Anastrozole, a Potent and Selective Aromatase Inhibitor, Versus Megestrol Acetate in Postmenopausal Women With Advanced Breast Cancer: Results of Overview Analysis of Two Phase III Trials

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Purpose: **To compare the efficacy and tolerability of anastrozole (1 and 10 mg once daily), a selective, oral, nonsteroidal aromatase inhibitor, and megestrol acetate (40 mg four times daily), in postmenopausal women who progressed following tamoxifen treatment.**

Patients and Methods: **Two randomized, double-blind for anastrozole, open-label for megestrol acetate, parallel-group, multicenter trials were conducted in 764 patients. Because both trials were identical in design, an analysis of the combined results was performed to strengthen interpretation of results from each trial.**

Results: **The median follow-up duration was approximately 6 months. The estimated progression hazards ratios were 0.97 (97.5% confidence interval [CI], 0.75 to 1.24) for anastrozole 1 mg versus megestrol acetate and 0.92 (97.5% CI, 0.71 to 1.19) for anastrozole 10 mg versus megestrol acetate. The overall median time to progression was approximately 21 weeks. Approximately one third of patients in each group benefited from treatment. Twenty-seven patients (10.3%) in the anastrozole 1-mg group, 22 (8.9%) in the anastrozole 10-mg group, and 20 (7.9%) in the megestrol acetate group had a complete or partial response, and 66 (25.1%), 56 (22.6%), and 66 (26.1%) patients, respectively, had stable disease for ≥ 24 weeks. For all end points, individual trial results were similar to the results of the combined analysis. Anastrozole and megestrol acetate were well tolerated. Gastrointestinal disturbance was more common among patients in the anastrozole groups than the megestrol acetate group; the difference between the anastrozole 10 mg and megestrol acetate groups was significant ($P = .005$). Significantly fewer patients in the anastrozole 1-mg ($P < .0001$) and 10-mg ($P < .002$) groups had weight gain than in the megestrol acetate group. More than 30% of megestrol acetate–treated patients had weight gain ≥ 5%, and 10% of patients had weight gain ≥ 10%. Patients who received megestrol acetate continued to gain weight over time.**

Conclusion: **Anastrozole, 1 and 10 mg once daily, is well tolerated and as effective as megestrol acetate in the treatment of postmenopausal women with advanced breast cancer who progressed following tamoxifen treatment. Moreover, anastrozole therapy avoids the weight gain associated with megestrol acetate treatment.**

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TAMOXIFEN CITRATE (Nolvadex; Zeneca Pharmaceuticals, Wilmington, DE), is considered the first-line hormonal therapy for postmenopausal women with advanced breast cancer.[1] In the adjuvant treatment of women with early-stage breast cancer, tamoxifen treatment prolongs survival,[2] extends disease-free survival,[3] reduces the incidence of new primary breast tumors,[3] and offers a favorable long-term tolerability profile.[3] Because a significant number of patients who receive tamoxifen for advanced or early-stage breast cancer will have disease progression, new therapies that are effective and well tolerated are needed to treat women with advanced breast cancer.

Two classes of drugs, progestins and aromatase inhibitors, are frequently prescribed for postmenopausal women who have progressed following tamoxifen therapy. Progestins are effective, but their use is associated with common side effects such as weight gain, which has been reported to occur in up to 64% of patients.[4] Megestrol acetate (Megace; Bristol-Myers Squibb, Princeton, NJ) the most commonly used progestin, is associated with nausea and vomiting, hot flashes, vaginal bleeding, edema, hypercalcemia, rash, heart failure, hypertension, thrombocytopenia, depression, and Cushingoid symptoms, in addition to weight gain.[5] Aminoglutethimide was the first aromatase inhibitor to be evaluated in clinical trials, and is commercially available for the treatment of breast cancer in Europe and Canada. The efficacy of aminoglutethimide is similar to other endocrine agents,

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but it is nonselective and inhibits adrenal synthesis of glucocorticoids and mineralocorticoids and requires concurrent administration of hydrocortisone. In addition, aminoglutethimide is associated with frequent adverse effects that have limited its clinical use.[5,6] A selective aromatase inhibitor, formestane, which is commercially available in some European countries, has no effect on steroidogenesis, but requires administration as a deep intramuscular injection and has been associated with injection-site reactions.[7] Since the development of aminoglutethimide and formestane, a series of aromatase inhibitors has been synthesized; many of these compounds are currently under clinical investigation. Enhanced potency and specificity, as well as reduced side effects, are desired characteristics of new aromatase inhibitors in development.[8]

