

A Randomized Phase II Trial of Two Dosage Levels of Letrozole as Third-Line Hormonal Therapy for Women with Metastatic Breast Carcinoma

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BACKGROUND. It is common practice to utilize a series of different hormonal agents in the treatment of postmenopausal women who, despite disease progression, continue to be candidates for hormonal therapy on a clinical basis. Letrozole is a new highly selective and potent aromatase inhibitor. There are limited data on third-line hormonal therapy in general, and this study was undertaken to evaluate letrozole in this context.

METHODS. A randomized trial involving two independent Phase II trials of two letrozole dosage levels, 0.5 mg and 2.5 mg per day, was performed. Eligibility requirements included failure on two prior hormonal therapies and measurable or evaluable disease.

RESULTS. Ninety-one patients, 46 receiving 0.5 mg and 45 receiving 2.5 mg of letrozole per day, were assessable for response. At the lower dose, 9 patients (20%) achieved an objective response; 6 patients (13%) had this documented on 2 occasions separated by 3 months. At the higher dose, 10 patients (22%) achieved a response; 8 patients (18%) had this documented on 2 occasions separated by 3 months. The median times to progression were 97 days for the lower dose and 154 days for the higher dose. Toxicity was considered acceptable.

CONCLUSIONS. Letrozole has definite antitumor activity as third-line hormonal therapy for women with metastatic breast carcinoma at doses of 0.5 and 2.5 mg per day. It is an effective and generally well-tolerated hormonal agent. *Cancer* 1997;80:218-24. © 1997 American Cancer Society.

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Additive hormonal therapy is the preferred modality of treatment for postmenopausal women with metastatic breast carcinoma. It is common practice to utilize multiple different hormonal agents in sequence in the treatment of patients who clinically continue to be candidates for hormonal therapy on the basis of tempo, sites, and extent of disease as well as response to prior hormonal therapy. Re-

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sponses to second-line hormonal therapy are well documented by clinical trials. Although third-line hormonal therapy is commonly employed, there is much less literature documenting efficacy in this setting. Recognizing this, Iveson et al.¹ performed a retrospective analysis of 55 patients who received third-line endocrine treatment. Eight patients (15%) achieved objective responses (7 partial responses [PR] and 1 complete response [CR]), according to International Union Against Cancer (UICC) criteria.² Tamoxifen remains the first-line hormonal therapy of choice for postmenopausal women. Megestrol acetate was the second-line hormonal treatment of choice until the recent availability of anastrozole, which has been shown to be at least as efficacious and associated with less weight gain.³ The current trial was conducted to evaluate letrozole, a new aromatase inhibitor, as a treatment for women with metastatic breast carcinoma who had failed two prior hormonal therapies.

Estrogens are considered to be the primary hormones that stimulate hormone-dependent breast carcinoma growth.⁴ The major source of estrogen in the postmenopausal or castrated woman is the adrenal cortex, which secretes precursors of estrone (E_1) and estradiol (E_2). Androstenedione, the major precursor of these estrogens, undergoes aromatization in peripheral tissues and in some breast carcinomas to E_1 , which is subsequently reduced to E_2 .^{5,6} Aminoglutethimide (AG) was a first-generation aromatase inhibitor possessing antitumor activity in postmenopausal women with metastatic breast carcinoma; 1 review of 929 patients showed an overall response rate of 32%.⁷ This agent did not achieve widespread popularity because of toxicity, but its efficacy provided the impetus for further work to identify more potent, specific, and tolerable aromatase inhibitors.^{4,8}

Letrozole (CGS 20267, FemaraTM) is a synthetic nonsteroidal benzhydryltriazole derivative that was shown in animal studies to be a highly selective and potent competitive aromatase inhibitor.⁹ Iveson et al.¹⁰ summarized the relative potency data for letrozole and AG. In vitro, using microsomal preparations of human placental aromatase, letrozole was 165 times as potent as AG; and in an in vivo assay of androstenedione-induced uterine hypertrophy, letrozole was 4 orders of magnitude more potent. Letrozole also differs from AG in its selectivity. Its inhibition of aldosterone occurred at concentrations 14,000 times greater than required for inhibition of estrogen production, and the difference for inhibition of corticosterone was even greater. Thus, letrozole is a highly selective aromatase inhibitor.

Two groups reported Phase I studies of letrozole administered at doses of 0.1, 0.5, and 2.5 mg per

day.^{10,11} Both of these studies, involving a total of 43 patients, demonstrated letrozole to be a very potent, specific, and well-tolerated aromatase inhibitor.

