A Phase III Trial Comparing Anastrozole (1 and 10 Milligrams), a Potent and Selective Aromatase Inhibitor, with Megestrol Acetate in Postmenopausal Women with Advanced Breast Carcinoma

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BACKGROUND. Anastrozole is a new oral aromatase inhibitor with highly potent and selective activity for the aromatase enzyme. In a Phase III trial, the efficacy and tolerability of anastrozole, given in doses of 1 and 10 mg orally once daily, and megestrol acetate, given in doses of 40 mg orally 4 times daily, were compared in 386 postmenopausal women with advanced breast carcinoma who progressed after tamoxifen therapy.

METHODS. The trial was randomized, double blind for anastrozole, open label for megestrol acetate, parallel group, and multicenter. Patients were randomly assigned to receive anastrozole, 1 mg (n = 128); anastrozole, 10 mg (n = 130); or megestrol acetate (n = 128). The primary efficacy measures were time to progression and tumor response; secondary measures were time to treatment failure, duration of response, quality of life, and time to death.

RESULTS. With a median duration of follow-up of 6 months, there was no statistical evidence of a difference between either 1 or 10 mg doses of anastrozole and megestrol acetate for any efficacy endpoint. According to rigid response criteria, 10%, 6%, and 6% of patients in the anastrozole 1 mg, anastrozole 10 mg, and megestrol acetate groups, respectively, had an objective response (complete response or partial response) and 27%, 24%, and 30% of patients in the respective groups had stable disease for a duration of 24 weeks or longer. Quality-of-life assessments revealed that anastrozole in a 1-mg dose was associated with better physical scores and anastrozole in a 10-mg dose with better psychologic scores than megestrol acetate. Both anastrozole and megestrol acetate were generally well tolerated. Among anticipated adverse events, gastrointestinal disturbance was more common among patients in the anastrozole groups, whereas weight gain occurred more frequently among patients in the megestrol acetate groups. Weight increases of 5% or more and 10% or more were more common among megestrol acetate-treated patients; moreover, patients in this group continued to gain weight over time.

CONCLUSIONS. Anastrozole, given in doses of 1 and 10 mg once daily, represents a well tolerated and effective therapeutic option for the treatment of postmenopausal women with advanced breast carcinoma who progress after tamoxifen treatment.
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KEYWORDS: anastrozole, megestrol acetate, aromatase inhibition, progestin, breast carcinoma, postmenopausal.

Hormonal therapy is well established as a primary therapy for postmenopausal women with advanced breast carcinoma. The antiestrogen tamoxifen citrate (Nolvadex, Zeneca Pharmaceuticals, Wilmington, DE), is regarded as the first-line therapy for this group of patients;[1] however, a percentage of patients will have a recurrence and require additional palliative treatment for their disease. Progestins are frequently used as second-line therapy for patients who have progressed after tamoxifen therapy, but their appeal is limited by the occurrence of weight gain and edema, as well as cardiovascular and thromboembolic side effects.[2]

The class of compounds known as aromatase inhibitors offers potential benefits in the management of breast carcinoma, particularly for postmenopausal patients with advanced disease. Although aminoglutethimide, a nonselective aromatase inhibitor, was the first to be evaluated extensively in clinical trials, its acceptance was limited by an association with a wide spectrum of adverse events, as well as a requirement for the concomitant administration of hydrocortisone.[3–5] Since the development of aminoglutethimide, new generations of aromatase inhibitors have been synthesized; all these compounds are substantially more potent than aminoglutethimide as inhibitors of the aromatase enzyme.[6]

One of the new aromatase inhibitors is anastrozole (Arimidex, Zeneca Pharmaceuticals), an achiral benzytriazole derivative, which has highly effective and selective activity for the aromatase enzyme.[7] Clinical trials have demonstrated that circulating serum estradiol concentrations, measured by a sensitive assay, are consistently suppressed to the limit of quantification of the assay with daily anastrozole doses of 1 mg and higher.[7] Doses of up to 10 mg daily have no effect on glucocorticoid or mineralocorticoid secretion as indicated by normal responses to adrenocorticotropic hormone stimulation tests.[7] Anastrozole is rapidly absorbed after oral administration, with maximal plasma concentrations occurring within 2 hours, and it possesses a half-life that supports once-daily oral administration.[7]

In the current trial, the authors compared the efficacy and tolerability of anastrozole and megestrol acetate in postmenopausal women with advanced breast carcinoma who progressed after tamoxifen treatment. Two daily doses of anastrozole, 1 and 10 mg, were selected for evaluation. The 1-mg daily dose provides the lowest dose of anastrozole to give maximum detectable reduction of serum estradiol concentrations, whereas the 10 mg daily dose offers the potential for enhanced antitumor activity and increased clinical benefit.