Anastrozole (Arimidex, Zeneca Pharmaceuticals), an achiral triazole derivative, is a new nonsteroidal, oral aromatase inhibitor with highly effective and selective activity for the aromatase enzyme.[9] Anastrozole has been investigated in a clinical trial program as a therapy for postmenopausal women with advanced breast cancer. In clinical pharmacology trials, circulating serum estradiol concentrations, measured by a sensitive assay, were consistently suppressed to the limit of quantification of the assay with daily anastrozole doses of 1 mg and higher.[9] Anastrozole was rapidly absorbed after oral administration, with maximal plasma concentrations occurring within 2 hours,[9] and it possesses a half-life that supports once-daily oral administration.[9]

In this report, we present the results of two phase III trials that compared the efficacy and tolerability of anastrozole and megestrol acetate in postmenopausal women with advanced breast cancer who progressed after tamoxifen treatment. Because both trials were identical in design, an analysis of the combined results was performed, which thereby strengthened interpretation of results from each trial. Anastrozole doses of 1 and 10 mg once daily were chosen for evaluation in these trials. The 1-mg daily dose was selected because it was the lowest dose of anastrozole to give maximum-detectable reduction of serum estradiol concentrations. In the absence of any safety concerns, the 10-mg daily dose was evaluated to determine whether a higher dose would offer enhanced antitumor activity and increased clinical benefit.

PATIENTS AND METHODS

Study Design

The two trials were randomized, double-blind for anastrozole, open-label for megestrol acetate, parallel-group, and multicenter studies. One trial was conducted at sites in North America (hereafter referred to as the North American trial), and one at sites in Europe, Australia, and South Africa (hereafter referred to as the European trial). Both trials compared the efficacy and tolerability of anastrozole 1 and 10 mg daily with megestrol acetate 40 mg four times daily for the treatment of postmenopausal women with advanced breast cancer. The primary objectives were to compare two dosages of anastrozole with megestrol acetate with respect to time to disease progression, tumor response, and tolerability. The secondary objectives were to compare the treatment groups with respect to time to treatment failure, response duration, and survival.

Patient Population

To enter the trials, patients were required to have progressed while receiving tamoxifen or other antiestrogen therapy for advanced breast cancer or relapsed during or after receiving adjuvant tamoxifen treatment; be postmenopausal, defined as having nonfunctioning ovaries through natural menopause or surgical, radiation, or chemical castration (women $>$ 50 years of age who did not menstruate during the preceding 12 months were considered postmenopausal, whereas women $<$ 50 years of age had to have a follicle-stimulating hormone concentration $>$ 40 IU/L to enter); and have a World Health Organization (WHO) performance status score $\leq$ 2. Patients were excluded if they had estrogen receptor-negative breast cancer (except when the patient had shown a previous response to tamoxifen treatment), exposure to more than one previous course of cytotoxic therapy for advanced disease (except adjuvant chemotherapy), exposure to more than one previous hormonal therapy for advanced breast cancer, or any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results. Written informed consent was obtained from all patients, and the studies were approved by the appropriate institutional review board at each site.

Treatment Program

Anastrozole was supplied as film-coated, white tablets that contained either 1 or 10 mg of drug. Megestrol acetate was supplied as white, circular, scored tablets that contained 40 mg of drug. Patients were randomly allocated to one of three oral treatment regimens: 1 mg of anastrozole once daily, 10 mg of anastrozole once daily, or 40 mg of megestrol acetate four times daily. Treatment continued until disease progression or until withdrawal from treatment for any reason other than progression. Patients who had disease progression were permitted to receive either cytotoxic therapy or other hormonal treatments. When patients withdrew before progression, they were monitored for time to progression.

Baseline screening assessments were completed within the 4 weeks before randomization. On day 1, the date of randomization, eligible patients underwent a complete physical examination. Each patient's disease was assessed clinically every 4 weeks for the first 24 weeks of treatment, and then every 12 weeks until week 48. After week 48, assessments were performed every 3 months until disease progression was detected. Bone scans were repeated every 24 weeks until disease progression or withdrawal. Radiographic examination of confirmed metastatic lesions was repeated every 12 weeks (or earlier when clinically indicated) during treatment and at withdrawal.

