European Journal of Cancer 1996;32A(3):404-412

AN 40391

Original Paper

A Randomised Trial Comparing Two Doses of the New Selective Aromatase Inhibitor Anastrozole (Arimidex)* With Megestrol Acetate in Postmenopausal Patients With Advanced Breast Cancer

W. Jonat,[1] A. Howell,[2] C. Blomqvist,[3] W. Eiermann,[4] G. Winblad,[5] C. Tyrrell,[6] L. Mauriac,[7] H. Roche,[8] S. Lundgren,[9] R. Hellmund[10] and M. Azab[10] on behalf of the ARIMIDEX Study Group

[1]University Women's Hospital, Eppendorf, Hamburg, Germany; [2]The Christie Hospital, Manchester, U.K.; [3]University Central Hospital, Helsinki, Finland; [4]Women's Hospital, Munich, Germany; [5]Department of General Oncology, Soder Hospital, Stockholm, Sweden; [6]Plymouth General Hospital, Plymouth, U.K.; [7]Institut Bergonie, Bordeaux, France; [8]Centre Claudius Regaud, Rue de Pont Saint-Pierre, Toulouse, France; [9]Regional and University Hospital, Trondheim, Norway; and [10]Medical Research Department, ZENECA Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, U.K.

The aim of this study was to compare the efficacy and tolerability of the new aromatase inhibitor 'ARIMIDEX' (anastrozole) with megestrol acetate in the treatment of advanced breast cancer in postmenopausal women. Anastrozole is a new potent and highly selective non-steroidal aromatase inhibitor. We conducted a prospective randomised trial comparing two doses of anastrozole (1 and 10 mg orally once daily) with megestrol acetate (40 mg orally four times daily) in postmenopausal patients with advanced breast cancer who progressed after prior tamoxifen therapy. All patients were analysed for efficacy as randomised (intention to treat) and for tolerability as per treatment received. Of the 378 patients who entered the study, 135 were randomised to anastrozole 1 mg, 118 to anastrozole 10 mg, and 125 patients to megestrol acetate. After a median follow-up of 192 days, response rate which included complete response, partial response and patients who had disease stabilisation for 6 months or more was 34% for anastrozole 1 mg, 33.9% for anastrozole 10 mg and 32.8% for megestrol acetate. There were no statistically significant differences between either dose of anastrozole and megestrol acetate in terms of objective response rate, time to objective progression of disease or time to treatment failure. The three treatments were generally well tolerated, but more patients on megestrol acetate reported weight gain, oedema and dyspnoea as adverse events while more patients on anastrozole reported gastro-intestinal disorders, usually in the form of mild transient nausea. Patients on anastrozole did not report higher incidences of oestrogen withdrawal symptoms. Anastrozole is an effective and well tolerated treatment for postmenopausal patients with advanced breast cancer. The higher 10 mg dose did not result in additional clinical benefit, but was well tolerated reflecting the good therapeutic margin with anastrozole. Based on this data, anastrozole 1 mg should be the recommended therapeutic dose.

Key words: aromatase, postmenopause, breast neoplasms, comparative study, megestrol, phase III clinical trials, random allocation

Eur J Cancer, Vol. 32A, No. 3, pp. 404–412, 1996

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

INTRODUCTION

After tamoxifen, progestins and the aromatase inhibitors are currently among the commonly used endocrine agents for the treatment of advanced breast cancer in postmenopausal women. In several randomised trials, these agents achieved similar efficacy to the anti-oestrogen tamoxifen [1–5]. However, progestins, such as megestrol acetate, are associated with a high incidence of weight gain, oedema and occasionally cardiovascular and thrombo-embolic side-effects [4,6,7]. Aminoglutethimide, a non-selective aromatase inhibitor, is associated with a high incidence of side-effects such as lethargy and rash and is often given alongside corticosteroid supplementation [2,8,9]. These side-effects have restricted the use of progestins and aminoglutethimide to second- and third-line treatments following tamoxifen.