The concept of utilizing aromatase inhibitors to treat breast carcinoma by reducing estrogen levels is attractive, and the availability of an effective, potent, and highly selective agent that is well tolerated would likely have widespread applicability in clinical management. Our randomized clinical trial involved two independent Phase II trials that assessed the antitumor activity and toxicity of two dosage levels of letrozole in women with metastatic breast carcinoma who had failed two prior hormonal regimens.

PATIENTS AND METHODS

This clinical trial involved postmenopausal women with metastatic breast carcinoma who fulfilled the following eligibility criteria: First, they had to have histologically confirmed breast carcinoma and progressive metastatic disease. A woman was considered to be postmenopausal if any one of the following criteria was met: (1) 12 months since last menstrual period (LMP); (2) 4–12 months since LMP, and follicle-stimulating hormone (FSH) in postmenopausal range; (3) maximum age 60 years, with a hysterectomy without oophorectomy and FSH in postmenopausal range; or (4) prior castration. Estrogen receptor (ER) and/or progesterone receptor (PgR) had to be positive or not obtained. If a ligand-binding assay was utilized, positive was defined as ≥ 10 fmol/mg cytosol protein; if immunocytochemistry methodology was utilized, positive was defined by institutional standards. Patients were required to have measurable or evaluable disease. Measurable disease was bidimensionally measurable except in the case of hepatomegaly due to metastatic disease, in which linear measurements of 5 cm or greater below a costal margin in the midclavicular line or xiphoid were acceptable. Evaluable disease was disease that was assessable but not measurable, and documentable on radiographs (e.g., mediastinal masses, pleural-based masses, or lytic bone metastasis) or photographs (e.g., soft tissue or skin metastasis). Specifically not evaluable were third-space fluid accumulations and blastic osseous metastasis.

Patients were required to have failed two, and only two, prior hormonal therapies. Patients were considered to have failed with tamoxifen in the adjuvant setting when disease recurrence was identified within 12 months of the last treatment with tamoxifen.

The following laboratory parameters were required: leukocyte count greater than 2000/ μ L, platelet count greater than 75,000/ μ L; serum calcium less than 10%, total bilirubin <0.8 mg/dL, and creatinine less than 1 mg/dL above the upper limit of normal by insti-

tutional standards. Patients must not have had an Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4 or prior treatment with any recognized aromatase inhibitor, adrenalectomy, or hypophysectomy. Patients could have received prior chemotherapy in the adjuvant setting and participated in no more than one prior chemotherapy program for metastatic disease. Patients with known brain metastasis or with hepatic metastasis estimated to involve more than one-third of the liver were not eligible.

Studies obtained before entry onto protocol included a medical history, physical examination with documentation of indicator lesion(s), hemoglobin, leukocyte and platelet counts, sodium, potassium, calcium, glucose, phosphorus, alkaline phosphatase, serum glutamic oxaloacetic transaminase, total bilirubin, creatinine, and chest radiograph. This trial was performed after approval by local institutional review boards in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services. Written informed consent was provided by each patient before entry on study.

Patients were stratified according to dominant disease status (soft tissue vs. osseous vs. visceral), ER and PgR status (PgR positive/ER positive or negative vs. ER positive/PgR negative or unknown vs. no receptor data), and ECOG performance score (0 or 1 vs. 2). Patients were then randomized to treatment with letrozole at a dose of either 0.5 mg daily or 2.5 mg daily. Letrozole was supplied by Ciba Geigy Corporation, Summit, NJ.

After initiation of therapy, patients were to be seen at 1 month for a toxicity check and were to be assessed for objective tumor status at 3 months and every 3 months thereafter. Treatment was continued if the status of the patient was stable or better and if no unacceptable toxicity had occurred. For both measurable and evaluable disease, a CR was defined as the disappearance of all evidence of tumor. For measurable disease, a PR was defined as at least a 50% reduction in the product of perpendicular diameters of indicator lesions, or, in the case of palpable hepatomegaly, a 30% reduction in the sum of linear measurements of the liver below both costal margins in the midclavicular line and the xiphoid. For measurable disease, progression was defined as a new lesion, at least a 25% increase in tumor size compared with pretreatment status in patients not achieving a response, or, in patients achieving a PR, an increase in indicator size from the smallest measurement by at least 50% of the decrease in size between the pretreatment measurements and smallest measurements at the point of maximum tumor reduction. For evaluable disease, an objective response that was less than a CR was termed

a regression (Reg) and was defined as a definite decrease in tumor that could be documented by radiographs, other imaging modalities, or photographs, and progression was defined as a definite increase in tumor size compared with the smallest size while on study. Stable disease was defined as failure to qualify for CR, PR, Reg, or progression. An additional criterion for progression was significant clinical deterioration that could not be attributed to treatment or to other medical conditions, such as weight loss of greater than 5% of body weight, worsening of tumor-related symptoms, or a decline in ECOG performance score of more than 1.

