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Anastrozole
In Early Breast Cancer

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Contents

Abstract

▲ Anastrozole, a nonsteroidal selective aromatase inhibitor, has recently been approved in the US and several other countries for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.

▲ In the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, anastrazole 1mg was significantly more effective than tamoxifen 20mg or combined treatment (17 and 19% relative risk reduction) for disease-free survival in postmenopausal women with early breast cancer.

▲ Anastrazole was also significantly more effective than tamoxifen for time to tumour recurrence and the odds of a primary contralateral tumour as a first event.

▲ During the first 2 years of treatment with anastrozole, tamoxifen or the combination, patient quality of life was similar in all treatment groups.

▲ Compared with tamoxifen, anastrozole was associated with a significantly lower incidence of vaginal bleeding, vaginal discharge, hot flushes, endometrial cancer, ischaemic cerebrovascular events, venous thromboembolic events and deep vein thrombosis including pulmonary embolism; tamoxifen was associated with a lower incidence of musculoskeletal disorders and fracture.

Features and properties of anastrozole	
New Indication	
Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer	
Mechanism of action	
Inhibition of aromatase-mediated conversion of adrenal androgens to estrogen	
Pharmacokinetics in postmenopausal volunteers (single-dose oral anastrozole 1mg)	
Peak plasma concentration	13.7 μg/L
Time to peak plasma concentration	2h
Time to steady state	9–10 days
Main route of elimination	Hepatic metabolism
Elimination half-life	40.6h
Dosage and administration	
Route of administration	Oral
Dose	1mg
Frequency of administration	Once daily
Adverse events	
Most frequent	Hot flushes, musculoskeletal disorders, fatigue, mood disturbances, nausea/vomiting

Breast cancer is a major cause of morbidity and mortality in both pre- and postmenopausal women, with approximately 200 000 women in the US undergoing therapy for breast cancer each year.[1,2] However, advances in the treatment of early breast cancer during the past two decades have led to a downward trend in mortality attributable to this disease.[3] During this time, the use of endocrine agents has increased substantially; tamoxifen is currently the most widely used endocrine drug for the management of all stages of breast cancer in pre- and postmenopausal women with estrogen-dependent tumours.[1]

The choice of endocrine therapy depends on the menopausal status of the patient, as this determines the source of estrogen production. In premenopausal women, the major site of estrogen production is the ovaries, whereas in postmenopausal women estrogen is primarily produced via aromatase, a cytochrome P450 enzyme complex which catalyses the production of estrogen from adrenal androgens in peripheral tissues (aromatisation).[1] The mechanism of action of most endocrine drugs involves either blockade of estrogen activity at the cellular level (antiestrogens, e.g. tamoxifen) or inhibition of estrogen production (aromatase inhibition or ovarian ablation). Aminoglutethimide, which was introduced in the late 1970s, has been the most widely used aromatase inhibitor, but because of its nonselectivity for aromatase, adverse events including lethargy and skin rash are common. More recently, newer agents have been developed which have higher selectivity for aromatase.[1]

Anastrozole is an orally active, nonsteroidal, selective aromatase inhibitor indicated for first-line treatment of postmenopausal women with advanced breast cancer;[4] anastrozole in advanced breast cancer has been reviewed previously (see Wiseman and Adkins[5]). This review focuses on the use of anastrozole as adjuvant treatment for postmenopausal women with hormone receptor–positive early breast cancer, an indication which has recently been approved in the US and other countries.