Approximately one third of human breast cancers are oestrogen-dependent and will regress following oestrogen deprivation [10]. In postmenopausal women, the major mechanism for oestrogen production is the peripheral conversion (by aromatase) of the adrenal steroid androstenedione to oestrone and subsequently to oestradiol [11]. In addition to peripheral aromatase activity, it is known that about two thirds of breast tumours show aromatase activity which appears to provide a local source of oestrogens within the breast tumour [12], and oestrogen levels are higher in breast tumour than in plasma [13]. It is, therefore, theoretically possible that high doses of an aromatase inhibitor, which could achieve higher tissue concentration of drug, might block oestrogen synthesis within the tumour more efficiently. To date, it has not been possible to adequately test this hypothesis, probably because lack of selectivity and poor tolerability of aminoglutethimide have limited its investigation to a relatively small range of doses of 250–1000 mg daily, with or without hydrocortisone [14–16].

Anastrozole (Arimidex) is an achiral benzyltriazole derivative which has been shown to be a potent and highly selective aromatase inhibitor in preclinical and phase I clinical studies [17]. At doses of 1 mg daily and higher, anastrozole suppressed oestradiol to the maximum degree measurable. Doses up to 10 mg daily were investigated in early studies and did not have any effect on glucocorticoid or mineralocorticoid secretion as indicated by normal responses to ACTH stimulation tests [17]. In addition, anastrozole is rapidly absorbed, with maximal plasma concentration occurring within 2 h of oral administration, and has a long elimination half-life of 30–60 h allowing once daily dosing [17].

This report describes a prospective randomised trial which investigated the efficacy and tolerability of two blinded doses of anastrozole (1 mg and 10 mg orally once daily) compared with that of megestrol acetate at its recommended therapeutic dose of 160 mg daily (40 mg × 4 daily) in the treatment of postmenopausal women with advanced breast cancer. Anastrozole 1 mg daily was the lowest dose producing maximal oestradiol suppression, while the 10 mg dose was the highest dose investigated in early clinical studies and which still showed selectivity and good tolerability; the use of anastrozole 10 mg dose offered the opportunity of achieving increased intratumour concentrations of the drug and hence providing more efficient aromatase inhibition at the tumour level, with potential additional clinical benefit.

PATIENTS AND METHODS

Patient population

Patients were eligible for this study if they were postmenopausal women progressing on first-line tamoxifen for advanced breast cancer, or if they were relapsing whilst either receiving or having completed adjuvant tamoxifen treatment. Postmenopausal women were defined as being >50 years with no menstruation for the last 12 months or who have castrate levels of follicle stimulating hormone (FSH) (>40 IU/l). Since tamoxifen and its active metabolites have a very long half-life and can remain in the cells for 1 or more months, it was considered not feasible to require a tamoxifen withdrawal period in practice as many patients would be unwilling to withhold active therapy after the development of progressive disease on tamoxifen. For patients who were known to be oestrogen receptor (ER) negative, prior evidence of response to endocrine therapy was required. For all other patients, no minimum period of adjuvant tamoxifen or prior response to tamoxifen was required.

Patients were excluded if they had life-threatening visceral disease (extensive hepatic involvement or any degree of cranial or leptomeningeal spread or pulmonary lymphangetic spread), had previously been exposed to more than one cytotoxic chemotherapy regimen for advanced disease, or had received more than one prior hormonal treatment for advanced breast cancer. There was no upper age limit and performance status was World Health Organisation (WHO) 0, 1, or 2. The study was approved by the ethics committee at each participating centre, and all patients gave written informed consent before enrolment. Patients with measurable lesions or evaluable but non-measurable lesions were eligible in the study. Patients with only blastic bone lesions were not considered to be evaluable.

