Aromatization of adrenal androgen precursors in peripheral tissues is the primary source of estrogen in postmenopausal women (5,16,17). Approximately 50–100 μg of estrone can be produced daily by the extraglandular conversion of androstenedione, and some of this estrone is converted to produce 10–20 pg/mL of circulating estradiol (5). In addition to its presence in adipose, muscle, ovarian, brain, and liver tissue, aromatase activity (5–100 pg/g tissue/hr) has also been detected in breast tumors (5,16,18,19). Although this tumor aromatase activity would appear to be too low to account for a significant amount of estradiol, biochemical measurements might underestimate local levels, since aromatase may be localized in specific tumor-cell types (e.g., stromal or fat cells) (5,16,20).

Aromatase inhibitors can be classified as either mechanism-based ("suicidal") or competitive inhibitors (3,16). Mechanism-based aromatase inhibitors (e.g., formestane) are enzyme-specific, steroidal compounds that act as substrate analogues, covalently binding to the active site of the aromatase enzyme complex and irreversibly inactivating it (3,5,16,17). Competitive aromatase inhibitors bind reversibly to the aromatase enzyme com-

Table 1

Results of Preclinical Studies Evaluating the Selectivity of Anastrozole[a]

P-450 enzyme	Species	Results
20,22-Desmolase (cholesterol side-chain cleavage)	Rat Monkey	No adrenal hypertrophy or histological changes at 100 times the MED.[b]
11-Hydroxylase (glucocorticoid production)	Monkey Dog	Margin of selectivity was 30-fold in monkeys, 100-fold in dogs. No increase in circulating concentrations of 11-deoxycorticosterone, no hypokalemia, no adrenal hypertrophy after 6–10 mg/kg doses.
18-Hydroxylase (aldosterone synthesis)	Rat	≥ 200-fold margin of selectivity. No effect on plasma aldosterone concentration, no effect on sodium or potassium excretion in saline-loaded animals given 10–20 mg/kg doses.
17-Hydroxylase/ 17,20-Desmolase (androgen production)	Rat Monkey Dog	No effect on prostate-gland weight or plasma concentrations of testosterone or luteinizing hormone in rats given 1–10 mg/kg/day for 7–21 days. Increased plasma testosterone concentrations in monkeys (≅2×) and dogs (9×); no inhibition of androgen production of 10–100 times the MED.
Lanosterol-14-demethylase (cholesterol synthesis)	Rat Dog	≥ 30-fold margin of selectivity. No reduction in plasma cholesterol following administration of 25 mg/kg in rats or 3 mg/kg in dogs.

[a]From reference 15.
[b]MED, maximum effective dose for aromatase inhibition.

plex and inhibit aromatization only for as long as they occupy the active site (3,5). Steroidal competitive aromatase inhibitors (e.g., 6α-bromo-androstenedione) are inherently specific but are associated with agonist and antagonist effects on estrogen, glucocorticoid, androgen, and progesterone receptors (5,16). Compared with steroidal inhibitors, nonsteroidal competitive inhibitors (e.g., aminoglutethimide) have a greater potential for blockade of several cytochrome P450-mediated steroidal hydroxylations, but tend not to exhibit steroidal agonist or antagonist activity (5,16).

The prototype aromatase inhibitor, aminoglutethimide, was initially developed as an anticonvulsant. This nonsteroidal competitive aromatase inhibitor provides 95%–98% inhibition of aromatase; however, aminoglutethimide also inhibits cholesterol side-chain cleavage, producing a "medical adrenalectomy" that necessitates corticosteroid replacement therapy (3,5,16). In addition, aminoglutethimide has low potency and is associated with a high incidence of side effects (35%) and discontinuation of therapy (5%) (5,16).

In recent years, the development strategy for aromatase inhibitors in the management of advanced breast cancer has been to synthesize agents with increased potency and selectivity, as well as an improved toxicity profile compared with aminoglutethimide. The third-generation, nonsteroidal, competitive aromatase inhibitor anastrozole was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced breast cancer in postmenopausal women following failure with tamoxifen therapy.