The primary endpoint was the objective response rate. If the true response probability was at most 0.05 for a given letrozole regimen, the regimen would be considered ineffective in this patient population. The smallest response probability that would be of sufficient interest to warrant subsequent study of the regimen in this population was 0.20. Thus, the three-stage design planned for each of these regimens was to test the null hypothesis that the true proportion of responses was at most 0.05, where the smallest regression probability that would imply the treatment regimen warranted further study was 0.20. The study design was chosen to provide 93% power for detecting a true response probability of 0.20 at an 0.06 level of significance.

The 3 stages were planned as follows: Fifteen patients were randomized to each of the regimens. If none of the 15 patients responded on a specific regimen, the regimen would be abandoned and deemed not to warrant further consideration in this population. If 1 or more patients responded to the regimen, 15 additional patients would be accrued to that regimen. If 1 or no objective responses were observed among the 30 patients accrued on the regimen, the regimen would not be recommended for further study in this patient population. Otherwise, an additional 15 patients would be accrued to the regimen. If five or more patients responded to the regimen, the regimen would be recommended for further study in this patient population.

Time to treatment failure was defined as time from registration to removal from the study due to disease progression, toxicity, refusal, or death without known progression. Time to progression was defined as time from registration to progression or death without known progression. Survival was defined as the time from registration to death. Confidence intervals for the true proportion of responses were constructed by the Duffy-Santner method,¹² and time-to-event distributions were estimated by the Kaplan-Meier method.¹³

TABLE 1
Patient Characteristics

Characteristic	Letrozole dose	
	0.5 mg/day	2.5 mg/day
No. of patients	46	45
Age (yrs)		
Median	65	66
Range	40–81	49–85
Disease-free interval (%)		
<1 yr	17	20
1–5 yrs	59	44
>5 yrs	24	36
Prior chemotherapy (%)		
None	54	62
Adjuvant setting only	37	24
Metastatic setting only	2	7
Both	7	7
ECOG performance score (%)		
0	35	44
1	50	40
2	15	16
Dominant disease status (%)		
Soft tissue	15	16
Osseous	33	42
Visceral	52	42
Indicator lesion status (%)		
Measurable	44	40
Evaluable	57	60
No. of metastatic disease sites (%)		
1	39	47
2	28	36
3	24	16
4	7	2
5	2	0
Hormonal receptors (%)		
PgR pos./ER pos. or neg.	61	64
ER pos./PgR neg. or unknown	26	24
Not obtained	13	11

ECOG: Eastern Cooperative Oncology Group; PgR: progesterone receptor; ER: estrogen receptor; pos.: positive; neg.: negative.

RESULTS

One hundred six patients were entered on this protocol. One patient refused therapy after randomization, never received letrozole, and was considered a cancellation. Fourteen patients (13%) were considered ineligible because of failure on only 1 prior hormonal regimen (5 patients), lack of measurable or evaluable disease (5 patients), negative ER and PgR values prior to entry on study (3 patients), or failure on more than 1 prior chemotherapy regimen for metastatic disease (1 patient). Ninety-one patients were fully eligible; 46 received 0.5 mg letrozole and 45 received 2.5 mg letrozole (Table 1). All patients had failed two separate prior

TABLE 2
Best Response to Letrozole Achieved

Indicator	Letrozole dose	
	0.5 mg/day	2.5 mg/day
Measurable	n = 20	n = 18
CR	0	2
PR	5	5
CR + PR	5 (25%)	7 (39%)
Evaluable	n = 26	n = 27
CR	0	0
Reg	4	3
CR + Reg	4 (15%)	3 (11%)
Total (CR + PR + Reg)	9/46 (20%)	10/45 (22%)

CR: complete response; PR: partial response; Reg: disease regression.

hormonal therapies, which involved tamoxifen and megestrol acetate in all cases except when the prior therapy involved tamoxifen and fluoxymesterone (3 patients), diethylstilbestrol (1 patient), goserelin (1 patient), or octreotide (1 patient).

Letrozole at 0.5 mg per Day

Nine (20%) of the 46 patients achieved an objective response (Table 2), and the 95% confidence interval (CI) for the true response percentage was 11–34%. Of these 9 patients, 6 were documented to have the response persisting on a subsequent assessment 3 months later. All patients without treatment failure have been followed for a minimum of 6 months. In addition to the patients achieving an objective response, 12 patients were stable at the 3-month evaluation and 9 patients (20% of the entire group) were stable at the 6-month evaluation.