Patients were withdrawn from active treatment for a serious adverse event, noncompliance with protocol procedures, unwilling or inability to continue the trial, withdrawal by an investigator, or clinically significant breast cancer progression. All patients who were withdrawn were monitored for survival.

Efficacy Assessments

Assessments of tumor response included the evaluation of both measurable and nonmeasurable disease. Measurable disease was defined as the presence of metastatic lesions measurable in one or two dimensions using physical or radiographic methods (including computed tomography scan) and osteolytic bone lesions. For measurable lesions, only physical or radiologic measurements were recorded. To ensure consistency and objectivity in the assignment of response categories, a computerized algorithm was used to assign responses based on the measurements. The program strictly applied the protocol definition of response based on Union Internationale Contre le Cancer (UICC) criteria.[10] Nonmeasurable disease was defined as single metastatic lesions smaller than 0.5 cm, malignant pleural effusion or ascites, positive bone scan, and osteoblastic bone lesions. For nonmeasurable lesions, partial responses were not permitted to be assigned, in accordance with the strict criteria for assessment. Therefore, responses were assigned only in the categories of complete response, stable disease, or progressive disease.

The best objective response over time was determined on the basis of objective responses at each visit. Complete or partial responses were assigned only when noted on successive visits at least 4 weeks apart. Measurable lesions of bone, chest, and abdomen were assessed at 12-week intervals. A best response of stable disease was assigned when responses of stable disease or better were observed for at least 24 weeks. If such responses had been observed for less than 24 weeks because a patient did not have measurements for 24 weeks at the time of data cutoff, then a best response of stable disease for less than 24 weeks was recorded.

Time to progression, time to treatment failure, time to death, and duration of response were calculated from the date of randomization. Time to progression represented the time to objective disease progression or death, whichever occurred first. Patients who had not reached progression at the time of data cutoff were right-censored in the analysis at the time of their latest visit. Time to treatment failure was the time to earliest occurrence of progression, death, or withdrawal. Time to death represented the number of days until death from any cause. Duration of response, which was recorded for those with either a complete or partial response, was the time to objective progression or death.

Quality-of-Life Assessments

The primary quality-of-life assessment was the validated Rotterdam Symptom Checklist.[11] Other quality-of-life variables that were scored and recorded were the types of analgesics used, severity of bone pain, and performance status or level of daily activity. Because of differences between the two trials in the frequency at which the Rotterdam dimensions were collected and differences in the relative time frame in the wording of subjective scores, data from quality-of-life assessments from the two trials were not combined.

Tolerability Assessments

Any detrimental change in a patient's condition after the trial began and during any follow-up period, unless related to disease progression, was considered an adverse event. Patients were solicited indirectly for adverse events; prompted by a question, each patient described anything that had bothered her. In addition to monitoring for adverse events, routine laboratory tests results were performed at baseline, at selected times during therapy, and at withdrawal. The results of clinical laboratory tests were reviewed for clinically relevant changes. Physical examinations were performed and weight, blood pressure, and pulse were recorded at baseline, at selected times during therapy, and at withdrawal.

Statistical Analysis

The trials were designed to compare anastrozole and megestrol acetate using time to progression as the primary end point. A population of 300 patients (100 in each treatment group) in each trial was deemed sufficient to detect a treatment difference of approximately 14 weeks in median time to progression with 80% power and a two-sided alpha level of 0.05, assuming a median time to progression of 26 weeks and a minimum follow-up time of 6 months.

To protect against an imbalance in treatment allocation across centers, the randomization scheme was stratified for center in each trial. In addition, treatments were allocated in blocks of size three in the North American trial and six in the European trial, such that treatment groups were balanced after every three or six patients at each center.

Efficacy analyses were analyzed on the basis of the treatment to which the patients were randomly assigned (intention-to-treat basis). Cox's proportional hazards model was used to analyze time to disease progression, time to treatment failure, and time to death. Logistic regression was used to analyze response data. All efficacy analyses were adjusted for the covariates of previous treatment status (adjuvant or for advanced disease) and hormone receptor status. The combined estimate of the treatment effect for a time-to-event variable for either dose of anastrozole compared with megestrol acetate was derived by fitting a Cox proportional hazards model with trial and treatment as covariates and then testing for significance of treatment. Log hazards ratios and standard errors were estimated and were used to calculate confidence intervals on the hazards ratio. Upper confidence limits ≤ 1.25 for a hazards ratio of either dose of anastrozole to megestrol acetate would allow an inference that the effects of anastrozole were not substantially inferior to the effects of megestrol acetate (ie, an upper confidence limit of 1.25 was considered to represent equivalence between anastrozole and megestrol acetate).