Study design

The study was a phase III randomised trial with parallel group design. Eligible patients were randomised on a 1:1:1 basis to receive orally either anastrozole 1 mg once daily or 10 mg once daily on a double-blind basis, or open-label megestrol acetate 40 mg four times daily. Randomisation was effected centrally using a computer generated random scheme. Subjects were allocated to treatment in balanced blocks which were assigned on a centre basis. All randomised patients were followed up until progression and/or death.

Systemic treatment for breast cancer, other than randomised treatment, was not permitted until disease progression. Radiotherapy was allowed, but irradiated lesions were considered non-evaluable for tumour response assessment unless for the assignment of progression.

Baseline screening assessments were completed within the 4 weeks prior to randomisation. On day 1 (the date of randomisation), eligible patients underwent a complete physical examination. Objective assessments for local and regional disease, together with biochemical, haematological and oestradiol measurements were made at day 1, weeks 4, 8, 12, 16, 20, 24 and every 12 weeks thereafter, until progression of the disease. Tumour evaluation included physical examination for superficial skin or soft tissue lesions, radionuclide bone scans, skeletal X-rays and chest X-rays for bone or pulmonary metastases. Head and liver CT scans were performed if clinically indicated.

Quality of life was assessed using the Rotterdam Symptom Checklist (RSCL) and a prospective subjective symptoms score. The RSCL was given to all patients for completion on day 1 and again every 12 weeks for 1 year, or until progression. The RSCL covers physical and psychological symptoms and the functional activity of the patient [18]. The subjective

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

symptom score was used at the same timepoints to evaluate analgesic use (4-grade scale), bone pain, and WHO performance status (5-grade scale each).

In the evaluation of tolerability, any detrimental change in the condition of patients during the trial other than breast cancer disease progression was recorded as an adverse event irrespective of causality. Adverse events were documented at each visit and monitored until they resolved.

Endpoints

The primary endpoints were time to objective disease progression, objective response rate and tolerability. The secondary endpoints were time to treatment failure, survival, duration of response, quality of life and subjective symptom scores. The assessment of tumour response included the evaluation of both measurable and evaluable non-measurable lesions. For measurable lesions, all measurements were source data audited and the measurements were then assessed by a validated computer algorithm which assigned tumour response category based on per cent tumour regression applying a strict interpretation of the UICC (International Union Against Cancer) criteria of response [19]. Complete response was only assigned if all lesions disappeared; partial response was only assigned if at least 50% regression of the sum of all measurable lesions was achieved; any 25% or more increase from the minimum recorded size of lesions or appearance of a new lesions was assigned objective progression. The use of the computer programme to assign the response category for measurable lesions from recorded measurements was adopted to decrease potential subjective bias of individual investigators in assigning responses to study patients. For all patients with only evaluable non-measurable lesions, including patients with osteolytic bone lesions, the category of partial response was not allowed to provide a rigorous objective response assessment. For all patients, complete or partial responses had to be confirmed by two successive tumour assessments at least 4 weeks apart. Response rate was calculated for all randomised patients (intention to treat basis) and non-evaluable patients were, therefore, included in the denominator as non-responders.

Time to progression, treatment failure, duration of response and survival were calculated from the date of randomisation. Time to progression was the time until objective evidence of progression or until death from any cause, whichever occurred first. Time to treatment failure was the time until objective progression, death or treatment withdrawal for any reason, whichever occurred first. Duration of response was the time to progression for responding patients.

Statistical analysis

The study was sized on the basis of the primary endpoints of time to progression and tumour response rate. A minimum of 300 patients recruited at a uniform rate over 12 months with a minimum follow-up of 6 months was expected to provide 80% power to detect a treatment difference of approximately 14 weeks in median time to progression, assuming an overall median of 26 weeks, at the two-sided alpha = 0.05 significance level. This size of study was expected to provide 90% power to detect a treatment difference of approximately 20% in tumour response rates, assuming an overall response rate of 25%, at the two sided alpha = 0.05 significance level.