Thirty-six patients have experienced treatment failure due to disease progression (31 patients), refusal (3 patients), toxicity (1 patient), and sudden death on Day 35 of the study (1 patient). The median time to treatment failure was 95 days (range, 19 days to 1.8+ years). Disease progression has occurred in 34 patients, with a median time to progression of 97 days (range, 26 days to 1.8+ years). Eighteen patients have died, and their estimated median survival was 1.7 years (Fig. 1).

Toxicities encountered are shown in Table 3. In general, the regimen was well tolerated. Because tolerability is an important consideration, the four patients removed for refusal or toxicity are presented. One patient with hypertension took 1 tablet of letrozole, and home-monitored blood pressure dropped from 200/82 to 134/52, leading her to discontinue letrozole. A second patient refused further letrozole after devel-

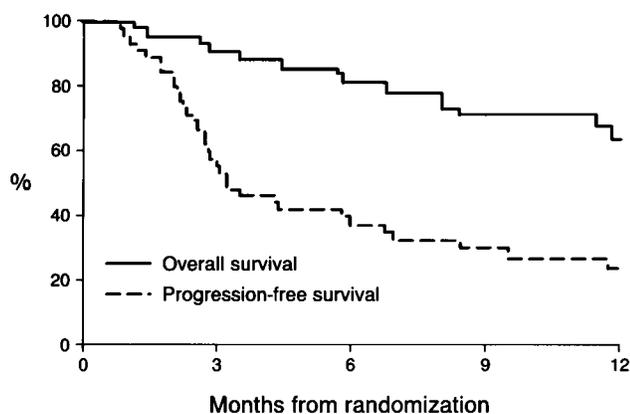


FIGURE 1. Progression free and overall survival are shown for patients who received letrozole at daily doses of 0.5 mg.

oping nausea, emesis, and diarrhea resulting in dehydration 5 months after administration of the drug began. A third patient discontinued letrozole after developing nausea and emesis in the setting of radiation therapy to the thoracic spine, which was given to treat nonindicator lesions. A fourth patient with baseline nausea and heartburn experienced emesis on letrozole, which improved after the drug was withdrawn.

Letrozole at 2.5 mg per Day

Ten (22%) of the 45 patients achieved an objective response (Table 2), and the 95% CI for the true response percentage was 13–36%. Of these 10 patients, 8 were documented to have the response persisting on a subsequent assessment 3 months later, and 1 has not yet had a subsequent assessment. All patients without treatment failure were followed for a minimum of 6 months. In addition to the patients who achieved an objective response, 16 patients were stable at the 3-month evaluation and 11 (24% of the entire group) were stable at the 6-month evaluation.

Thirty-three patients have experienced treatment failure due to disease progression (32 patients) or toxicity (1 patient). The median time to treatment failure was 154 days (range, 13 days to 1.7+ years). Disease progression has occurred in 33 patients, with a median time to progression of 154 days (range, 13 days to 1.7+ years). Sixteen patients have died, and their estimated median survival was 1.7 years (Fig. 2).

Toxicities encountered in the 44 patients with toxicity data are shown in Table 3. In general, this regimen was well tolerated. The single patient who was removed from study for toxicity experienced decreased performance score, weight loss (4.5 kg), and Grade 3 malaise after 3 months of therapy. The patient experienced weight gain, improvement in appetite, and reso-

TABLE 3
Toxicities

Toxicity	Letrozole dose	
	0.5 mg/day % of 46	2.5 mg/day % of 44
Nausea		
Any	28	18
≥Grade 3 ^a	2	0
Emesis		
Any	11	11
≥Grade 3	7	0
Heartburn		
Any	9	9
≥Grade 3	0	0
Diarrhea		
Any	4	7
≥Grade 3	0	2
Anorexia		
Any	13	16
≥Grade 3	0	0
Lethargy		
Any	13	5
≥Grade 3	2	0
Headache		
Any	17	14
≥Grade 3	0	0
Hot flashes		
Any	17	20
≥Grade 3	0	0
Edema		
Any	4	5
≥Grade 3	4	0

^a Grade was determined by Common Toxicity Criteria.

lution of malaise after letrozole was withdrawn and administration of fluoxymesterone was begun.