1. Pharmacodynamic Profile

Aromatase Inhibition and Suppression of Estrogen

- In a double-blind crossover study, anastrozole 1 or 10mg administered once daily for 28 days to 12 postmenopausal women with advanced or recurrent breast cancer reduced the total body aromatisation from the baseline value of 2.25% to 0.074 and 0.043%, respectively (96.7 and 98.1% inhibition) [$p < 0.005$].[6] Similarly, in 12 postmenopausal women with estrogen receptor-positive metastatic breast cancer, anastrozole 1mg once daily for 6 weeks inhibited total body aromatisation by 97.3% versus baseline.[7]
- Neoadjuvant treatment with anastrozole 1mg once daily for 15 weeks reduced mean intratumoural and plasma concentrations of estrone, estradiol and estrone sulfate by 72.9–94.2% from baseline in 12 postmenopausal women with estrogen receptor-positive locally advanced noninflammatory breast cancer.[8] Mean baseline intratumoural concentrations of estrone, estradiol and estrone sulfate were 173.6, 217.9 and 80.7 fmol/g; mean baseline plasma concentrations were 70.6, 18.4 and 578.8 pmol/L, respectively.
- Results from a randomised, double-blind study in 23 postmenopausal women with large estrogen receptor-rich breast tumours showed that once-daily anastrozole 1 or 10mg for 12 weeks effectively blocks estrogen synthesis both peripherally and within the breast.[9] Patients were given an 18-hour infusion of ^{3}H-androstenedione and ^{14}C-estrone both before surgery and 12 weeks after treatment with anastrozole.
- Analysis of tumour tissue and blood samples showed peripheral and *in situ* tumour aromatase activity were reduced by 94 and 89% (both dosages of anastrozole).[9] Although the effect of anastrozole on tumour estrone uptake was inconsistent, median tumour estrone and estradiol concentrations decreased by 70 and 67% (both dosages), compared with baseline.
- Anastrozole had similar effects on plasma estrogen concentrations in healthy postmenopausal

Japanese (n = 22) and Caucasian (n = 23) women in a nonblind, parallel-group study.[10] The women received once-daily anastrozole 1mg for 16 days. Mean plasma estradiol and estrone sulfate concentrations were reduced from baseline by 87.3 and 93.0% in Japanese women, compared with 87.2 and 93.3% in Caucasian women. Baseline concentrations of estradiol and estrone sulfate were 21.4 and 561 pmol/L in the Japanese volunteers, and 25.9 and 476 pmol/L in the Caucasian volunteers.

Other Endocrine Effects

- Anastrozole is a specific inhibitor of aromatase and shows little, if any, effect on other enzyme systems. In contrast to the aromatase inhibitor aminoglutethimide, which inhibits several enzymes involved in adrenocorticosteroid synthesis, anastrozole ≤10 mg/day has no significant effect on adrenal glucocorticosteroid or mineralocorticoid synthesis in postmenopausal women.[11,12]
- Inhibition of estrogen synthesis by anastrozole did not alter concentrations of androgenic precursors in postmenopausal women.[11-14] Plasma concentrations of aldosterone, hydrocortisone, androstenedione, dehydroepiandrosterone sulfate and 17-hydroxyprogesterone remained similar to those at baseline during anastrozole treatment in both postmenopausal women with advanced breast cancer and postmenopausal volunteers. Anastrozole also had no effect on the adrenocorticotrophic hormone-stimulated release of hydrocortisone or aldosterone, or on plasma concentrations of luteinising hormone or follicle stimulating hormone (urofollitropin).
- Anastrozole 5–10 mg/day, unlike aminoglutethimide, had no effect on thyroid stimulating hormone (TSH), which inhibits thyroxine synthesis resulting in a compensatory increase in TSH.[15]