ANASTROZOLE

Potency and Specificity

Anastrozole {2,2′-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene] bis (2-methyl-propionitrile)} has a high intrinsic potency and is able to inhibit human placental aromatase activity in vitro by 50% at a concentration of 0.043 μg/mL (15 nM) (9,11,15). In vivo studies of aromatase activity in rats have shown that an oral 0.1 mg/kg dose of anastrozole inhibits ovulation when administered to mature females on day 2 or 3 of the estrous cycle, and inhibits androstenedione-induced uterine hypertrophy when administered to prepubertal animals for 3 days (9,11,15). Daily oral anastrozole doses ≥ 0.1 mg/kg have been shown to inhibit peripheral aromatase activity in male pig-tailed monkeys, resulting in 50%–60% reductions in circulating estradiol levels (9,15).

The high selectivity of anastrozole for aromatase has been demonstrated in a series of studies evaluating its effect on other cytochrome P450 enzymes involved in steroidogenesis in rat, dog, and monkey models (Table 1) (9,11,15). At concentrations up to ≥200 times that of its maximally effective aromatase-inhibitory dose, anastrozole did not produce pathological changes in the adrenal gland nor affect aldosterone concentrations, sodium or potassium excretion, or testosterone synthesis (9,11,15). In comparison, fadrozole (another aromatase inhibitor) has been shown to increase 11-deoxycorticosterone concentrations in monkeys, and to reduce aldosterone concentrations, as well as alter

Table 2

Estrogen Suppression by Anastrozole[a]

Population	Dose regimen	Results
29 Male volunteers (6–7/dose)	0–60 mg, single dose escalation	Doses ≥ 7.5 mg produced at least an 80% suppression of estradiol.
14 Healthy postmenopausal female volunteers	0.5 or 1 mg daily for 14 days	Estradiol lowered to limits of detection of assay by 3–4 days of treatment in 2/6 patients in 0.5 mg group and 7/7 patients in 1 mg group. Suppression maintained for at least 6 days after study drug discontinued.
8 Healthy postmenopausal female volunteers 7 days; placebo	3-mg single dose, followed 3 days later by 3 mg daily for 7 days; placebo crossover	Estradiol levels lowered 70% (first dose) to 80% (subsequent dosing) compared with placebo. Suppression maintained for 4 days after last dose. Circulating levels of estrone minimally suppressed by first dose, significantly decreased with subsequent dosing.
19 Postmenopausal women with advanced breast cancer	5 mg/day for first 14 days, followed by 10 mg/day for an additional 14 days	Estradiol concentration suppressed 80% from baseline to limits of detection of assay. Estrone lowered 69%–86%; estrone sulfate lowered 83%–92%.

[a]From references 9–12, 15.

Table 3

Tumor Response in Two Phase III Clinical Trials Involving 263 Patients Given Arimidex® (1 mg daily) and 253 Patients Given Megestrol Acetate (40 mg q.i.d.)[a]

	Number	Response[b]	Stable Disease[c]	Progression	Prog Time[d]
Trial #1					
Arimidex®	128	10.2%	26.6%	48.4%	170 days
Megestrol acetate	128	5.5%	29.7%	51.6%	151 days
Trial #2					
Arimidex®	135	10.4%	23.7%	58.5%	132 days
Megestrol acetate	125	10.4%	22.4%	56.0%	120 days

[a]From references 12–14.
[b]Either a complete or partial objective tumor response.
[c]Stable for ≥ 6 months.
[d]Median time to progression; conservative estimate based on strict UICC criteria.

sodium and potassium excretion in rats at doses only 5 times its aromatase-inhibitory dose (9,11).