Additional analyses were performed to assess the effects of the prognostic factors of prior hormonal treatment history, presence or absence of measurable disease, and presence or absence of visceral disease on time to progression and time to treatment failure. Likelihood ratio tests were performed to rule out qualitative interactions when treatment by prognostic factor interactions existed. Because the two anastrozole groups were compared with the megestrol acetate group, Bonferonni adjustments were made for the analyses of each end point. For tumor response data, an approach similar to the method outlined earlier was used.

Safety analyses were performed according to the treatment actually received. Adverse events that might be expected to occur on the basis of the pharmacology of anastrozole and megestrol acetate were prospectively identified and analyzed; these adverse events included weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness. Objective measurements of weight gain were also analyzed; the proportion of patients who had weight gain of greater than 5% and greater than 10% during the study compared with pretherapy were assessed. The incidence of adverse events was compared between patients treated with anastrozole 1 mg and those treated with megestrol acetate and between those treated with anastrozole 10 mg and those given megestrol acetate. Fisher's exact test was used for the statistical comparisons;

a two-sided alpha level of 0.01 was used to allow for multiple comparisons.

Interim analyses of each trial were performed in 1994 to enable independent data-monitoring committees to evaluate periodically efficacy and safety data from the two trials and recommend that the trials be continued or stopped, or recommend a change to the study design. In the North American trial, two interim analyses of objective response and time to progression were performed, whereas in the European trial one interim analysis was performed. In each trial, the O'Brien and Fleming adjustment was used in the analysis of both objective response and time to progression; the significance level for all end points was adjusted using the Bonferroni method. After reviewing interim results, the independent committees monitoring the two trials recommended that each of the trials be continued.

RESULTS

Patient Characteristics

Seven hundred sixty-four patients from 49 centers in North America and 73 centers in Europe, Australia, and South Africa were entered into the two trials and randomized to one of the three treatment groups. The groups formed by randomization were well balanced with respect to demographic and pretreatment characteristics (Table 1). Although there was an apparent imbalance in treatment allocation for the three groups, it was believed to be an artifact related to the large proportion of centers in the European trial in which the total number of patients recruited was not divisible by six. (Treatments were allocated in blocks of six in the European trial, compared with blocks of three in the North American trial.) Three patients did not receive therapy, and one patient who was randomized to 1 mg of anastrozole received 10 mg of anastrozole. All 764 patients were included in the efficacy analyses in accordance with the intention-to-treat approach. The median follow-up duration was approximately 6 months.

Time to Progression

Results for time to disease progression showed both doses of anastrozole to be equivalent to megestrol acetate. The individual trial results were similar to the combined results. Progression of disease occurred in 159 patients (60%) in the anastrozole 1-mg group, 146 (59%) patients in the anastrozole 10-mg group, and 163 (64%) patients in the megestrol acetate group. The comparisons of the 1-mg and 10-mg of anastrozole versus megestrol acetate groups did not differ significantly with respect to time to progression. The estimated progression hazards ratio for anastrozole 1 mg versus megestrol acetate was 0.97 (97.5% confidence interval [CI], 0.75 to 1.24). Similarly, the estimated progression hazards ratio for anastrozole 10 mg versus megestrol acetate was 0.92 (97.5% CI, 0.71 to 1.19). No differences could be detected between the two anastrozole doses and megestrol acetate. The overall median time to progression was approximately 21 weeks. A Kaplan-Meier plot of time to progression is presented in Fig 1.

Tumor Response

The best objective tumor response rates for the 1- and 10-mg anastrozole groups did not differ significantly from that for the megestrol acetate group. The individual trial results were similar to the combined results. Approximately one third of patients in each treatment benefited from therapy. Twenty-seven patients (10.3%) in the anastrozole 1-mg group, 22 (8.9%) in the anastrozole 10-mg group, and 20 (7.9%) in the megestrol acetate group had either a complete or partial response to treatment, and 66 (25.1%), 56 (22.6%), and 66 (26.1%) patients in the respective groups had stable disease for $\geq$ 24 weeks (Table 2). The estimated odds ratio for response for anastrozole 1 mg versus megestrol acetate was 1.32, with a 97.5% CI of 0.66 to 2.65. Similarly, the estimated odds ratio for response for anastrozole 10 mg versus megestrol acetate was 1.15, with a 97.5% CI of 0.55 to 2.36. Tumor responses were observed in all sites of disease, with the best responses in patients with soft tissue disease (complete or partial responses of 34% anastrozole 1 mg, 28% anastrozole 10 mg, and 27% megestrol acetate). The percentage of patients with soft tissue disease at entry was low: 12% and 15% of patients in the anastrozole 1- and 10-mg groups and 16% of patients in the megestrol acetate group. Responses were observed in patients who progressed after receiving adjuvant tamoxifen, as well as in patients who received tamoxifen for advanced disease.