An early interim analysis, included in the protocol, was conducted on primary endpoints only (time to progression and response rate). To allow for this, the O'Brien and Fleming method adjustment to the significance levels was used [20], and hence for the final analysis on these endpoints, significance was set at 4.8% level. In addition, for each endpoint, two analyses were conducted—anastrozole 1 mg versus megestrol acetate, and anastrozole 10 mg versus megestrol acetate. Therefore, in order to allow for this multiple testing, the level set for significance was then halved. Thus, the objective response and time to progression were assessed at the 2.4% level of significance, and other efficacy endpoints including quality of life and subjective scores at the 2.5% level. All objective efficacy endpoints were analysed on the basis of the treatment to which the patients were randomly assigned (intention to treat), while tolerability analyses were conducted on the basis of treatment actually received by the patients.

Time to treatment failure, time to disease progression and death were subjected to Cox's Proportional Hazards Model. The proportion of responders (complete response and partial response) was compared between treatment groups, using logistic regression. The estimated treatment effect was presented as an odds ratio with appropriate confidence intervals. For the Cox's Proportional Hazards Model and the logistic regression analyses, the hormone receptor status at entry and the disease status were used as covariates, and a test for treatment by covariate interaction was performed. RSCL scores were analysed by analysis of covariance (physical and psychological dimensions) and the Wilcoxon ranked-sum test (functional dimension). Subjective scores were analysed using logistic regression. Pharmacological adverse events, identified prospectively, were compared between treatments using Fisher's Exact Test. In addition, pairwise comparisons between anastrozole and megestrol acetate groups were performed on the number of patients with weight gain of at least 5% and at least 10% using Fisher's Exact Test.

RESULTS

Study population

A total of 378 postmenopausal advanced breast cancer patients from 73 centres were randomised into the trial between April 1993 and June 1994: 135 were randomised to receive anastrozole 1 mg once daily, 118 to receive anastrozole 10 mg once daily and 125 to receive megestrol acetate 40 mg four times daily. A total of 376 of the 378 randomised patients started study treatment. Patients' baseline characteristics are shown in Table 1. There were no clinically significant imbalances in the three treatment groups. A slightly greater percentage of patients on anastrozole 10 mg had experienced a prior response to tamoxifen for advanced disease, while a greater percentage of patients on anastrozole 1 mg had visceral lesions.

Efficacy endpoints

At the time of data cut-off for the analyses, the median duration of follow-up was 192 days for anastrozole 1 mg, 185 days for anastrozole 10 mg and 182 days for megestrol acetate.

There were no statistically significant differences between anastrozole 1 mg or 10 mg daily and megestrol acetate with respect to median time to progression (132, 156 and 120 days, respectively), time to treatment failure (121, 128 and 115 days, respectively) and survival (84.4%, 81.4% and 77.6% respectively). Figure 1a,b shows the Kaplan–Meier plots for time to disease progression and survival, respectively. Similar numbers of objective responses were observed in the three

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

Table 1. Patients' baseline characteristics

	Anastrozole 1 mg/day ($n = 135$)	Anastrozole 10 mg/day ($n = 118$)	Megestrol acetate 40 mg four times daily ($n = 125$)
WHO performance status			
0	51%	42%	45%
1	37%	39%	42%
2	12%	18%	14%
3	0	1%	0
Mean age and range (years)	65 (38–97)	66 (44–87)	64 (40–84)
Mean weight and range (kg)	67 (44–104)	67 (35–118)	67 (45–130)
Mean height and range (cm)	160 (140–176)	160 (135–178)	161 (143–175)
Prior therapy			
Adjuvant tamoxifen only	49%	39%	42%
Median disease free interval (months)*	27	28	32
Tamoxifen for advanced disease	51%	61%	58%
Prior response to tamoxifen†	36%	51%	37%
Prior chemotherapy	30%	28%	26%
Prior radiotherapy	60%	61%	64%
Receptor status			
ER+	62%	54%	58%
PR+	42%	37%	41%
ER and PR unknown	34%	39%	38%
Measurable disease	81%	75%	79%
No measurable disease	19%	25%	21%
Disease sites			
Soft tissue	42%	42%	42%
Bone	59%	56%	62%
Visceral	54%	43%	42%
Liver	21%	18%	19%
Disease extent			
Soft tissue only	11%	19%	20%
Bone only	22%	25%	29%
Visceral only	21%	16%	13%
Mixed	44%	39%	38%
Not evaluable	2%	2%	0