Anastrozole was not associated with direct progestogenic, estrogenic, or androgenic activity in rats, even at up to 10 times its maximally effective aromatase-inhibitory dose (11,12). In addition, in rats, mice, dogs, and cats, anastrozole did not show any significant pharmacological activity other than aromatase inhibition (11,15). Anastrozole did not affect autonomic, neuromuscular, or respiratory function at an intravenous dose of 1 mg/kg. At an oral dose of 10 mg/kg, anastrozole did not affect the central nervous system (CNS), cardiovascular function (other than causing a small reduction in blood pressure and shortening of the electrocardiographic Q–T interval in dogs), renal function, gastrointestinal motility, gastric acid secretion, pain perception, inflammatory response, clotting ability, or local anesthetic activity.

Anastrozole's high selectivity and lack of adverse effect on steroidogenesis were also demonstrated in clinical pharmacology studies (9–12,15). In healthy postmenopausal volunteers and patients with advanced breast cancer, anastrozole did not affect cortisol or aldosterone secretion, response to adrenocorticotrophic hormone (ACTH), or thyroid-stimulating hormone (TSH) concentrations when administered at up to 10 mg daily (i.e., up to 10 times the recommended daily dose).

Estrogen Suppression

Clinically significant suppression of serum estradiol (by 80% of its pretreatment baseline value) following 0.5–10 mg daily oral doses of anastrozole was demonstrated in four clinical pharmacological studies using a highly sensitive, validated radioimmunoassay method with a 3.7 pmol/L detection limit (Table 2) (9–12,15). In these studies, only about one third of postmenopausal volunteers and patients who were given 0.5 mg anastrozole achieved estrogen suppression close to the assay limit of detection, whereas 100% of those given 1 mg, 75% of those given 3 mg, 95% of those given 5 mg, and 100% of those given 10 mg achieved estrogen suppression to the lower limit of the assay (9,11,15). Therefore, a 1 mg daily dose of anastrozole is considered to be the minimal dose that provides maximal estrogen suppression (Table 2).

In a recent pharmacological study involving postmenopausal women with breast cancer who were given 1 mg anastrozole daily for 28 days, whole-body aromatase activity was reduced by 96% (21). Plasma concentrations of estradiol and estrone were reduced by approximately 85%, from 19.3 pmol/L at pretreatment to 3.0 pmol/L, and from 72.0 pmol/L to 11.1 pmol/L, respectively. In addition, plasma concentrations of estrone sulfate were reduced from 426.2 pmol/L to 32.5 pmol/L (92% reduction).

Clinical Trials

In two phase III, multicenter, randomized, parallel-group trials, postmenopausal women with advanced breast cancer whose disease had progressed following antiestrogen (tamoxifen) therapy were given either anastrozole (1 mg/day) or the progestin megestrol acetate (40 mg q.i.d.), and were evaluated with respect to objective response and time to disease progression (Table 3), as well as duration of response, survival, and quality of life (12–14). Approximately one-third of the patients given either anastrozole or megestrol acetate derived clinical benefit from this therapy (i.e., a positive objective tumor response or stabilization of disease for at least 6 months) (Table 3). There were no statistically significant differences between the treatment groups with respect to tumor response or time to pro-

Table 4

Comparison of the Incidence of Potentially Drug-Related[a] Adverse Events in Two Phase III Clinical Trials Involving 262 Patients Given Arimidex® (1 mg daily) and 253 Patients Given Megestrol Acetate (40 mg q.i.d.)[b]

	Arimidex®	Megestrol acetate
Withdrawn due to AE	2.7%	4.0%
Gastrointestinal disturbance	29.4%	21.3%
Hot flushes	12.6%	13.8%
Edema	7.3%	13.8%
Thromboembolic disease	3.4%	4.7%
Vaginal dryness	1.9%	0.8%
Weight gain	1.5%	11.9%[c]
≥5% weight gain	12.6%	34.4%[c]
≥10% weight gain	2.3%	10.7%[c]

[a]Anticipated to be potentially causally related to one or both therapies based on drug pharmacology.
[b]From references 12–14.
[c]Significantly different from Arimidex treatment group at $p \leq 0.01$.

gression, indicating that anastrozole (1 mg once daily) was as effective as the standard regimen of megestrol acetate (40 mg q.i.d.) in these patients.