The duration of response ranged from approximately 3 to 18 months in the three treatment groups. Among all responders, $\geq$ 70% were without progression for at least 24 weeks (74% anastrozole 1 mg, 81% anastrozole 10 mg, and 70% megestrol acetate). These percentages represented a conservative estimate, as many of the patients were continuing treatment and were censored at the time of data cutoff.

Treatment Failure

Treatment failure occurred in 169 patients (64%) in the anastrozole 1-mg group, 160 (65%) in the anastrozole 10-mg group, and 174 (69%) in the megestrol acetate group. For the majority of patients who reached treatment failure in each treatment group (51% anastrozole 1 mg, 53% anastrozole 10 mg, and 55% megestrol acetate), the reason for treatment failure was disease progression. Therefore, the inferences for time to treatment failure are the same as those generated for time to progression, and

Table 1. Demographic and Pretreatment Characteristics

Parameter	Anastrozole 1 mg (n = 263) No.	%	Anastrozole 10 mg (n = 248) No.	%	Megestrol Acetate (n = 253) No.	%
Age, years						
Mean	65		66		65	
Range	29-97		41-91		39-90	
Weight* (kg)						
Mean	68		69		67	
Range	31-112		35-131		42-130	
Previous treatment						
Surgery	346	94	230	93	237	94
Cytotoxic chemotherapy	98	37	92	37	89	35
Radiotherapy	153	58	146	59	156	62
Receptor status						
ER+, PR+	134	51	115	46	119	47
ER+, PR−	45	17	34	14	34	13
ER+, PR unknown	14	5	17	7	20	8
ER−, PR+	4	2	4	2	5	2
ER−, PR−	4	2	12	5	11	4
Unknown	62	24	66	27	64	25
Duration of tamoxifen treatment for advanced disease†‡						
No. of patients	128		138		148	
Median disease-free interval, weeks	93		96		89	
Relapsed during adjuvant tamoxifen treatment†‡						
No. of patients	121		92		102	
Median disease-free interval, weeks	128		133		165	
Previous best response to tamoxifen for advanced disease						
No. of patients	137		148		151	
Complete	12	9	17	12	16	11
Partial	22	16	33	22	30	20
Stable disease	64	47	59	40	60	40
Progression	12	9	15	10	16	11
Unknown	27	20	24	16	29	19
WHO performance status score						
0	138	53	109	44	116	46
1	91	35	101	41	103	41
2	34	13	34	14	32	13
3	0	0	4	2	1	<1
4	0	0	0	0	1	<1
Measurable disease	191	73	168	68	180	71
No measurable disease	72	27	80	32	73	29
Sites of metastatic disease§						
Soft tissue	99	38	95	38	92	36
Bone	166	63	149	60	156	62
Visceral	124	47	102	41	113	45
Liver	46	18	38	15	41	16
No evidence of liver involvement	217	83	210	85	212	84
No assessable metastatic disease‖	7	3	14	6	3	1
Extent of metastatic disease¶						
Soft tissue only	32	12	36	15	41	16
Bone only	75	29	66	27	77	30
Visceral only	42	16	34	14	38	15
Mixed	107	41	98	40	94	37
No assessable metastatic disease‖	7	3	14	6	3	1

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

*Weight was recorded for 256 patients in the anastrozole 1-mg group, 235 in the anastrozole 10-mg group, and 244 in the megestrol acetate group.

†For treatment of primary disease (after mastectomy or lumpectomy) and metastatic lesions.

‡Patients who did not receive tamoxifen and for whom duration of treatment could not be calculated are not included.

§Patients may be in > 1 category.

‖Includes patients with excised or irradiated local or distant disease at entry, patients with local or distant metastases that were excised or eradicated before entry, and 1 patient who had no assessable disease.

¶Categories are mutually exclusive.

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