Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate

By A. Buzdar, J. Douma, N. Davidson, R. Elledge, M. Morgan, R. Smith, L. Porter, J. Nabholtz, X. Xiang, and C. Brady

Purpose: To compare two doses of letrozole (0.5 mg and 2.5 mg every day) and megestrol acetate (40 mg qid) as endocrine therapy in postmenopausal women with advanced breast cancer previously treated with antiestrogens.

Patients and Methods: This double-blind, randomized, multicenter, multinational study enrolled 602 patients, all of whom were included in the primary analysis in the protocol. Patients had advanced or metastatic breast cancer with evidence of disease progression while receiving continuous adjuvant antiestrogen therapy, had experienced relapse within 12 months of stopping adjuvant antiestrogen therapy given for at least 6 months, or had experienced disease progression while receiving antiestrogen therapy for advanced disease. Tumors were required to be estrogen receptor– and/or progesterone receptor–positive or of unknown status. Confirmed objective response rate was the primary efficacy variable. Karnofsky Performance Status and European Organization for Research and Treatment of Cancer quality-of-life assessments were collected for 1 year.

Results: There were no statistically significant differences among the three treatment groups for overall objective tumor response. Patients treated with letrozole 0.5 mg had improvements in disease progression ($P = .044$) and a decreased risk of treatment failure ($P = .018$), compared with patients treated with megestrol acetate. Letrozole 0.5 mg showed a trend ($P = .053$) for survival benefit when compared with megestrol acetate. Megestrol acetate was more likely to produce weight gain, dyspnea, and vaginal bleeding, and the letrozole groups were more likely to experience headache, hair thinning, and diarrhea.

Conclusion: Given a favorable tolerability profile, once-daily dosing, and evidence of clinically relevant benefit, letrozole is equivalent to megestrol acetate and should be considered for use as an alternative treatment of advanced breast cancer in postmenopausal women after treatment failure with antiestrogens.

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UNTIL A CURE can be found, the treatment of advanced breast cancer focuses on slowing or stopping tumor growth for as long as possible and maintaining the patient's quality of life. Endocrine therapy, an effective, minimally toxic, palliative treatment, represents the best therapeutic option for many patients. Tamoxifen is currently the most widely used endocrine therapy. Approximately 40% to 50% of patients who relapse after tamoxifen may achieve clinical benefit from second-line endocrine agents.[1-3] Progestins and nonspecific aromatase inhibitors have been the most commonly used second-line agents, with megestrol acetate and aminoglutethimide historically selected as the mainstay of second-line therapy. However, new molecules have been discovered that more specifically target aromatase.[4] These include anastrozole, formestane, and letrozole, and all of them seem to provide better tolerability and more convenient administration than megestrol acetate or aminoglutethimide.[5-7] Response rates for the new options seem to be similar in metastatic breast cancer. About 20% to 30% of patients achieve an objective response with an additional 10% to 20% of patients achieving stable disease.[4,6-9] Thus, the more specific aromatase inhibitors are a reasonable choice for second-line therapy.

Letrozole is a highly potent, orally active, nonsteroidal competitive inhibitor of the aromatase enzyme system that effectively inhibits the conversion of androgens to estrogens, both in vitro and in vivo.[10,11] In postmenopausal patients with advanced breast cancer, daily doses of letrozole from 0.1 to 5 mg suppress plasma levels of estradiol, estrone, and estrone sulfate to more than 75% to 95% from baseline in all patients, with no clinically relevant effects on other hormones of the endocrine system, including glucocorticoids, mineralocorticoids, and thyroid hormones.[12-15]

Two large randomized, controlled, multinational studies were conducted to assess the efficacy and safety of letrozole

From the University of Texas M.D. Anderson Cancer Center and Baylor College of Medicine, Houston, TX; St Thomas Medical Group, Nashville, TN; Baptist Medical Center, Columbia, SC; Ziekenhuis Rijnstate, Arnhem, the Netherlands; North Middlesex Hospital, London, and St Margaret's Hospital, Essex, United Kingdom; and Cross Cancer Institute, Edmonton, Alberta, Canada.