MATERIALS AND METHODS

Patient Population

To enter the trial, patients were required to have progressed while receiving tamoxifen or other antiestro-

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gen therapy for advanced breast carcinoma or to have had a recurrence during adjuvant tamoxifen treatment; be postmenopausal, defined as having nonfunctioning ovaries through natural menopause or surgical, radiation-induced, or chemical castration (women older than 50 who did not menstruate during the preceding 12 months were considered postmenopausal, whereas women younger than 50 had to have a follicle-stimulating hormone concentration of >40 IU/L to enter); and have World Health Organization (WHO) performance status score of ≤2. Patients were excluded if they had estrogen receptor negative breast carcinoma (except when a patient had showed 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 carcinoma, or any concurrent medical illness or laboratory abnormalities that would compromise their safety or prevent interpretation of results. Written informed consent was obtained from all patients, and the trial was approved at each site by an Institutional Review Board.

Trial Design

The trial design was randomized, double blind for anastrozole, open label for megestrol acetate, and parallel group. The primary efficacy measures were time to progression and tumor response; secondary efficacy measures were time to treatment failure, duration of response, quality of life, and time to death.

Anastrozole was supplied as film-coated, white tablets containing either 1 or 10 mg of the medication. Megestrol acetate was supplied as white, circular, scored tablets containing 40 mg of the medication. Patients were randomly allocated to 1 of 3 oral treatment regimens: 1 mg of anastrozole once daily, 10 mg of anastrozole once daily, or 40 mg of megestrol acetate 4 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 having 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, unwillingness or inability to continue in the trial, withdrawal by an investigator, or clinically significant breast carcinoma progression. All patients who were withdrawn were monitored for survival.

Efficacy Assessments

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.

Assessments of tumor response included 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 the 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 the International Union Against Cancer (UICC) criteria.[8] Nonmeasurable disease was defined as single metastatic lesions smaller than 0.5 cm, malignant pleural effusion or ascites, a 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 <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 <24 weeks was recorded.

Quality-of-Life Assessments

The primary quality-of-life assessment was the validated Rotterdam Symptom Checklist,[9] which was completed by the patients before treatment, every 4 weeks for 24 weeks, and subsequently every 12 weeks until disease progression, for up to 1 year. 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.

Pharmacokinetic Assessments

Blood samples for determination of anastrozole concentrations were collected before therapy and at selected times during therapy. Plasma concentrations of anastrozole were determined using a validated gas chromatographic method that employed capillary gas chromatographic separation with electron capture detection. The assay method was validated over a concentration range of 3 to 100 ng/mL, using 0.5-mL plasma samples. The quantitation limit for anastrozole using this method was 3 ng/mL.

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

A population of 300 patients was deemed sufficient to detect a treatment difference of approximately 14 weeks in median time to progression with 80% power and a 2-sided alpha level of 0.05, assuming a median time to progression of 26 weeks, a uniform recruitment over a 1-year period, and a minimum follow-up of 6 months. To protect against an imbalance in treatment allocation across centers, the randomization scheme was stratified for center. In addition, treatments were allocated in blocks of three patients at each center.

Efficacy analyses were performed on the basis on an intention to treat basis: data were included in the analysis according to randomized treatment. The Cox proportional hazards model was used to analyze time to disease progression, time to treatment failure, and time to death. For each of the treatment comparisons, the results were expressed as hazard ratios, with corresponding confidence intervals (CI) of 97.7% for time to progression and 97.5% for time to treatment failure and death. The model included variables for treatment, estrogen receptor status, progesterone receptor status, and hormonal treatment history. Time to progression, treatment failure, and death were also summarized using Kaplan–Meier curves, which were used to estimate the median time for each endpoint. Logistic regression was used to analyze response data. Because of the low number of patients with response data, the analysis was performed with treatment as the only covariate. Duration of response was summarized for patients who had a best objective response of complete or partial response and using Kaplan–Meier curves. Rotterdam Symptom Checklist scores were analyzed by analysis of covariance, the Wilcoxon rank sum test, and logistic regression; the physical and psychologic scores were analyzed by the first two methods, whereas the functional score was analyzed by logistic regression.