2. Pharmacokinetic Profile

- A mean peak plasma concentration of 13.7 μg/L was reached 2 hours after oral administration of a single 1mg dose to seven healthy postmenopausal women.[12] Administration of anastrozole with food does not affect the extent of absorption, and anastrozole is approximately 40% bound to plasma proteins.[4]
- Steady-state concentrations of anastrozole were reached after 9–10 days of once-daily administration (0.5–10 mg/day), and were approximately 3- to 4-fold higher than after single-dose administration in postmenopausal women.[11,12]
- Results from a pharmacokinetic substudy of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial (see section 3) showed that after 3 months' administration of once-daily anastrozole 1mg to 138 postmenopausal women with early breast cancer the geometric mean minimum plasma concentration (C_{min}) was 37.4 μg/L (measured 20–28 hours post-dose).[16] In patients who received once-daily anastrozole 1mg plus tamoxifen 20mg, anastrozole C_{min} at steady state was 25.5 μg/L; the ratio of the geometric mean values was 0.73 (90% confidence interval [CI] 0.67–0.80), indicating that the mean concentration of anastrozole was 27% lower in the presence of tamoxifen than with anastrozole alone ($p < 0.001$). C_{min} for tamoxifen, however, was similar with or without coadministration of anastrozole (94.8 and 95.3 μg/L).[16]
- Approximately 10% of an orally administered dose of anastrozole is excreted unchanged in the urine within 72 hours.[15] Anastrozole is extensively metabolised in the liver via *N*-dealkylation, hydroxylation and glucuronidation, with about 60% of the dose excreted in the urine as metabolites.[4] The mean terminal elimination half-life after administration of a 1mg dose of anastrozole to 14 healthy postmenopausal women was 40.6 hours.[15]
- Increasing age does not significantly affect the pharmacokinetics of anastrozole in postmenopausal women. Because renal clearance is not a significant pathway for anastrozole, systemic clearance of the drug is not significantly altered in patients with renal insufficiency.[4] Although hepatic metabolism accounts for about 85% of anastrozole elimination, plasma concentrations of the drug in patients with mild to moderate hepatic impairment are similar to those seen in patients with normal

liver function; no studies have been reported in patients with severe hepatic dysfunction.[4] However, in the UK, anastrozole is contraindicated in patients with severe renal and moderate or severe hepatic disease.[17]

3. Therapeutic Efficacy

The Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial

The ATAC trial was conducted to determine if anastrozole was non-inferior or superior to tamoxifen, or if anastrozole in combination with tamoxifen was superior to tamoxifen alone, for adjuvant therapy in postmenopausal patients with early breast cancer.[18] The trial is ongoing and has a planned duration of 5 years.

ATAC Trial Design

The ATAC trial was a randomised, double-blind, placebo-controlled, parallel-group, multicentre study in 9366 postmenopausal women with histologically proven, operable invasive breast cancer who had completed primary surgery and, in some instances, chemotherapy, and who were candidates for hormonal adjuvant therapy.[18] Patients included in the trial were considered postmenopausal if they had undergone bilateral ovariectomy, were aged >60 years or were aged between 45 and 59 years with an intact uterus and had been amenorrhoeic for either ≥12 months or <12 months with follicle stimulating hormone concentrations within the postmenopausal range.

Patients were excluded from the trial if they had metastatic disease or a previous history of invasive malignant disease (excepting squamous or basal-cell carcinoma of the skin or cone-biopsied cervical intraepithelial neoplasia). Patients who had started chemotherapy >8 weeks after surgery or completed it >8 weeks before the start of randomised treatment were excluded, as were patients who did not undergo chemotherapy but had completed primary surgery >8 weeks before starting randomised treatment. Patients who were unwilling to stop using any hormonal drug, including hormone replacement therapy, were also ineligible.[18]

Of the 9 336 eligible patients, 3 125 received once-daily anastrozole 1mg plus placebo, 3 116 received once-daily tamoxifen 20mg plus placebo, and 3 125 received once-daily anastrozole 1mg plus tamoxifen 20mg (combination); patients could start trial therapy while receiving radiotherapy. There were no clinically relevant between-group differences in baseline characteristics. The average age of patients was 64.2 years and the majority of patients were lymph-node negative (61.0%), had a tumour ≤2cm in maximum diameter (63.8%) and had hormone (estrogen and progesterone) receptor-positive tumours (83.7%); 8.2 and 8.0% of patients had negative or other hormone receptor status. Patients who had received chemotherapy were randomised once their blood count had returned to within the normal range after their last course of treatment. Patients were followed up at months 3 and 6, then every 6 months. The median duration of follow-up was 33.3 months and the median duration of treatment was 30.7 months.[4,18]