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Address reprint requests to Aman Buzdar, MD, Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, Box 424, 1515 Holcombe Blvd, Houston, TX 77030; email: abuzdar@mdanderson.org.

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in postmenopausal women with advanced breast cancer who progressed despite antiestrogen therapy. Results from the first study indicated that once-daily treatment with letrozole 2.5 mg demonstrated a significantly higher objective tumor response rate than both letrozole 0.5 mg every day (qd) (P = .004) and 160 mg of megestrol acetate qd (P = .04), with overall objective tumor response rates of 24%, 13%, and 16%, respectively.[8] Letrozole 2.5 mg was also notably more effective than megestrol acetate, considering the duration of objective response (median, 33 months v median, 18 months; P = .02) and time to treatment failure (TTF) (P = .04).[8,16]

Results from the second study indicated that once-daily treatment with letrozole 2.5 mg was superior to aminoglutethimide 250 mg given twice daily along with corticosteroid supplementation for time to progression (TTP) (P = .008), TTF (P = .003), overall survival (P = .002), and duration of clinical benefit.[17] The majority of adverse experiences were mild or moderate in severity. The five most frequently reported adverse events in letrozole-treated patients were musculoskeletal pain, fatigue, headache, nausea, and arthralgia.

The present multicenter, international, double-blind, randomized study was conducted to compare two doses of once-daily letrozole, 0.5 mg and 2.5 mg, to megestrol acetate qid in postmenopausal women with advanced breast cancer previously treated with an antiestrogen. Previously published studies involving the new generation of aromatase inhibitors had a limited follow-up period. Data reported here, beginning with the first visit of the first enrolled patient, cover a 4-year period that included a 30-month enrollment period and 18 months of follow-up from the first visit of the last patient enrolled. In addition, a survival update was performed 37 months after the first visit of the last patient enrolled. Fifty-six patients were still on treatment at the time of the primary analysis, which included objective response rate (ORR), duration of response, TTP, and TTF.

PATIENTS AND METHODS

Patients

Postmenopausal women with histologically or cytologically confirmed breast cancer who presented with either locally advanced or locoregionally recurrent disease or had metastatic disease were enrolled onto the study. Tumors were required to be either estrogen receptor (ER) and/or progesterone receptor (PgR) positive. Unknown status of ER and PgR was acceptable for study entry if no assay had been conducted. Patients were eligible if they had either relapsed while receiving continuous adjuvant antiestrogen therapy (eg, tamoxifen) or had relapsed within 12 months of stopping adjuvant antiestrogen therapy that had been administered for at least 6 months. Patients were also eligible if they progressed while receiving first-line antiestrogen therapy for advanced disease. Patients were permitted to have received up to two regimens of chemotherapy for advanced disease before trial entry provided that at least one had been administered before antiestrogen therapy. At the start of the study, patients were required to have the bulk (> 50%) of their tumor burden measurable and/or assessable. This criterion was found to unduly restrict patient enrollment, so inclusion criteria were amended to require patients to have at least one measurable and/or assessable tumor lesion. Patients were entered onto the study within 3 months of objective evidence of disease progression.

Patients included women previously treated with chemotherapy, corticosteroids, immunotherapy/biologic response modifiers (eg, interferon), antiestrogen treatment, either as adjuvant therapy or as therapy for advanced disease, or neoadjuvant treatment with endocrine therapy or chemotherapy. Patients were required to have discontinued any systemic anticancer treatment at the time of study entry. Any radiation therapy was completed at least 14 days before study entry. Patients had to have recovered from all reversible toxicities of any therapy administered before study entry. All patients were required to be postmenopausal as defined by one of the following criteria: women ≥ 50 years of age who had not menstruated during the preceding 12 months or had castrate follicle-stimulating hormone levels (> 40 IU/L), women less than 50 years of age who had castrate follicle-stimulating hormone levels, or women who had undergone a bilateral oophorectomy.