*For patients relapsing on or after adjuvant tamoxifen. † Complete and partial response in patients treated for advanced disease. PS, performance status; ER, oestrogen receptor; PR, progesterone receptor.

treatment groups (Table 2). Since partial response was not allowed for patients with evaluable non-measurable lesions, almost all responders in this subgroup were assigned a stable disease category. This included patients with only bone osteolytic lesion. Response rates including patients with stable disease for ≥6 months were 34.1% for anastrozole 1 mg, 33.9% for anastrozole 10 mg and 32.8% for megestrol acetate. There was no significant difference among the three treatment arms in their response rate in subgroups of patients according to the presence or absence of measurable lesions, disease status, receptor status and prior response to hormonal therapy (Table 3). Responses were observed in patients progressing on adjuvant tamoxifen as well as in patients who received tamoxifen treatment for advanced disease. The highest response rate was achieved in the subgroup of patients with soft tissue only disease (Table 3). Since the protocol did not specify a specific tamoxifen withdrawal interval, we analysed the response rate according to whether patients had short (<3 months) or long (>3 months) tamoxifen withdrawal interval before entering the study and there was no difference.

The median duration of response was 261 days for anastrozole 1 mg, 257 days for megestrol acetate and was not reached at the time of the analysis for anastrozole 10 mg. The duration of response was greater than 24 weeks in 74% of patients responding to anastrozole treatment. There was a high rate of completion of quality of life questionnaires throughout the study. The percentage of patients who completed the questionnaire from the total number of expected patients at each follow-up timepoint was more than 90% at entry, more than 75% at week 12 and more than 70% at week 24. There were no differences between the treatment groups in the physical or the functional dimensions of the quality of life questionnaire. At week 12, there was statistical evidence that megestrol acetate was associated with some benefit in the psychological dimension compared with anastrozole at 1 mg ($P = 0.008$) or 10 mg ($P = 0.003$). However, this difference was not apparent at 24 weeks. Subjective symptom scores revealed no difference between treatments in analgesic use. Anastrozole 10 mg was associated with less bone pain at 12 weeks than megestrol acetate ($P = 0.011$). Anastrozole 1 mg was associated with

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

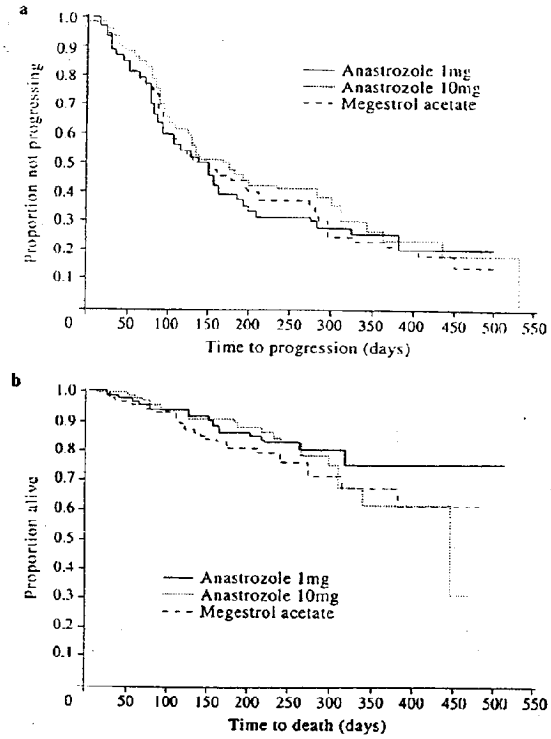

Figure 1. (a) Kaplan–Meier probability of time to progression. (b) Kaplan–Meier probability of time to death.