Primary Endpoints

- Disease-free survival (time to the earliest occurrence of local or distant recurrence, new primary breast cancer or death from any cause) was significantly increased in anastrozole recipients compared with tamoxifen (17% relative risk reduction; $p = 0.013$) [figure 1] or combination therapy recipients (19% relative risk reduction; $p = 0.006$); there was no significant difference in disease-free survival between the tamoxifen and combination therapy groups. Disease-free survival estimates at 3 years were 89.4, 87.4 and 87.2% in the anastrozole, tamoxifen and combination therapy groups, respectively. In patients who were hormone receptor-positive, the risk reduction for disease-free survival was increased to 22% (hazard ratio [HR] 0.78, 95% CI 0.65–0.93; $p = 0.005$) for anastrozole versus tamoxifen.[18]

Secondary Endpoints

- The time to recurrence (defined similarly to disease-free survival but censoring non-breast cancer deaths prior to recurrence) was significantly increased in the anastrozole group compared with the

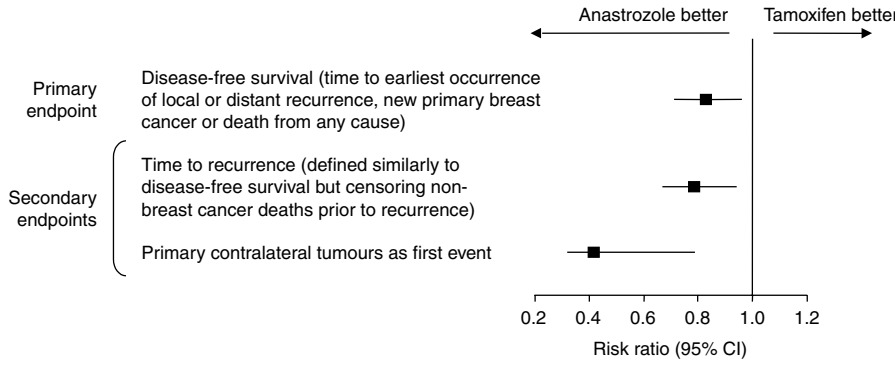

Fig. 1. Therapeutic efficacy of anastrozole in postmenopausal women with early breast cancer: results from the randomised, double-blind, placebo-controlled, multicentre Arimidex, Tamoxifen Alone or in Combination (ATAC) trial.[18] 9336 patients received anastrozole 1mg, tamoxifen 20mg or anastrozole 1mg plus tamoxifen 20mg once daily for a median 30.7 months. The median duration of follow-up was 33.3 months. **CI** = confidence interval.

tamoxifen (HR 0.79, 95% CI 0.67–0.94; p = 0.008) [figure 1] or combination (HR 0.75, 95% CI 0.63–0.89; p = 0.0007) groups; there was no significant difference in tumour recurrence between the tamoxifen and combination groups. Although tumour recurrence rates were similar among the anastrozole (2.49%), tamoxifen (2.30%) and combination (2.82%) groups at the end of the first year of treatment, at the end of the second and third years, annual recurrence rates were lower in the anastrozole group (2.61 and 2.94%) than in the tamoxifen (4.28 and 3.72%) or combination (4.11 and 3.71%) groups (HR ≤ 0.77 for all comparisons; 95% CI not stated).[18]

- Compared with tamoxifen, the odds of a primary contralateral breast tumour as a first event were reduced by 58% (p = 0.007) with anastrozole (figure 1). The number of contralateral tumours as a first event was 14, 33 and 28 in the anastrozole, tamoxifen and combination groups; the incidence was not significantly different in the tamoxifen and combination groups (p = 0.5).[18]
- Of the 75 new contralateral tumours in the three treatment groups, 62 were invasive. When only these tumours were taken into consideration, the odds of developing an invasive tumour were reduced by 70% with anastrozole compared with tamoxifen (relative risk 0.30, 95% CI 0.14–0.63; p = 0.001).[18]