All patients were estimated to have, in the opinion of the investigator, a life expectancy of at least 6 months and a Karnofsky performance status score of ≥ 50%. All laboratory results were required to be within the limits defined by the study protocol, which included creatinine less than 1.5 times the upper limit of normal (ULN), total bilirubin less than 1.5 times ULN, transaminases less than 2.6 times ULN, WBC count ≥ 3,000/mm^3, granulocyte count ≥ 1,500/mm^3, hemoglobin ≥ 8.5 g/dL, platelet count ≥ 75,000/mm^3, and total calcium less than 11.6 mg/dL.

Exclusion criteria included the existence of malignancies at other sites ≤ 5 years before study entry or concurrent with study participation, with the exception of cone-biopsied in situ carcinoma of the cervix or uterus and adequately treated basal and squamous cell carcinoma of the skin. Patients were also excluded if they had inflammatory breast cancer; extensive hepatic metastases, defined as more than 33% of the liver replaced by metastases noted on sonogram and/or computed tomography scan; metastases to the CNS; pulmonary lymphangitic metastases involving more than 50% of the lung; history of deep venous thrombosis or pulmonary embolism within 3 years unless the thrombosis was known to be directly related to tumor obstruction of circulation; severe uncontrolled cardiac disease (eg, congestive heart failure of the New York Heart Association ≥ Class III); crescendo angina; myocardial infarction within 6 months before study entry; or uncontrolled diabetes mellitus.

All patients gave written informed consent to participate in the study, which was approved by the local institutional review board or ethics committee for each study site. The study was conducted according to Good Clinical Practice guidelines.

Study Design

This was a randomized, double-blind, parallel-group, multicenter, international, comparative phase III study conducted in 120 centers throughout the United States, Canada, and Europe. Enrollment of 602 patients occurred over a 30-month period. Patients were randomly assigned to one of three treatment arms: letrozole 0.5 mg qd, letrozole 2.5 mg qd, or megestrol acetate 40 mg qid. Randomization was performed for each country without stratification by center. To preserve the double-blind design of the study, patients received either one tablet letrozole 0.5 mg or letrozole 2.5 mg once daily in the morning and one

placebo capsule (matching a megestrol acetate tablet) qid, or one 40-mg capsule megestrol acetate qid plus one placebo tablet (matching a letrozole tablet) once daily. Changes in drug dosage were not permitted by the protocol; however, justifiable discontinuation of study medication for up to 3 consecutive weeks was acceptable under certain circumstances.

Patients were allowed to receive radiotherapy to areas not being evaluated for tumor response or corticosteroids (topical or aerosol) for obstructive airway disease or nonmalignant skin lesions. Patients who received anticancer treatments, concomitant corticosteroid treatments other than those noted, bisphosphonates, or investigational drugs were not eligible participants for this study. A single treatment course of bisphosphonate, however, was permitted during the study for the treatment of hypercalcemia resulting from tumor flare, if saline hydration, diuretics, or calcitonin had been ineffective.

Patient visits were scheduled at the beginning of study participation, at 2 weeks, 4 weeks, monthly through 6 months, and then every 3 months. Patients who responded with either a complete response (CR) or partial response (PR) or had stable disease continued treatment until disease progression or withdrawal for another reason. On discontinuation from the study, patients were to be followed until death or until lost to follow-up for a period of 60 months from their first study visit. Patient survival information was collected every 6 months.

Patients were evaluated for tumor response at 3 months after the start of therapy and then every 3 months thereafter. An evaluation was also done if the patient discontinued treatment. Tumor response was evaluated by the investigator at the site according to International Union Against Cancer criteria specified by the protocol and by a designated central radiologist at each site who remained blinded. Measurable disease, whether bi- or unidimensional, was assessed either by palpation or on radiologic assessment (x-ray, abdominal ultrasound, or computed tomography scan). For multiple lesions, the tumor size equaled the sum of the products of the diameters of all lesions. Nonmeasurable, assessable tumors were not measurable by ruler or caliper but were assessed and evaluated by physical or radiologic evaluation. Response or increasing disease could only be estimated. Methodology for tumor assessment was to remain consistent throughout the course of the study. Full tumor evaluation, including the above procedures, was performed at baseline and at months 6 and 9. At month 3 and at visits subsequent to month 9, only areas positive for disease were evaluated unless warranted by the development of signs and symptoms indicating disease progression. All evaluations of objective tumor response (CR or PR) required confirmation after at least 4 weeks. Patients who did not show persistence of the initially observed response at the confirmatory evaluation were not considered to be responders.