better performance status scores at 12 weeks than megestrol acetate ($P = 0.007$) and the odds ratio still favoured anastrozole 1 mg at 24 weeks, although the difference did not reach the critical level of statistical significance for the analysis ($P = 0.046$). Both anastrozole doses produced consistent suppression of oestradiol levels to below the limit of detection of the assay in more than 90% of patients during the treatment period.

Tolerability

The most frequently reported adverse events which were considered by the investigators to be probably drug-related were weight gain (8%) and dyspnoea (5.6%) on megestrol acetate; headache and hot flushes on anastrozole 10 mg (5% each); and nausea on anastrozole 1 mg (4.5%). The incidence of side-effects was, therefore, low for both anastrozole doses. Headaches, hot flushes and nausea were all described as mild or moderate and transient in nature. With the exception of more weight gain and oedema in the megestrol acetate group compared to anastrozole 1 mg, there were no significant differences between the treatment groups in side-effects (Table 4). The numbers of patients with absolute weight gain of at least 5 or 10% from baseline were also statistically significantly greater on megestrol acetate compared with either dose of anastrozole (Figure 2a). In addition, weight continued to be gained with time whilst patients were being treated with megestrol acetate (Figure 2b). In general, at the time of this analysis, all three treatments were well tolerated. The incidence of withdrawals because of adverse events irrespective of causality was low: 3% for anastrozole 1 mg (4 patients), 3.4% for anastrozole 10 mg (4 patients) and 4.8% for megestrol acetate (6 patients), with no particular adverse event predominating in any group.

DISCUSSION

Aminoglutethimide which represented the first generation of aromatase inhibitors has demonstrated clinical activity at least similar to tamoxifen and progestins in several randomised trials [2, 5, 21], but it has a poor side-effect profile, and is often prescribed with corticosteroid replacement due to its non-selectivity [2, 8, 9]. More recently, a selective second generation aromatase inhibitor (4-hydroxyandrostenedione) has been clinically investigated in breast cancer, mainly in Europe, and it induced clinical remissions in uncontrolled trials that were comparable with published data with other hormonal agents [22, 23]. One controlled study suggested comparable efficacy to tamoxifen [24]. However, 4-hydroxyandrostenedione has a poor oral bioavailability, limiting its use to parenteral treatment which is associated with local injection reactions [22, 23]. A number of new third generation aromatase inhibitors which are potent, selective, and orally bioavailable are currently under clinical investigation [25]. This study reports efficacy of the new selective aromatase inhibitor, anastrazole compared with a standard hormonal treatment, megestrol acetate. Time to treatment progression, time to treatment failure, survival and objective response rate were similar for the three treatment groups.

Outcome of advanced breast cancer can be related more to patient characteristics than to treatment differences. In this

Table 2. Best objective response for all randomised patients

	Anastrozole 1 mg/day ($n = 135$)	Anastrozole 10 mg/day ($n = 118$)	Megestrol acetate 40 mg four times daily ($n = 125$)
Response rate (CR + PR + SD ≥6 months) (%)	46 (34.1)	40 (33.9)	41 (32.8)
Complete response (%)	2 (1.5)	3 (2.5)	3 (2.4)
Partial response* (%)	12 (8.9)	12 (10.2)	10 (8)
Stable disease ≥6 months (%)	32 (23.7)	25 (21.2)	28 (22.4)
Stable disease <6 months (%)	10 (7.4)	18 (15.3)	14 (11.2)
Progression (%)	79 (58.5)	60 (50.8)	70 (56)

*Partial response category was not allowed for any patient with evaluable non-measurable lesions only (includes patients with osteolytic bone lesions).

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.