Subgroup Analyses

- The tumour recurrence rate was more than three times higher in patients with hormone receptor-negative tumours than in those with hormone receptor-positive tumours (HR 3.54, 95% CI 3.00–4.19). In patients who were hormone receptor-positive, HRs for disease-free survival were 0.78 (95% CI 0.65–0.93; p = 0.005) for anastrozole versus tamoxifen, 0.76 (95% CI 0.63–0.91; p = 0.002) for anastrozole versus combination therapy, and 1.02 (95% CI 0.87–1.21; p = 0.8) for the combination versus tamoxifen. Disease-free survival estimates at 3 years were 91.2, 89.3 and 88.9% in the anastrozole, tamoxifen and combination groups. A between-treatment analysis of disease-free survival among hormone receptor-negative patients was not reported.[18]
- Time to recurrence of breast cancer in hormone receptor-positive patients was significantly greater with anastrozole than with tamoxifen (p = 0.003) or the combination (p = 0.0001); there was no significant difference between tamoxifen and the combination (quantitative data not reported). In patients with hormone receptor-negative tumours or tumours of other status, there was no significant difference between anastrozole and tamoxifen in time to recurrence. Similarly, in the 21.3% of patients who had undergone previous chemotherapy,

the time to tumour recurrence was not significantly different between the two treatments arms.[18]

Quality of Life

- During the first two years of treatment, anastrozole had no detrimental impact on patient quality of life; patient quality of life was similar in all treatment groups. In a substudy of the ATAC trial (reported as an abstract), 1 021 patients completed the Functional Assessment of Cancer-Breast questionnaire (together with an endocrine subscale) at baseline and at months 3, 6, 12 and every 6 months thereafter. At month 3, patients in all treatment groups showed a marginal improvement in quality of life and, after a slight worsening, stable endocrine scores (quantitative data were not reported).[19]

4. Tolerability

- Anastrozole was generally well tolerated in postmenopausal women with early breast cancer enrolled in the ATAC trial. Significantly fewer anastrozole recipients than tamoxifen recipients (7.8 vs 11.1%; $p < 0.0001$) discontinued treatment prematurely because of adverse events; 10.9% of combination recipients withdrew prematurely because of adverse events.
- Compared with tamoxifen, anastrozole was associated with a significantly lower incidence of vaginal bleeding ($p < 0.0001$), vaginal discharge ($p < 0.0001$), ischaemic cerebrovascular events ($p = 0.0006$), venous thromboembolic events ($p = 0.0006$), deep vein thrombosis including pulmonary embolism ($p = 0.02$) and hot flushes ($p < 0.0001$) [figure 2].[18]
- Among patients with an intact uterus at baseline, the incidence of endometrial cancer was significantly lower with anastrozole than with tamoxifen (0.1 vs 0.5%, $p = 0.02$); 0.3% of the combination group developed endometrial cancer.[18] Endometrial histology results from a substudy in 168 patients who were enrolled in the ATAC trial and who received anastrozole (n = 63), tamoxifen (n = 54) or the combination (n = 51) for 2 years, demonstrated a trend towards fewer endometrial abnormalities (predominantly polyps oc-