Response was defined as CR, PR, no change, or progressive disease. A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumor size of 50% or more (either measured or estimated in the case of measurable or assessable disease), confirmed by two observations not less than 4 weeks apart. In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumor response included both confirmed CR and PR. Secondary efficacy measures included duration of response, duration of clinical benefit, TTF, TTP, and time to death (TTD). Duration of response was defined as the time from the date of randomization to the earliest date of documented disease progression or death from cancer or unknown cause. The time was censored at the cutoff date for analysis for patients still in response. Duration of clinical benefit was calculated only for those patients who had a confirmed objective tumor response or stable disease for $\geq$ 6 months. In these patients, duration of clinical benefit was calculated in the same manner as duration of response. TTP was defined as the time from randomization to the earliest date of disease progression, cancer-related death, or death from an unknown cause during therapy, or the time was censored at the cutoff date for analysis for patients without progressive disease. All deaths for which the reason was neither unknown cause nor malignant cause were reviewed before the treatment codes were unblinded so that the censoring mechanism could be identified on the database for analysis. TTP was censored if the patient remained on trial treatment at the date of the last patient's last visit (data cutoff date) without any evidence of disease progression, or if she was withdrawn from the trial for any reason other than unsatisfactory therapeutic effect or death from cancer or unknown cause. TTF was defined as the time from the date of randomization to the earliest date of disease progression, discontinuation of therapy for any other reason, or death, or the time was censored at the cutoff date for analysis for patients still on therapy without evidence of disease progression. TTD was defined as the time from the date of randomization to the date of last known alive or death from any cause.

Tumor symptoms were evaluated at every visit. Assessments of Karnofsky performance status and measures of quality of life, including physical, role-related, emotional, cognitive, and social functioning; fatigue; nausea or vomiting; pain; dyspnea; insomnia; appetite loss; constipation; diarrhea; and financial difficulties, using the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30 version 2.0)[18,19] were obtained each month for the first 6 months and at 9 and 12 months. These assessments, though not part of the planned efficacy or safety analyses, were planned to support the safety and tolerability data collected during this trial. Patients received a complete physical examination at study initiation and at 3, 6, 9, and 12 months. Safety was assessed using the National Imstitutes of Health/National Cancer Institute common toxicity criteria and selected laboratory parameters to score severity of adverse experiences.[20] Additionally, routine measurements of weight, blood pressure, pulse rate, ECG, chest x-ray, hematology/chemistries, and urinalysis were completed.

Statistical Methodology

The sample size for this trial was computed as the number of patients needed within one letrozole (0.5 mg or 2.5 mg daily) treatment group to detect at least a 13% difference from the megestrol acetate 160 mg treatment group for the confirmed ORRs (CR + PR). The sample size was calculated assuming 80% power, alpha level of 0.05, and two-sided, to show that either one of the two letrozole treatment groups was superior to the megestrol acetate treatment group, assuming a response rate for letrozole equal to 28% and a response rate for megestrol acetate equal to 15%. A total of 513 patients (171 per treatment arm) were required. Therefore, approximately 590 patients were planned in order to obtain the required 513 completed patients. Actual enrollment was closed at 602 patients.