DISCUSSION

Letrozole demonstrated clear evidence of antitumor activity at both dosage levels. At the lower dose (0.5 mg/day), 9 patients (20%) achieved an objective response, and 6 patients (13%) had this documented on 2 assessments 3 months apart. Howell et al.¹⁴ reported that patients treated with hormonal therapy who maintain a “no-change” status for a minimum of 5 months have time to progression and survival comparable to those achieving a PR, and they considered the reporting of this information to be of value. In our study, an additional 9 patients (20%) had stable disease for at least 6 months. The level of benefit provided by letrozole at 0.5 mg/day depended on the criteria utilized. When a traditional criterion was used to document an objective response on at least 2 occasions separated by at least 1 month, 13% achieved a re-

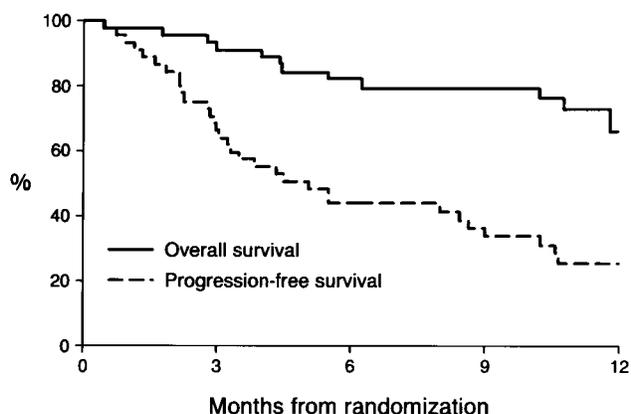


FIGURE 2. Progression free and overall survival are shown for patients who received letrozole at daily doses of 2.5 mg.

sponse, whereas 39% received benefit when we considered achievement of a response on at least 1 assessment or stable disease lasting at least 6 months.

Considering the higher dose of letrozole (2.5 mg/day), 10 patients (22%) had an objective response; 7 patients (16%) had this on 2 assessments 3 months apart. An additional 11 patients (24%) had stable disease for at least 6 months. Thus, depending on criteria utilized as discussed under lower dose letrozole, a range of 16–47% of patients achieved benefit.

The objective response rates for both dosage levels can be put into some perspective by noting the level of activity reported for megestrol acetate, which in the past was the second-line hormonal agent of choice for women with metastatic breast carcinoma. Sedlacek¹⁵ reported that the overall response rate for this agent was 16% in 6 clinical trials. Thus, even in the third-line setting, letrozole appears to have at least comparable activity.

The sample sizes for this protocol were chosen for Phase II goals, and the study was not powered for a direct comparison. However, the question of dose-response with letrozole has been addressed by others. Dowsett et al.¹⁶ recently reported that the daily doses of 0.5 and 2.5 mg inhibited aromatization in vivo to a substantial and similar degree (i.e., 98.4% and >99.1%, respectively). On this basis, they conclude that there is no reason to expect a higher level of antitumor activity at the higher dose. Of particular relevance to letrozole dosage is the clinical trial of Dombernowsky et al.,¹⁷ in which 551 patients with progressive measurable or evaluable breast carcinoma were randomized in a double-blind fashion to letrozole at 0.5 mg/day, letrozole at 2.5 mg/day, or megestrol acetate at 160 mg/day. UICC criteria were utilized with confirmation of response on 2 occasions separated by 4 weeks and

verification by independent blind external review. They found that letrozole at 2.5 mg/day was significantly better than letrozole at 0.5 mg/day in terms of response rate, time to treatment failure, time to progression, and survival, but there was no significant difference in tolerability. Also of note was that letrozole was also significantly better than megestrol acetate in terms of response rate, duration of response, time to treatment failure, and tolerability. The finding in their study that the higher dose of letrozole gave superior results needs confirmation and, if confirmed, provides a reasonable basis for further study of higher doses of this agent.

The finding by Dowsett et al.¹⁶ of a similar and high level of aromatase inhibition by both 0.5 and 2.5 mg dosage levels of letrozole does not preclude a superior antitumor benefit for the higher dose. It has been established that a substantial proportion of breast carcinomas have aromatase activity.⁶ It is plausible that measurements of aromatase inhibition as performed on urine samples may not reflect the levels of aromatase inhibition in tumors themselves. Lønning¹⁸ has noted that a major area for future research is the examination of the effect of aromatase inhibitors on intratumoral hormone concentrations.

We conclude that letrozole at doses of 0.5 mg/day and 2.5 mg/day has definite antitumor activity as third-line hormonal therapy for women with metastatic breast carcinoma. Both doses of this agent are well tolerated, and, although our study was not designed for a formal comparison, there was no indication that the higher dose was more toxic. Letrozole is an effective and well-tolerated hormonal agent.

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