Objective tumor response, based on conservative interpretation of the stringent Union Internationale Contre le Cancer (UICC) criteria, was observed in approximately 10% of patients given anastrozole and 8% of those given megestrol acetate. Although these rates appear low, they are consistent with those reported in other studies of second-line hormonal treatment using UICC criteria in patients in whom tamoxifen therapy failed (22–26). In addition, the observed response rates were not unexpected, since 36% of the patients in these two phase III studies had had previous cytotoxic therapy, 46% had visceral lesions, 43% relapsed while receiving adjuvant tamoxifen, 62% had bone metastases, and 28% had nonmeasurable disease and therefore could not attain a partial-response (PR) classification.

Anastrozole was well-tolerated in both clinical trials, with the incidence of withdrawal because of adverse events and the type, severity, and incidence of individual adverse events generally comparable with the results found with megestrol acetate. In contrast, the number of patients gaining weight, as well as the amount of weight gained, was significantly greater with megestrol acetate than with anastrozole ($p \leq 0.01$); also, more patients receiving megestrol acetate continued to gain weight over time (Table 4). Although some benefit may be realized in patients with cachexia, persistent, continuing weight gain is undesirable, psychologically distressing, and may be problematic for patients undergoing chronic treatment of breast cancer.

Role in Clinical Practice

Postmenopausal women with estrogen receptor-positive, metastatic breast cancer and who do not have rapidly progressing visceral disease or tumor-related lung or liver dysfunction are suitable candidates for endocrine therapy. The nonsteroidal antiestrogen tamoxifen is currently the most widely used first-line hormonal agent in patients with metastatic breast cancer (6,27). However, up to 53% of patients who initially respond to tamoxifen eventually exhibit tamoxifen-resistant disease and require treatment with an alternative endocrine agent (27). For these patients, the third-generation aromatase inhibitor anastrozole offers a new option for second-line hormonal therapy.

Cross-resistance from tamoxifen, to anastrozole has not been observed, and clinical experience supports the safety and efficacy of anastrozole in the management of advanced breast cancer in postmenopausal women with disease progression following treatment with tamoxifen (12–14). Aromatase-inhibitory doses of anastrozole do not affect the cytochrome P450 hydroxylase or lyase enzymes involved in steroidogenesis, and corticosteroid replacement therapy is therefore unnecessary in patients treated with anastrozole (12). In addition, alterations in TSH concentrations have not been observed with anastrozole (12). Anastrozole can be given orally in a convenient, once-daily dosing regimen; is well-tolerated; and is not associated with weight gain (12–14). A potential

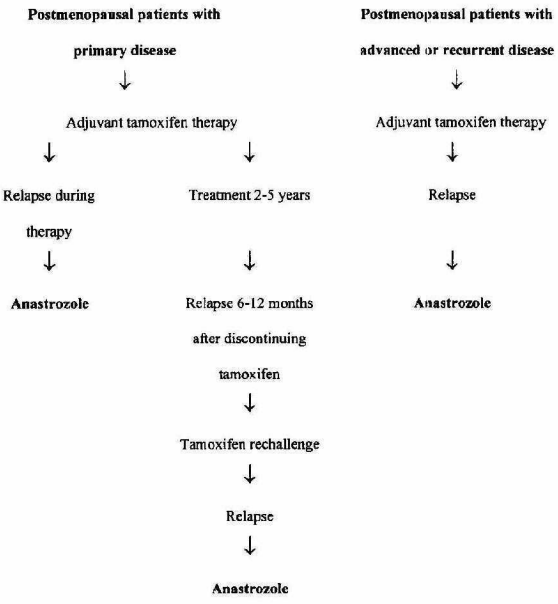

Figure 2. Potential algorithm for hormonal treatment of metastatic breast cancer.

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