All analyses were based on the intent-to-treat approach. All statistical tests performed were two-sided, with a .05 level of significance. Two-sided 95% confidence intervals for the odds ratio for each treatment comparison were also presented. No adjustments for multiple comparisons or multiple end points were made. The primary efficacy variable was the confirmed best overall objective tumor response rate and was analyzed using a logistic regression procedure both adjusted and unadjusted for prognostic baseline covariates (disease-free interval, dominant site of disease, prior antiestrogen therapy, stage of disease, and locally advanced, locoregionally recurrent, or metastatic breast cancer at study entry). Although there were two letrozole arms, the

Table 1. Patient Demographics and Baseline Data

Baseline Prognostic Variable	Letrozole 0.5 mg (n = 202) No. of Patients	%	Letrozole 2.5 mg (n = 199) No. of Patients	%	Megestrol Acetate (n = 201) No. of Patients	%	All Patients (n = 602) No. of Patients	%
Age								
≤ 55 years	32	16	33	17	38	19	103	17
56-69 years	84	42	90	45	84	42	258	43
≤ 70 years	86	43	76	38	79	39	241	40
Median, years	66.5		65.5		65.9		66.0	
Dominant site								
Viscera	101	50	95	48	97	48	293	49
Bone	57	28	68	34	53	26	178	30
Soft tissue	44	22	36	18	51	25	131	22
No. of anatomic sites involved								
1	111	55	100	50	113	56	324	54
2	73	36	70	35	64	32	207	34
3	18	9	30	15	24	12	71	12
Disease-free interval								
Stage IV	24	12	33	17	16	8	73	12
< 24 months	49	24	37	19	50	25	136	23
≥ 24 months	129	64	129	65	135	67	393	65
Receptor status								
ER unk and PgR unk	31	15	39	20	40	20	110	18
ER^+ or PgR^+	57	28	48	24	57	28	162	27
ER^+ and PgR^+	111	55	112	56	104	52	327	54
ER^- and PgR^-	1	< 1	0	0	0	0	1	< 1
ER^- and PgR unk	2	1	0	0	0	0	2	< 1
Prior antiestrogen therapy								
Adjuvant only	83	41	70	35	78	39	231	38
Advanced only	103	51	112	56	104	52	319	53
Both	16	8	17	9	19	10	52	9
Response to prior antiestrogen therapy								
Responder (CR+PR)	37	18	42	21	45	22	124	21
SD + unk ≥ 6 months	61	30	70	35	62	31	193	32
PD + unk < 6 months	20	10	16	8	16	8	52	9
N/A (adjuvant only)	83	41	70	35	78	39	231	38
Not assessable	1	< 1	1	< 1	0	0	2	< 1
Previous chemotherapy								
None	130	64	117	59	115	57	362	60
Adjuvant only	46	23	48	24	57	28	151	25
Advanced only	15	7	19	10	24	12	58	10
Both	11	5	15	8	5	3	31	5
Karnofsky performance status								
100%	66	33	58	29	51	25	175	29
< 100%	136	67	140	70	140	75	426	71
Missing	0	0	1	< 1	0	0	1	< 1
No. of prior endocrine therapies								
None (adjuvant only)	83	41	70	35	78	39	231	38
1	116	57	126	63	120	60	362	60
> 1	3	2	3	2	3	2	9	2
Stage of disease								
I/II	6	3	7	4	7	4	20	3
III	11	5	11	6	11	6	33	6
IV	185	92	181	91	183	91	549	91

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; unk, unknown.

statistical significance was based only on pair comparison. Cochran Mantel-Haenszel tests were performed to compare ORRs according to the covariates that were thought to have an effect on overall objective response (disease-free interval, dominant site of disease, stage of disease at study entry, and history of antiestrogen therapy). A Cox proportional hazards regression analysis was performed on the intent-to-treat population for the median time to event and 95% confidence intervals for variables, including duration of response, duration of clinical benefit, time to response, TTP, TTF, and TTD. No adjustments for multiple comparisons or multiple end points were made. A longitudinal analysis on quality of life was performed using a pattern-mixture model. The criterion for the pattern classification was based on whether the patient was receiving the study drug 6 months or longer. Adverse experiences were summarized in terms of the number of