Data on adverse events were recorded 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 the incidence for each group was recorded; these adverse events included weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness.

RESULTS

Patient Characteristics

Three hundred and eighty-six patients from 49 centers in North America were entered and randomized to 1 of the 3 treatment groups (Table 1). One patient was randomized to receive anastrozole 10 mg but elected not to receive therapy; she was included in the analysis of efficacy but not in the analysis of safety.

The median duration of follow-up time for patients was 179 days for the anastrozole 1 mg group, 182 days for the anastrozole 10 mg group, and 176 days for the megestrol acetate group.

Efficacy

Table 2 summarizes the analysis of time to progression, time to treatment failure, and time to death for the anastrozole groups and the megestrol acetate group. Kaplan–Meier curves for time to progression and time to death are displayed in Figures 1 and 2. The results for time to disease progression, time to treatment failure, and time to death showed both

TABLE 1
Demographic and Pretreatment Characteristics

Parameter	Anastrozole 1 mg (n = 128)	Anastrozole 10 mg (n = 130)	Megestrol acetate (n = 128)
Age (yrs)			
Mean	65	66	66
Range	29–93	41–91	39–90
Weight[a] (kg)			
Mean	70	70	67
Range	31–112	40–131	42–110
Previous treatment (no., %)			
Surgery	124 (97)	126 (97)	122 (95)
Cytotoxic chemotherapy	58 (45)	59 (45)	57 (45)
Radiotherapy	72 (56)	74 (57)	76 (59)
Receptor status (no., %)			
ER+, PR+	80 (63)	76 (59)	70 (55)
ER+, PR−	25 (20)	20 (15)	17 (13)
ER+, PR unknown	4 (3)	6 (5)	14 (11)
ER−, PR+	2 (2)	0	3 (2)
ER−, PR−	1 (1)	8 (6)	8 (6)
Unknown	16 (13)	20 (15)	16 (13)
WHO performance status score (no., %)			
0	69 (54)	59 (45)	60 (47)
1	41 (32)	55 (42)	51 (40)
2	18 (14)	13 (10)	15 (12)
3	0	3 (2)	1 (1)
4	0	0	1 (1)
Previous treatment (no., %)			
Adjuvant tamoxifen	60 (47)	54 (42)	50 (39)
Tamoxifen for advanced disease	68 (53)	76 (58)	78 (61)
Duration of tamoxifen treatment for advanced disease[b,c]			
No. of patients	60	69	76
Median duration of treatment (wks)	100	105	86
Relapsed during adjuvant tamoxifen treatment[c]			
No. of patients	57	47	50
Median disease free interval (wks)	136	158	189
Previous best response to tamoxifen (no., %) for advanced disease			
Complete	3 (4)	5 (7)	7 (9)
Partial	6 (9)	8 (11)	12 (15)
Stable disease	31 (46)	34 (45)	27 (35)
Progression	3 (4)	5 (7)	5 (6)
Unknown	25 (37)	24 (32)	27 (35)
Measurable disease (no., %)	82 (64)	79 (61)	81 (63)
No measurable disease (no., %)	46 (36)	51 (39)	47 (37)
Sites of metastatic disease (no., %)[d]			
Soft tissue	42 (33)	45 (35)	39 (31)
Bone	87 (68)	83 (64)	79 (62)
Visceral	51 (40)	51 (39)	60 (47)
Liver	18 (14)	17 (13)	18 (14)
No evidence of liver involvement	110 (86)	113 (87)	110 (86)
No evaluable metastatic disease[e]	5 (4)	12 (9)	3 (2)
Extent of metastatic disease (no., %)[f]			
Soft tissue only	17 (13)	14 (11)	16 (13)
Bone only	45 (35)	37 (29)	41 (32)
Visceral only	14 (11)	15 (12)	22 (17)
Mixed	47 (37)	52 (40)	46 (36)
No evaluable metastatic disease[e]	5 (4)	12 (9)	3 (2)

Er: estrogen receptor; PR: progesterone receptor; WHO: World Health Organization.

[a] Weight was not recorded for all patients.

[b] For treatment of primary disease (after mastectomy or lumpectomy) and metastatic lesions.

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

[d] Patients may be in more than one category.

[e] 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 one patient who had no evaluable disease.

[f] Categories are mutually exclusive.

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