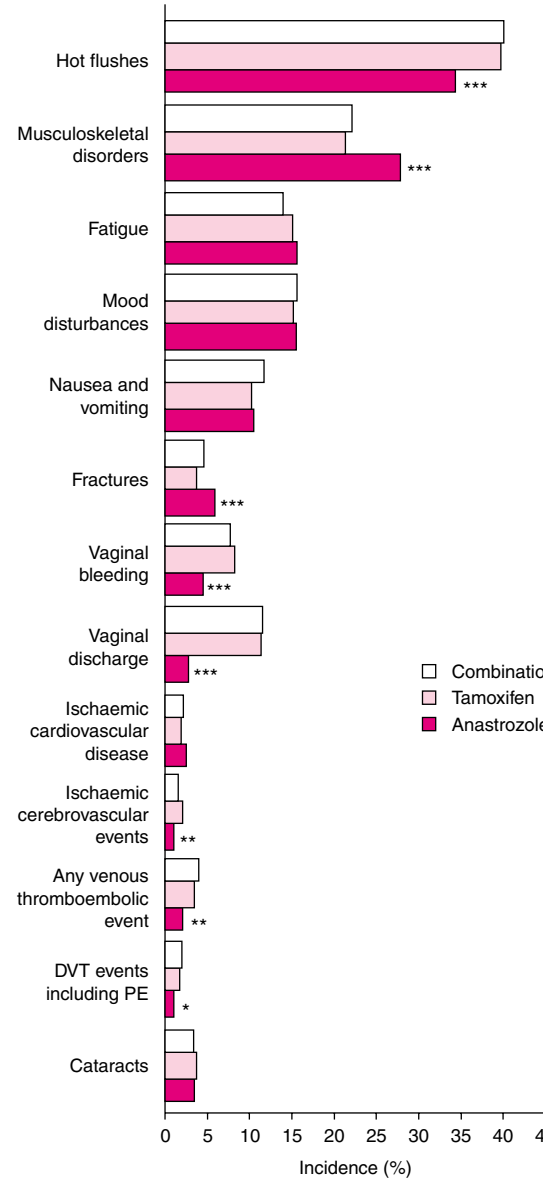

Fig. 2. Tolerability of anastrozole in comparison with tamoxifen or the combination of anastrozole plus tamoxifen; results from the randomised, double-blind, placebo-controlled, multicentre Arimidex, Tamoxifen Alone or in Combination (ATAC) trial.[18] 9336 postmenopausal women with early breast cancer received anastrozole 1mg, tamoxifen 20mg or anastrozole 1mg plus tamoxifen 20mg once daily. The median duration of treatment was 30.7 months. **DVT** = deep venous thromboembolic; **PE** = pulmonary emboli. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ vs tamoxifen.

curring *de novo*) with anastrozole compared with tamoxifen.[20] Of anastrozole, tamoxifen and combination recipients, 9, 17 and 27% had endometrial abnormalities ($p = 0.18$ for anastrozole vs tamoxifen). Furthermore, mean endometrial thickness at year 2, as measured by transvaginal ultrasound, was unchanged from baseline in anastrazole recipients (3.0mm), whereas the thickness had increased to 7.0mm in tamoxifen and combination recipients (baseline measurements were 3.9 and 3.0mm, respectively) [p values not reported]. *De novo* atypical hyperplasia occurred in 1.9% of tamoxifen recipients only.[20]

- There were no significant between-group differences in the incidence of new primary tumours other than contralateral breast tumours or endometrial cancer (colorectal, head and neck, lung, melanoma, ovary, skin or other).[18]
- The average weight gain in each group was 1.65kg (increase of 2.5%) over 2 years.[18]
- Tamoxifen was associated with a lower incidence of musculoskeletal disorders and fractures (both $p < 0.0001$) compared with anastrozole (figure 2). Although the incidence of hip fractures was the same in the anastrozole and tamoxifen groups (0.4%), there was a higher incidence of spine (0.7 vs 0.3%) and wrist/Colles' fractures (1.2 *vs* 0.8%) in the anastrozole group (statistical analysis not performed).[18]

5. Dosage and Administration

The recommended dosage of anastrazole in postmenopausal women with early breast cancer is 1mg once daily (taken orally).[4] The optimal duration of treatment with anastrozole is not currently known; the recommended duration of tamoxifen therapy is 5 years, which is the planned duration of treatment in the ongoing ATAC trial.[18]

6. Anastrozole: Current Status in the Treatment of Early Breast Cancer

Anastrozole has recently been approved in the US and several other countries for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. In the ATAC trial, disease-free survival was significantly greater with anastrozole than with tamoxifen or anastrozole plus tamoxifen. The probability of tumour recurrence was also significantly lower in the anastrozole group than in the tamoxifen or combination groups. Tamoxifen was associated with a lower incidence of musculoskeletal disorders and fracture than anastrozole. However, compared with tamoxifen, anastrozole was associated with a significantly lower incidence of vaginal bleeding, vaginal discharge, hot flushes, endometrial cancer, ischaemic cerebrovascular events, venous thromboembolic events and deep vein thrombosis including pulmonary embolism. The ATAC trial is ongoing with a planned duration of 5 years.

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