Table 2. Overall Tumor Response

Variable	Letrozole 0.5 mg (n = 202)		Letrozole 2.5 mg (n = 199)		Megestrol Acetate (n = 201)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Objective response	42	21	32	16	30	15
95% CI	15.2-26.4		11.0-21.2		10.0-19.9	
Complete response	8	4.0	9	4.5	4	2.0
Partial response	34	16.8	23	11.6	26	12.9
Stable disease < 6 months	25	12.4	27	13.6	31	15.4
Stable disease ≥ 6 months	25	12.4	21	10.6	17	8.5
Disease progression	93	46.0	102	51.3	102	50.7
Not assessable*	17	8.4	17	8.5	21	10.4

*Patients with unconfirmed complete or partial response, patients not assessable, or tumor response evaluation not done.

patients who experienced an event in each treatment arm, and by relationship to treatment, severity of the event, and duration of exposure to study medication.

RESULTS

Patients

A total of 602 patients from 120 centers in seven countries were randomized in the study over a 30-month period, with approximately two thirds of the enrolled patients treated in the United States. All analyses were based on the intent-to-treat approach, where the intent-to-treat population was defined as the set of randomized patients who took at least one dose of trial medication. All patients, regardless of their length of trial treatment, were included in the intent-to-treat analysis.

Of the 602 patients included in the intent-to-treat analyses, a total of 23 patients (3.8%) were considered noneligible and therefore were excluded from the acceptable patient analyses of tumor. A separate analysis of the primary end points conducted on the acceptable patient population showed no difference in results to the same analysis on the intent-to-treat population.

The primary analysis was based on an unadjusted statistical model. An analysis adjusted for key baseline variables was also conducted, and results were consistent with the presented unadjusted analysis. Randomization was similar in the three treatment arms (letrozole 0.5 mg, n = 202; letrozole 2.5 mg, n = 199; megestrol acetate, n = 201). Table 1 shows that the three treatment arms were similar with respect to demographics, disease characteristics, and extent of prior treatment at the beginning of the study. The median duration of treatment was approximately 5 to 7 weeks longer for the letrozole 0.5 mg arm when compared to the letrozole 2.5 mg and megestrol acetate treatment arms (171.5 days, 120.0 days, and 136.0 days, respectively). The prognostic factors identified as having a significant impact on the various outcome variables for efficacy (age, disease-free interval, number of anatomic sites involved, best response to prior antiestrogen therapy, and stage of disease at study entry) were evenly distributed in all three arms and were present in frequencies expected in this population of patients. Results of χ^2 and Kruskal-Wallis tests showed no statistically significant difference among treatment groups at the .05 level of significance for any of the demographic, cancer history, or baseline prognostic variables. No patients had prior exposure to letrozole or megestrol acetate.

Table 3. Confirmed Best Overall Objective Tumor Response

Confirmed Best Overall Objective Tumor Response	Treatment Comparisons		
	0.5 mg/MA	2.5 mg/MA	2.5 mg/0.5 mg
Odds ratio	1.50	1.09	0.73
P	.13	.75	.22
95% CI	0.89-2.51	0.64-1.88	0.44-1.21

NOTE. An odds ratio greater than 1 favors the treatment before the ratio symbol (/), whereas an odds ratio less than 1 favors the treatment after the ratio symbol.

Abbreviations: 0.5 mg, letrozole 0.5 mg; 2.5 mg, letrozole 2.5 mg; MA, megestrol acetate 160 mg.

Efficacy

Best objective overall tumor response. Although the letrozole treatment groups had somewhat higher response rates than the megestrol acetate–treated group (Table 2), no statistically significant differences were noted when the groups were analyzed by logistic regression to compare the number of patients with a confirmed objective response (CR + PR) (Table 3). Table 4 presents the response rates (CR + PR) by treatment within each baseline covariate. However, no statistically significant differences between treatments were detected within subgroups.

Duration of response and clinical benefit. Median duration of objective tumor response was 23 months for letrozole 0.5 mg, 25 months for letrozole 2.5 mg, and 30 months for megestrol acetate (Table 5). Median duration of

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